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Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy ☆

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ABSTRACT

Purpose: There is no consensus on what constitutes adequate negative margins in breast-conserving therapy (BCT). We review the evidence on surgical margins in BCT for early-stage invasive breast cancer.

Methods: Meta-analysis of studies reporting local recurrence (LR) relative to quantified final microscopic margin *status* and the threshold *distance* for negative margins. The proportion of LR was modelled using random effects logistic meta-regression.

Results: Based on 21 studies (LR in 1,026 of 14,571 subjects) the odds of LR were associated with margin *status* [model 1: odds ratio (OR) = 2.02 for positive/close versus negative; model 2: OR = 1.80 for close versus negative, 2.42 for positive versus negative ($P < 0.001$ both models)] but not with margin *distance* [1 mm versus 2 mm versus 5 mm ($P > 0.10$ both models)], adjusting for median follow-up time. However, there was weak evidence in *both* models that the odds of LR decreased as the threshold distance for declaring negative margins increased. This bordered significance in model 2 [OR for 1 mm, 2 mm, 5 mm: 1.0, 0.75, 0.51 ($P = 0.097$ for trend)], and was not significant in model 1 [OR for 1 mm, 2 mm, 5 mm: 1.0, 0.85, 0.58 ($P = 0.11$ for trend)] but was evident when one study (of women $\leqslant 40$ years) was excluded from this model [OR for 1 mm, 2 mm, 5 mm: 1.0, 0.72, 0.52 ($P = 0.058$ for trend)]: this trend was rendered *insignificant* by adjustment for the proportion of subjects receiving a radiation boost or the proportion of subjects receiving endocrine therapy.

Conclusions: Margin *status* has a prognostic effect in all women treated for invasive breast cancer; increasing the threshold *distance* for declaring negative margins is weakly associated with reduced odds of LR, however adjustment for covariates (adjuvant therapy) removes the significance of this effect. Adoption of wider margins, relative to narrower widths, for declaring negative margins is unlikely to a have substantial additional benefit for *long-term* local control in BCT.

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1. Introduction

The realisation that both tumour burden and tumour biology contribute to clinical outcomes in breast cancer has provided a foundation for an effective treatment strategy – one that combines optimal local control with appropriately selected systemic therapies. Randomised controlled trials (RCT) have established the effectiveness and safety of breast-conserving therapy (BCT) [breast-conserving surgery (BCS) and radiation therapy] in the loco-regional treatment of invasive breast cancer.[1–6] The addition of radiotherapy to BCS has been shown to confer a survival benefit at long-term follow-up, providing an estimated 5.4% absolute reduction in breast cancer death at 15 years.[6] BCS aims to achieve a balance between complete resection of the tumour with negative margins and avoiding excessive resection of (healthy) breast tissue to provide a good cosmetic outcome for the woman[7,8] to help maximise the psychosocial benefits of breast preservation.[9] Decades of experience with BCT have provided knowledge on the various patient, tumour and therapeutic factors that influence the risk of local in-breast recurrence after BCT in invasive breast cancer[6–8,10–12] including the status of the surgical margins.

There is a general agreement that the risk of local recurrence (LR) is increased if the surgical margins are positive (tumour cells are present at the resection margin)[8,10,12] although estimates vary between studies. Despite the immediate therapeutic and long-term prognostic implications of margin status, there is no consensus on what constitutes adequate negative margins in breast oncology.[10,12–16] Furthermore, there is neither agreement nor consistent evidence that increasing negative margin width reduces LR.[10,12–16] Relentless debate and non-consensus on this issue are reflected in variations in practice at the level of individual clinicians, services, countries and cancer clinical guidelines[11,15,17,18] and highlighted in ongoing discussion on what might constitute adequate surgical margins[10,12–15] and in the lack of agreement on the width of the margins required in BCT even in expert consensus reports.[12]

Since RCT evaluation of this issue is not feasible, and given that individual prognostic studies lack sufficient power to estimate the effect of varying margin widths on local control,[19–21] we examined the impact of margins in breast cancer through a study-level meta-analysis. The evidence on surgical margins in women with early-stage invasive breast cancer treated with BCT was systematically reviewed to (a) determine the effect of margin status on LR, including the effect of various thresholds used to define negative (and relative positive or close) microscopic margins and (b) examine whether an ideal negative distance or width can be defined for margins in relation to maximising local control.

2. Materials and methods

2.1. Criteria for study eligibility and quality

Studies were included in our systematic review if they reported data allowing calculation of the *proportion* of LR in relation to margin status and threshold distance, and where: (1) subjects had early-stage invasive breast cancer (clinical or pathological stages I and II in *at least* 90% of subjects); (2) all were treated with BCT [BCS and radiation, at minimum whole-breast radiotherapy (WBR)]; (3) used quantitatively defined microscopic margins where negative margins, and positive and/or close margins, are defined relative to a specific *distance or width* from the cut edge of the specimen; (4) had a *minimum* median or mean follow-up time of 4 years and (5) provided (aggregate or categorical) data on age.

Eligibility criteria were defined with consideration of epidemiological principles in evaluating prognostic studies – namely, that subjects were assembled at a relatively common point in the course of disease and that studies allowed adequate follow-up time for clinical end-points to have occurred.[22,23] Our criteria therefore integrated cancer stage and a *minimum* follow-up time as a quality filter, complemented by microscopic margins and WBR as inclusion criteria to reflect standards of care. Studies were ineligible for this analysis if they: did not quantify margins (positive/negative margins not further defined); used non-standard margin definitions; did not report data for negative margins and included only subjects with the same margin status. In addition to the quality filter, information to help appraise studies was extracted including design, population characteristics, follow-up and treatment. These were partly adapted from a framework[22] and recommendations[23] for assessing the internal validity of studies dealing with prognosis in meta-analysis, but also considered risk-related information in breast cancer.

2.2. Literature search and data extraction

We systematically searched the literature (MEDLINE and EBM reviews including Cochrane databases, from 1965 to May 2010) for primary studies that met eligibility criteria, using the search and study identification strategy summarised in Fig. 1. One investigator (NH) screened abstracts identified in the literature search and full-text of potentially relevant studies. Data from eligible studies ($n = 21$)[19–21,24–41] were extracted *independently* by two of five investigators (N.H., M.L.M., J.M.D., M.B. and L.S.) using pre-defined data extraction forms (available from authors). Disagreement was resolved through arbitration by one investigator (N.H.). Details of the search strategy and criteria-based selection of eligible studies (including related studies[42–52] and excluded studies[53–65]) are presented in Fig. 1. Where two or more papers reported on the same cohort, the most recent study was preferentially used (provided it reported margin-specific data for LR) to avoid duplicate data – Fig. 1 includes details on potential overlapping cohorts.

2.3. Extracted variables

Descriptive and quantitative data were extracted from each study for the following variables: margin definition and categories, LR definition and outcomes data, duration of (and losses to) follow-up, years of study recruitment, design, median age, stage (distribution, node status, aggregate tumour size), time to LR, surgery (type of BCS, re-excision),

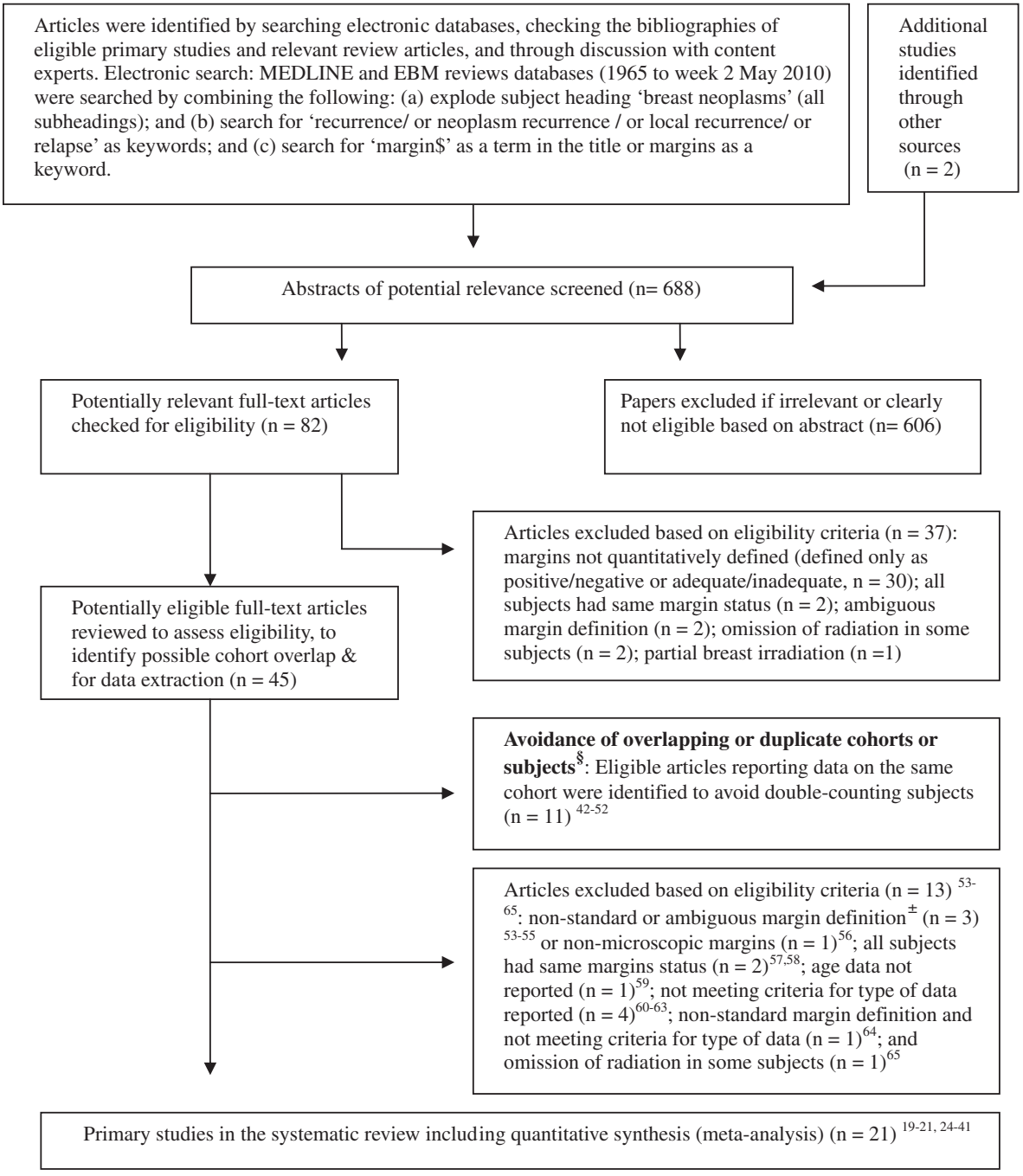

Fig. 1 – Literature search and study selection strategy (flow-diagram partly adapted from PRISMA* recommendations[74]). §Avoidance of overlapping cohorts or duplicate subjects in the above search strategy: primary studies were reviewed to ensure that study populations did not overlap by checking subject sources and study time-frame. Where two or more papers reported data for the same cohort, the most recent paper was preferentially used in this review, provided it included margin-specific outcomes data. Overall, potential overlap in our meta-analysis was estimated as <100 subjects [estimated for Voogd[28] and Ewertz[39]; and Karasawa[31] (single centre) and Karasawa[36] (multi-centre)]. ±Margin definition: described in Section 2. *Adapted from the PRISMA Group[74] (accessed October 2009 via www.prisma-satement.org)

radiation therapy [WBR dose, boost (proportion given boost and dose), total dose to tumour bed, node irradiation], systemic therapy (endocrine or chemotherapy use and type), systemic relapse, hormone receptors, menopausal status, tumour grade, lympho-vascular invasion and extensive intraductal component.

2.4. *Classification and definitions of variables*

2.4.1. *Margins*

Study-specific information on the quantified definition of the final microscopic margins, from excision or re-excision, was extracted and classified using two reported dimensions for

margins: margin *status* (whether negative, close or positive) and margin *distance* (the width used as the threshold for declaring negative margins relative to positive or close). To standardise synthesis of the evidence on microscopic margins, we considered a *standard* classification for positive margins to be based on the presence of any cancer, invasive cancer and/or ductal carcinoma in situ (DCIS), at the transected or inked surgical margin. Negative margins were defined as the absence of tumour within a specified distance (mm) of the resection margin, with a close margin indicating the presence of tumour within that distance *but not at* the resection margin. Studies reporting a margin distance for negative relative to positive (without differentiating close from positive) were also considered. To allow for variable classification of margins across studies, two models were developed: model 1 included all studies (comparison of combined positive/close with negative) and model 2 included studies allowing comparisons across three margin categories (positive, close and negative).

Where an unknown category was reported for margins, this was due to any of the following: specimen not being inked; specimen fragmented or removed in pieces; microscopic margins not given in the pathology report or specimen not available for determination of margins (in studies where specimens were reviewed.[19,21,28,33]) Since the unknown category cannot contribute meaningful data on the effect of margins, it has not been included in analytic models (data for subjects in this category were included in descriptive analyses).

2.4.2. *Local recurrence (LR)*

Definition of LR as a clinical end-point was classified into two categories: *LR (first)*, for studies reporting LR as the *first site of relapse* (including studies of LR-only as first-event, and studies where LR may have occurred simultaneously with regional and/or distant relapse) and *LR (any)*, for studies reporting LR occurring at *any* time (including LR as the first site of relapse and/*or* concurrent with or after regional or distant relapse, *or* LR not further specified).

2.4.3. *Covariates*

Extracted variables were classified based on quantitative data; for analytic purposes, additional information was categorised for stage, surgery and losses to follow-up. Studies were classified into two categories for stage: (1) all subjects had stages I and II invasive breast cancer and (2) $\geqslant$90% of subjects were estimated to have had stages I and II breast cancer, based on reported stage-distribution or derived from tumour size and node data distribution. Therefore, category 2 studies included some stage 0 (DCIS) or stage III or stage unknown in <10% of subjects. The type of BCS was classified using descriptive information (based on the recommendation of an expert surgeon (JMD)) as: (1) gross excision, excision biopsy, tumourectomy; (2) wide local excision (1 cm gross margin); (3) segmental excision; (4) various BCS techniques in the same study or (5) BCS not further defined. Studies reporting quadrantectomy[19,26,27,31,32,36] in some subjects were also examined separately. Studies reporting information on losses to follow-up were compared with those not reporting any information on this variable.

2.5. *Statistical analysis*

Descriptive analyses were used to examine the distribution of study-level variables. For continuous measures, the median, range, and inter-quartile range (IQR) were calculated. The proportion of women who had a LR was modelled using random effects logistic meta-regression. Random study effects were included in all models to allow for anticipated heterogeneity between studies beyond what would arise from within study sampling error alone. Taking account of both within and between study variability provides valid standard errors, confidence intervals and *P*-values. Statistical significance was set at $P < 0.05$ (two-sided); $P < 0.1$ was considered as weak evidence of association.

Modelling was used to assess whether the odds of LR were associated with margin status and distance, adjusted for the study median follow-up time; margin status and distance were tested for interaction. Each covariate (see Extracted Variables) was fitted both univariately (in a model that did not include margins) and also jointly with margin status and distance, and median follow-up time (adjusted model). Study-specific median age and median follow-up time were fitted as continuous variables. Covariates that showed *at least* a weak association ($P < 0.1$) with LR *either* univariately or in the adjusted models were further examined and reported in the models; local recurrence type was considered clinically relevant and also included in modelling. Covariates reported in less than half of the studies were not considered reliable for modelling.

In Model 1, which included all studies, margin status was fitted as a dichotomous variable (positive/close versus negative) and distance was fitted as a categorical variable (1 mm versus 2 mm versus 5 mm), using 1 mm as the referent category. Each model was refitted to test for trend across distance categories (coded as 1, 2 and 3) by treating the categories as equally spaced on a continuous scale. Model 1 was also examined after excluding one study,[38] as this was the only study restricted to an age-subgroup (women $\leqslant$ 40 years). In Model 2, which included studies reporting data across three margin categories, margin status was fitted as three categories: positive versus close versus negative (referent category); distance was fitted as for Model 1. All models were fitted using Proc NL mixed in SAS. Model parameter estimates were used to compute the predicted log odds of recurrence for both margin status and distance, adjusted for median follow-up time. Model 2 was used to compute the predicted probability of LR (and 95% confidence interval) at 10 years for all combinations of margin status and distance. Additional details of statistical modelling are included in Appendix 1.

3. Results

Twenty-one studies[19–21,24–41] were eligible for inclusion in this review; study-specific characteristics are summarised in (online-only) Appendix 2. Studies were retrospective, except for Bellon et al.[35] which was an RCT of sequencing of therapy (counted as one cohort in this analysis). Voogd et al.[28] scored margins for the combined BCS arms of two RCTs. Table 1 reports descriptive analyses: the median of the reported

Table 1 – Summary descriptive characteristics of studies in a meta-analysis of the effect of surgical margins on local recurrence in women with invasive breast cancer.

Variable	Number of studies providing data[a]	Median estimate	Inter-quartile range (range where appropriate)
Cohort characteristics			
Recruitment time-frame (year)			
Start	21	1980	1976–1987
End	21	1994	1992–1998
Mid-interval	21	1988	1983–1993 (1980–2000)
Number of subjects in each study[b]	21	583	348–940 (48–3899)
Median (or mean) follow-up time (months)	21	104.4	60.0–121.2 (51.6–159.6)
Median time to local recurrence (months)	12	52.3	42.7–60.0
Proportion with systemic relapse/metastases as first (or first and only) event[c]	10	10.9%	6.1–21.5%
Age (years)			
Median (or mean)	20	52.8	49.5–56.5 (37.5–60.6)
Minimum value in study-specific age range	18	24.0	22.0–25.0
Maximum value in study-specific age range	19	86.0	78.0–89.0
Menopausal status			
Premenopausal	6	52.0%	32.0–55.5%
Postmenopausal	6	47.6%	33.9–62.0%
Perimenopausal	6	3.0%	0–7.4%
Tumour characteristics			
Stage distribution[d]			
0	10	0%	0–1.4%
I	10	55.0%	52.5–56.0%
II	10	44.4%	43.1–45.9%
III	10	0%	0–0% (maximum 0.9%)
Unknown or NR	10	0%	0–0% (maximum 1.6%)
Node status			
Positive	21	25.0%	17.8–27.6%
Negative	21	71.2%	62.3–74.2%
Unknown or NR	21	1.6%	0–10.1%
Median tumour size (cm)	6	1.6	1.5–2.0
Tumour grade distribution			
Grade I	9	25.2%	22.8–32.1%
Grade II	9	35.5%	32.0–41.0%
Grades I and II combined	10	64.9%	57.5–71.7%
Grade III	10	24.9%	15.7–31.3%
Unknown or NR	10	5.2%	0–21.5%
Oestrogen receptor (ER) status			
Positive	16	42.8%	38.4–51.5%
Negative	15	20.5%	16.8–30.3%
Unknown or NR	16	31.4%	20.1–42.0%
Progesterone Receptor (PR) status			
Positive	12	40.6%	33.5–47.0%
Negative	12	22.0%	19.4–28.0%
Unknown or NR	12	38.4%	23.8–44.7%
Extensive intraductal component (EIC) (present)	12	10.7%	7.8–17.9%
Lympho-vascular invasion (LVI) (present)	10	15.7%	7.6–31.7%
Treatment variables			
Re-excision rate	10	50.6%	48.0–59.1%
Received chemotherapy[e]	17	24.6%	18.3–28.6%
Received endocrine therapy	18	23.3%	18.7–37.9%
Received any systemic therapy	11	48.3%	33.4–80.1%
Radiation therapy (doses in Gray, Gy)			
Whole breast radiotherapy (WBR)[f]:			
Median (or mean) WBR dose	15	46.8 Gy	45.0–50.0 Gy
Minimum dose in study-specific WBR range	8	44.5 Gy	41.8–49.0 Gy
Maximum dose in study-specific WBR range	8	51.6 Gy	50.0–54.0 Gy

(*continued on next page*)

Table 1 – (*continued*)

Variable	Number of studies providing data[a]	Median estimate	Inter-quartile range (range where appropriate)
Radiotherapy boost			
Received boost	18	99.0%	87.1–100% (20.5–100%)
Median boost dose	6	10.0 Gy	10.0–12.6 Gy
Minimum dose in study-specific boost range	13	10.0 Gy	10.0–15.0 Gy
Maximum dose in study-specific boost range	13	18.0 Gy	16.0–20.0 Gy
Total dose to tumour bed (TDT)			
Median TDT	10	62.0 Gy	61.0–64.0 Gy
Minimum TDT in study-specific range	8	51.0 Gy	50.0–59.0 Gy
Maximum TDT in study-specific range	5	72.4 Gy	70.0–73.0 Gy
Received radiation to regional nodes[g]	7	10.5%	1.7–28.4%

[a] Variables reported in fewer than half of the included studies were not considered in our models.
[b] Three studies reported data per treated breast resulting in 42 additional treated breasts in 16,824 subjects (these have been counted as subjects in analysis – therefore our total is 16,866).
[c] Reported in 12 studies; however we excluded two studies[21,39] (reporting systemic relapse combined with other cancers and/or contralateral breast cancer) from analysis of this variable.
[d] Stage distribution (where specified) – 11 studies included only subjects with stages I and II invasive breast cancer (only some of these studies reported exact distribution) and 10 studies included stages I and II in the vast majority of subjects (see Section 2 for details); overall approximately 96% of subjects had stages I and II invasive breast cancer.
[e] Type of chemotherapy varied across studies (further details available from the authors).
[f] Whole breast radiotherapy (WBR) is an inclusion criterion in this review (all subjects had WBR).
[g] Use of nodal irradiation was reported in 12 studies; however specific data were provided in only 7 studies.

median follow-up times was 104.4 months (IQR 60-121.2) and the median time to LR (based on 12 studies) was 52.3 months (IQR 42.7-60.0). Approximately 96% of subjects had stages I and II invasive breast cancer. The odds of LR did not differ between studies reporting no losses to follow-up (or declaring small subject losses between 0.4 and 3.7%,[27,32,35,41]) and studies that did not report on losses to follow-up.

For analytic purposes, one study using one high-power field[28] as threshold distance for negative was included in the 1 mm group, and one study using 3 mm[32] was included in the 5 mm group. Neuschatz et al.[20] reported two potential thresholds for distance: 5 mm was used in our analysis to balance the distribution of studies across distance categories (the effect of margin distance in this primary study is consistent with the trends in our models).

3.1. *Effect of margins on LR*

3.1.1. *Model 1*

Based on 21 studies[19–21,24–41] reporting LR in 1026 of the 14,571 subjects with data on positive and/or close and negative margins (from 16,866 subjects), study-specific and crude pooled odds ratios (OR) are shown in Fig. 2. The proportion of subjects with LR stratified by the threshold distance for negative margins is shown in Fig. 3. Model estimates of effect are presented in Table 2 (model 1): the odds of LR were associated with margin status ($P < 0.001$) and median follow-up time ($P = 0.027$), but not with margin distance ($P = 0.26$). There was no evidence of interaction: effect of margin status did not vary by distance or vice versa ($P = 0.90$). The odds of LR did not differ significantly for 5 mm versus 1 mm ($P = 0.12$); 2 mm versus 1 mm (P=0.58) or for 5 mm versus 2 mm ($P = 0.16$). The odds of LR slightly decreased as the distance for declaring negative margins increased ($P = 0.11$ for trend). Two of the studies in model 1 reported loco-regional recurrence[30,39]: exclusion of these studies did not substantially alter model estimates.

The underlying LR rates by median year of study recruitment generally declined over time, particularly post-1990 (online-only Fig. 4); the 'outlier' study (triangle top of Fig. 4) is that from Vujovic et al.[38] which is a study of women $\leqslant 40$ - years. Median year of study recruitment was associated with the underlying LR rates ($P = 0.021$) in univariate analysis, but not in the adjusted model ($P = 0.37$).

Examination of model 1 after excluding the study from Vujovic et al.[38] (see Analysis) showed generally similar estimates as those with all studies retained, however the exclusion of this study[38] increased the evidence for an association between margin *distance* and the odds of LR in both the unadjusted and the adjusted models. Unadjusted for follow-up time, the *P*-value for association with margin *distance* reduces to 0.009, and the estimated effect of distance showed that the OR for 1 mm (referent category), 2 mm and 5 mm altered to 1.0 (referent), 0.55 [95% confidence interval (CI) 0.31, 0.96] and 0.37 (95% CI 0.20, 0.68), respectively ($P = 0.0031$ for trend). Adjusted for median follow-up time, the *P*-value for distance reduces to 0.16 [0.058 for trend]. The estimates for the effect of margin *distance*, adjusted for median follow-up time (excluding Vujovic et al.[38] from model 1) altered the OR for 1 mm (referent category), 2 mm and 5 mm to 1.0 (referent), 0.72 (95% CI 0.39, 1.31) and 0.52 (95% CI 0.26, 1.03), respectively ($P = 0.058$ for trend).

3.1.2. *Effect of Covariates in model 1*

Only covariates meeting pre-defined criteria for potential association or relevance (see Analysis) were further examined for effect on model estimates reported in Table 2 which included all the 21 studies (model 1). In Table 3, we summarise

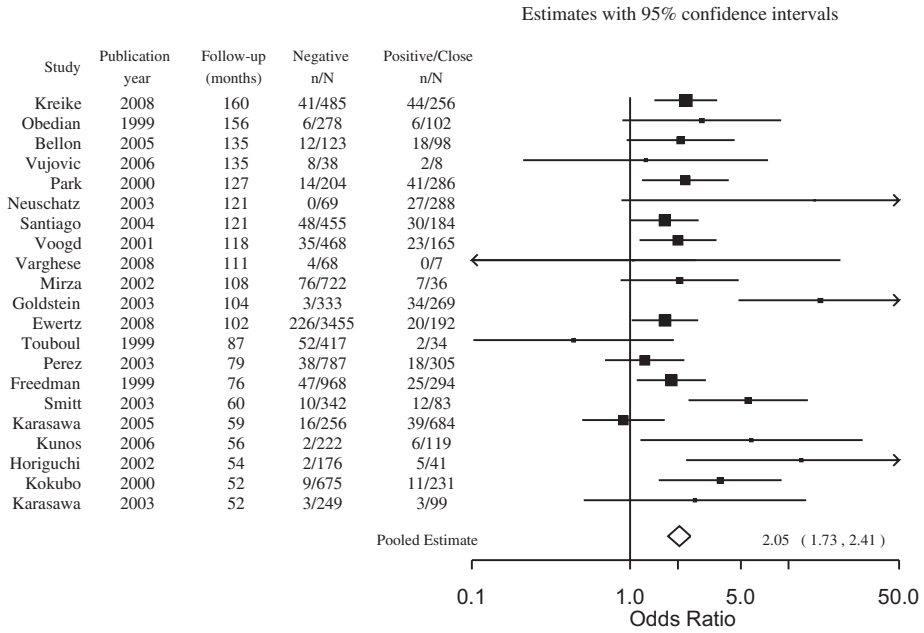

Fig. 2 – The effect of margin status (positive/close relative to negative) on local recurrence: study-specific odds ratios, ordered by median follow-up time. Figure shows a crude pooled odds ratio of 2.05 (95% CI: 1.73–2.41) [modelled pooled odds ratio, *adjusted* for median follow-up time, was 2.02 (95% CI: 1.71–2.38)]. Data for Neuschatz[20] were based on a 5 mm threshold distance for negative margins; data for Mirza[30] and Ewertz[39] are for loco-regional recurrence.

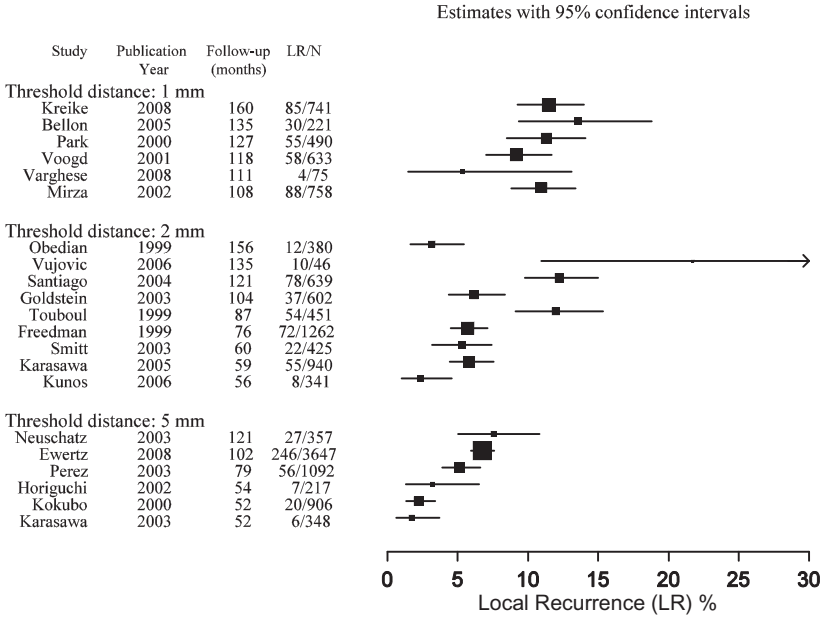

Fig. 3 – Study-specific proportion with local recurrence (LR) stratified by threshold distance for negative margins, ordered by median follow-up time. Data for Neuschatz[20] were based on a 5 mm distance; data for Perez[32] were based on a 3 mm distance (this was included in the 5 mm group in our analysis); data for Mirza[30] and Ewertz[39] were for loco-regional recurrence.

the results for these covariates, showing association with LR in a univariate analysis and the association once each of these covariates was entered into a model that included *margins and median follow-up time* (the remaining associations were for age, endocrine therapy, type of surgery and median year of study recruitment). The adjusted odds of LR were only associated with age ($P = 0.048$). There was no evidence of interaction between follow-up time and margin status ($P = 0.65$) or distance ($P = 0.43$).

Adjusting model 1 for covariates (Table 3) did not alter the effect of margin *status*: there was a significant association ($P < 0.001$) between margin status and the odds of LR in *all*

Table 2 – Models of the effect of surgical margins on local recurrence (LR) in early-stage[a] invasive breast cancer.

	Model estimates for the effect of margins (unadjusted)			Model estimates adjusted for study-specific median follow-up time (months)		
	Odds of LR (odds ratio)	95% CI	*P*-value[b] [*P* for trend]	Odds of LR (odds ratio)	95% CI	*P*-value[b] [*P* for trend]
Model 1 – 21 studies with median 8.7 years follow-up (based on study-specific median follow-up time for 16,866 subjects; 14,571 with known margins were included in model estimates)[c]						
Constant	0.09	0.06–0.14		0.027	0.009–0.084	
Margin status			<0.001			<0.001
Negative	1.0	–		1.0	–	
Positive/close	2.03	1.72–2.40		2.02	1.71 – 2.38	
Threshold distance[d] for negative margins			0.019 [0.005]			0.27 [0.11]
1 mm	1.0	–		1.0	–	
2 mm	0.62	0.34–1.14		0.85	0.46–1.56	
5 mm	0.37	0.19–0.72		0.58	0.28–1.17	
Model 2 – 16 studies with median 9.0 years follow-up (based on study-specific median follow-up time for 11,409 subjects; 9,555 with known margins were included in model estimates)						
Constant	0.08	0.05–0.13		0.040	0.01–0.14	
Margin status			<0.001			<0.001
Negative	1.0	–		1.0	–	
Close	1.80	1.44–2.26		1.80	1.43–2.25	
Positive	2.43	1.94–3.04		2.42	1.94–3.02	
Threshold distance[e] for negative margins			0.045 [0.014]			0.23 [0.097]
1 mm	1.0	–		1.0	–	
2 mm	0.59	0.33–1.06		0.75	0.39–1.45	
5 mm	0.39	0.19–0.82		0.51	0.23–1.16	

[a] Approximately 96% with stages I and II invasive breast cancer.
[b] *P* reports the *P*-value for association, *P* in square brackets gives *P for trend* and reflects whether there was statistical evidence of a decrease in the odds of LR as the threshold distance for declaring negative margins increased.
[c] Estimates for model 1 based on re-analysis after excluding from model one study (of women $\leqslant$ 40 years[38]) are shown in Section 3.
[d] *Model 1*: Based on 6 studies using 1 mm, 9 studies using 2 mm and 6 studies using 5 mm (5 studies that used 5 mm and 1 study that used 3 mm), as the threshold for declaring negative margins.
[e] *Model 2*: Based on 5 studies using 1 mm, 8 studies using 2 mm, and 3 studies using 5 mm (2 studies that used 5 mm and 1 study that used 3 mm), as the threshold for declaring negative margins.

adjusted analyses. Two of the adjusted models (type of surgery and LR type) showed a significant trend indicating a decrease in the odds of LR as the *distance* for negative margins increased. In all other adjusted models there was no statistical evidence of a decrease in the odds of LR as the threshold distance for negative margins increased (Table 3), and particularly in the model adjusting for the proportion of subjects who received endocrine therapy ($P = 0.24$ for trend).

Examination of model 1, after excluding the study from Vujovic et al.,[38] also found that the trend for a decrease in the odds of LR as the distance for negative margins increased ($P = 0.058$ for trend) was no longer significant once adjusted for the proportion of subjects who received endocrine therapy ($P = 0.24$ for trend).

Although age was weakly associated with the odds of LR ($P = 0.066$), this was not significant ($P = 0.33$) if the study from Vujovic et al.[38] (with the lowest median age) was excluded. This probably reflects the relatively homogeneous distribution of median age across studies (Table 1). Tumour grade was weakly associated with LR in univariate analysis ($P = 0.091$) but this was reported in only 10 studies. Effect of distance was non-significant when adjusted for grade ($P = 0.86$); however model reanalysis on the same 10 studies but omitting the covariate for grade also showed no effect for distance ($P = 0.78$). Hence, the non-significant adjusted effect for margin distance is more likely due to loss of studies than adjusting for grade.

3.2. *Model 2*

Based on the 16 studies[19–21,24–28,32–37,40,41] reporting LR in 674 of the 9555 subjects with data on each of positive, close and negative margins (from 11,409 subjects), estimates of effect are presented in Table 2 (model 2). The odds of LR were significantly associated with margin status ($P < 0.001$) but not distance category ($P = 0.19$); the odds of LR did not differ significantly for 5 mm versus 1 mm ($P = 0.10$), 2 mm versus 1 mm ($P = 0.37$) or 5 mm versus 2 mm ($P = 0.21$). However, this model had only 3 studies in the 5 mm category. The odds of LR decreased as the distance for declaring negative margins increased ($P = 0.097$ for trend).

3.2.1. *Effect of covariates in model 2*

Table 4 shows the covariates associated with LR ($P < 0.1$) in a univariate analysis, and the results after entering each covariate (and also local recurrence type) into a model that also included margins. Adjusting model 2 for covariates did not alter the effect of margin *status*: there was a significant association ($P < 0.001$) between margin status and the odds of LR in *all* the adjusted models (Table 4). For margin distance, two of the

Table 3 – Model 1 – A model estimating the effect of surgical margins on local recurrence (LR) in invasive breast cancer adjusted for covariates (covariates examined in model 1 were selected using criteria described in Analysis).

Covariate (covariate definition and categories described in Section 2)	No. of studies	P for association of covariate with LR		Margin status[a] (adjusted OR)		Threshold distance for negative margins (adjusted OR)			P for trend for the effect of distance
		Unadjusted	Adjusted for margins and follow-up time	Negative	Positive/ close	1 mm	2 mm	5 mm	Trend[b] adjusted for covariate
Effect of margins (adjusted for follow-up time)	21	–	–	1.0	2.02**	1.0	0.85	0.58	0.11
Age	20	0.066	0.048	1.0	1.95**	1.0	0.95	0.65	0.20
Median-year of study recruitment	21	0.021	0.37	1.0	2.02**	1.0	0.84	0.59	0.12
Proportion had endocrine therapy	18	0.002	0.13	1.0	2.08**	1.0	0.80	0.63	0.24
Type of BCS (five categories)	21	0.061	0.23	1.0	2.02**	1.0	0.84	0.44*	0.024
LR type (first versus any)	21	0.56	0.13	1.0	2.02**	1.0	0.84	0.48*	0.047

Table shows the OR for margin status and threshold distance for negative margins adjusted for study-specific median follow-up time *and* each covariate (first row gives OR for margin status and distance adjusted for median follow-up time to allow comparison with the results that follow).

[a] *P*-value for the effect of margin status on LR was significant ($P < 0.001$) in all models and has not been included in table. *P*-value for estimate: †$P < 0.1$, *$P < 0.05$, **$P < 0.01$ (relative to the referent group).

[b] Trend: *P* for trend reflects whether there was statistical evidence of a decrease in the odds of LR as the threshold distance for declaring negative margins increased – a significant *P* value indicates evidence of a trend.

Table 4 – Model 2 – A model estimating the effect of surgical margins on local recurrence (LR) in invasive breast cancer adjusted for covariates (covariates examined in model 2 were selected using criteria described in Analysis).

Covariate (covariate definition and categories described in Section 2)	No of studies	P for association of covariate with LR		Margin status[a] (adjusted OR)			Threshold distance for negative margins (adjusted OR)			P for trend for the effect of distance
		Unadjusted	Adjusted for margins & follow-up time	Negative	Close	Positive	1 mm	2 mm	5 mm	Trend[b] adjusted for covariate
Effect of margins (adjusted for follow-up time)	16	–	–	1.0	1.80**	2.42**	1.0	0.75	0.51†	0.097
Median-year of study recruitment	16	0.079	0.11	1.0	1.82**	2.43**	1.0	0.69	0.45*	0.039
Proportion had endocrine therapy	13	0.090	0.56	1.0	1.87**	2.55**	1.0	0.70	0.59	0.26
Proportion had radiation boost	15	0.019	0.25	1.0	1.79**	2.41**	1.0	0.68	0.60	0.21
LR type (first versus any)	16	0.46	0.19	1.0	1.79**	2.41**	1.0	0.69*	0.40*	0.040

Table shows the OR for margin status and threshold distance for negative margins adjusted for study-specific median follow-up time *and* each covariate (first row gives OR for margin status and distance adjusted for median follow-up time to allow comparison with the results that follow)

[a] *P*-value for the effect of margin status on LR was significant ($P < 0.001$) in all models and has not been included in table. *P*-value for estimate: †$P < 0.1$, *$P < 0.05$, **$P < 0.01$ (relative to the referent group).

[b] Trend: *P* for trend reflects whether there was statistical evidence of a decrease in the odds of LR as the threshold distance for declaring negative margins increased – a significant *P* value indicates evidence of a trend.

adjusted models rendered *insignificant* the observed trend for the effect on LR of increasing distance. In the model adjusting for the proportion of subjects given a radiation boost, the trend for the effect of distance was not significant ($P = 0.21$). Similar findings were shown adjusting for endocrine therapy ($P = 0.26$); however, only 13 studies were in this analysis and

Table 5 – Predicted probabilities of local recurrence (LR) at 10 years from *Model 2* (adjusted for median follow-up time).[a]

Threshold distance[b] for negative margins	Overall probability of LR as end-point[c] (95% confidence interval)			Probability of LR as first (or first and only) relapse (95% confidence interval)		
	Margin status			Margin status		
	Positive	Close	Negative	Positive	Close	Negative
1 mm	15.8% (10.5, 23.0)	12.2% (8.0, 18.2)	7.2% (4.7, 10.8)	15.1% (10.1, 21.8)	11.6% (7.7, 17.2)	6.8% (4.5, 10.2)
2 mm	12.4% (8.2, 18.2)	9.5% (6.3, 14.1)	5.5% (3.7, 8.3)	10.9% (6.9, 16.7)	8.3% (5.2, 12.9)	4.8% (3.1, 7.5)
5 mm	8.8% (4.8, 15.4)	6.7% (3.6, 11.9)	3.8% (2.1, 7.0)	6.6% (3.2, 13.3)	5.0% (2.4, 10.2)	2.8% (1.3, 6.0)

[a] Predicted probabilities of LR at 10 years in the above table are estimated from Model 2 (based on data for 9555 subjects with known margin status from 11,409 subjects, in 16 studies with an underlying average LR rate of 6.6% for a median 9.0 years of follow-up time).
[b] Based on 5 studies using 1 mm, 8 studies using 2 mm, and 3 studies using 5 mm (2 studies that used 5 mm and 1 study that used 3 mm), as the threshold for declaring negative margins.
[c] Probability of LR as end-point: overall probability counting LR as first event or LR occurring at any time.

there was also no significant trend for distance ($P = 0.21$) if the proportion who had endocrine therapy was *not* included as a covariate in modelling these 13 studies, indicating that the lack of association may be due to loss of studies from the analysis. Predicted probabilities of LR from model 2, adjusted for median follow-up time, are shown in Table 5.

There was little or no evidence of an association between stage-group categories (see Section 2, covariates) and LR in the margins-adjusted models ($P = 0.32$, $P = 0.104$ for models 1 and 2, respectively).

4. Discussion

The selection of a specific distance or width to declare negative microscopic margins in BCT has been based on long-held opinions and deeply entrenched practice using arbitrarily chosen thresholds (such as 1 mm, 2 mm, 3 mm, 5 mm or wider). Some experts recommend that 'absence of tumour at the inked margin' represents adequate negative margins.[66] We have systematically examined the evidence on the association of surgical margins with LR in early-stage invasive breast cancer, providing estimates of effect that factor *both* the final margin status and the threshold distance used to declare negative margins. Data synthesis across studies showed that positive and close margins significantly increase the odds of LR (OR 2.02; $P < 0.001$) relative to negative margins (in the model of 3 margin categories OR is 1.0 for negative, 1.8 for close and 2.42 for positive; $P < 0.001$). Allowing for that effect, the *distance* used to declare negative margins did not independently contribute to the risk of LR ($P = 0.27$ and $P = 0.23$ in models 1 and 2, respectively, adjusted for follow-up time) *when tested for association*. However, there was consistent weak evidence in both models that the odds of LR decreased as the threshold distance for negative margins increased (Table 2). This was more evident in model 2 ($P = 0.11$ and $P = 0.097$ *for trend* in models 1 and 2, respectively), although the exclusion from model 1 of a study (based on young women)[38] increased the evidence of this trend ($P = 0.058$ *for trend*). Direct comparison between threshold distance categories for negative margins indicated that there was no statistically significant improvement in local control in using a wider threshold (e.g. 5 mm) for negative margins relative to a narrower distance (e.g. 1 mm), allowing for differences across studies in follow-up time.

Interpretation of our findings should be considered against the understanding that BCS strives to achieve a delicate balance between local control and cosmesis, and cosmetic outcomes are substantially affected by the amount of tissue removed and poorer cosmesis has implications for quality of life. Therefore, although the ORs for LR (Table 2) show some decline with increasing distance for negative margins, the evidence for this trend is weak and only bordered statistical significance. Furthermore, in model 2, this trend was no longer significant once the ORs were adjusted for the proportion of subjects who received a radiation boost, and similar findings were shown for the proportion of subjects who received endocrine therapy in this model (however the latter was a less robust analysis). Adjustment for the proportion of subjects who received endocrine therapy in model 1 similarly reduced the significance of the trend for a decrease in the odds of LR as the distance for negative margins increased (and this was a consistent finding whether the study from Vujovic et al.[38] was retained or excluded from the model). Overall, our findings suggest that adopting a wider margin (e.g. 5 mm) is unlikely to produce a substantial additional benefit for long-term local control over using a narrow distance (e.g. 1 mm) for declaring negative margins. At the least, clinicians opting to use a wider distance for negative margins should consider our findings in deciding surgical and radiation treatment, and in particular whether re-excision is justified where a negative margin is in the range of 1–2 mm.

Our analysis was based on studies defining quantitatively the distance (width) used to declare negative margins, and hence does not provide direct evidence on whether 'absence of tumour cells on the inked margin' as a definition of negative margins is sufficient to minimise LR. However, given that *close* margins were found in our analysis to be consistently associated with a higher rate of LR than negative margins this supports defining a minimal margin distance to declare negative margins. Therefore, based on our meta-analysis, it may be reasonable to define a *minimum* distance of 1 mm for negative margins in BCT of invasive breast cancer.

Examination of covariates demonstrated that the association between margin *status* and the odds of LR was significant in *all* the adjusted models. The microscopic status of the surgical margin, though not an exact test (reliant on examination of representative tissue sections), is a strong and robust prognostic factor for LR in all treatment groups. For the distance

used to declare negative margins, the weak trend indicating a decrease in the odds of LR as the distance increased was not evident when adjusted for various factors shown in both models (Tables 3 and 4) and as outlined earlier in the Discussion. These findings also suggest that any potential benefit for LR of using a wider distance rather than a narrow distance to declare negative margins may be negated by the use of other local or systemic treatments. With regards to adjuvant systemic therapy, subjects treated with endocrine therapy in the studies included in our analysis received predominantly Tamoxifen, and none were reported to have received biological agents (such as Herceptin). Recent studies using the aromatase inhibitors as endocrine therapy,[67,68] and trials of agents targeting HER2,[69,70] have established that these treatments reduce both local and systemic recurrence. Interpretation of our findings should consider the increasing use of these effective systemic therapies, including newer endocrine, chemotherapeutic and targeted agents, which reduce overall LR rates and hence may possibly further reduce any potential benefit of using wider distances for declaring negative margins.

This work focuses on the relative effect of surgical margins; the absence of a significant effect in our models for some variables may be due (at least in part) to the use of *study-level* information rather than individual patient data, or the absence of data for variables not reported in some studies: both are general limitations of study-level meta-analysis. The relatively homogeneous distribution of some covariates across studies (such as median age and aggregate dose of WBR) also accounts for a lack of evidence of association (or of strong association) of these factors. This does not mean that these factors are unimportant for LR, but rather that the variables (at an aggregate level) were similar across studies and did not account for differences in LR in our models of the effect of margins. The absence of an effect for some variables, such as lympho-vascular invasion and extensive intraductal component, may be due to the lack of association in the data or due to the availability of data on these variables in only half of eligible studies.

Negative surgical margins do not guarantee the absence of residual cancer within the breast; histological studies using serial sub-gross sectioning of the breast have shown that additional cancer can be found in the breast in a substantial proportion of women despite adequate surgical resection.[71,72] A negative margin predicts that residual tumour burden is minimal and is likely to be controlled with radiotherapy and systemic therapies. Ours is the first work to report empiric evidence across a large number of cohorts on the prognostic impact of margin status *and* distance and provides several insights into this much-debated topic in BCT. First, the association between negative distance and LR exhibits a weak dose–response pattern, rather than a simple threshold effect. Second, the effect of margin *distance* is less important when patients receive other treatments known to reduce LR, as shown in adjusted analyses for use of radiation boost or endocrine therapy (while estimates of the effect of margin *status* are unaltered by adjustment for these covariates). Third, margin distance appears to be associated with a non-significant reduction in the odds of LR across all categories of margin status, including positive – this has not been previously identified. Possible explanations for this finding include (but are not limited to) the process of margin evaluation and/or the amount of tumour in a positive margin. Since several oriented margins in a breast specimen are evaluated routinely, determination of close or positive margins usually reflects that one margin is 'non-negative' relative to the threshold distance used in a specific study. By inference, all the remaining margins are also evaluated using the pre-specified distance for negative, hence that distance may weakly contribute to local control across all categories of margin status. We did not have quantitative information on the amount or the type of tumour at the margin: only two eligible studies[19,21] reported LR according to whether the presence of tumour in positive margins was focal or extensive, and whether it was invasive or *in situ* or both. It is possible that detailed histological data may have allowed exploration of whether these factors modify the risk of LR in relation to margin distance. The studies reporting histological information indicated that increasing amounts of either invasive cancer or DCIS at the margin (the extent of margin 'positivity') were associated with the risk of LR,[19,21] and that the risk of LR did not significantly differ whether margin involvement was by invasive cancer alone or DCIS alone or both together.

Since LR rates in breast cancer are reported to have decreased over time,[45,73] due to various factors including population screening, greater use of (and improved) local and systemic treatments and other factors associated with quality of care including routine evaluation of microscopic margins,[45,73] some may argue that our models might not reflect the impact of margins in contemporary practice. We have demonstrated that the underlying LR rates across studies included in this review have declined with time; the association between LR rates and the timeframe of study-cohort recruitment was evident in both of our models; however this was not significant in the adjusted models of the effect of margins ($P = 0.37$ and $P = 0.11$ in models 1 and 2). Furthermore, adjusting for this variable did not substantially change the estimates of effect for margins. This indicates that the prognostic value of margin status is not diminished by temporal declines in LR rates.

This meta-analysis is the first to demonstrate across studies the association between the threshold distance for negative margins and LR in invasive breast cancer. The implications for practice are that the association between margins and the risk of LR is largely driven by margin status (by whether positive, close or negative), and that the threshold distance for declaring negative margins does not contribute to that risk at a statistically significant level. Modelled estimates of effect demonstrate a weak trend indicating a decrease in the odds of LR as the distance for negative margins increases; however adjusting for covariates (in particular, adjuvant therapies) removes the significance of this trend. Taken as a whole, and considering that BCS must achieve good cosmetic outcomes to confer the psychosocial benefit of breast preservation, we conclude that the adoption of wide margins (e.g. 5 mm) for declaring negative margins in BCT is unlikely to have a substantial additional benefit for long-term local control over using a narrow margin (e.g. 1 mm) as the threshold for declaring negative margins in invasive breast cancer.

Conflict of interest statement

The authors of this manuscript have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.07.043.

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