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Breast Cancer Res Treat (2009) 114:403–412
DOI 10.1007/s10549-008-0023-4

REVIEW

Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis

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Received: 29 January 2008 / Accepted: 9 April 2008 / Published online: 18 April 2008

Abstract *Purpose* The purpose was to establish the impact on survival of early detection of a local recurrence of breast cancer as compared to late detection. *Design* A meta-analysis was carried out using Cochrane review manager software (RevMan version 4.2). Studies were included if women were treated for primary breast cancer without evidence of distant metastasis at primary diagnosis and if these concerned routine follow-up strategies focusing on the early detection of curable recurrences. Data regarding the risk for death were derived from each study. Multi level models were used to study heterogeneity by using MLWin. *Results* Thirteen studies concerning 2,263 patients were included. Early detection of breast cancer recurrences during follow-up gave a significantly better survival as compared to late detected recurrences (HR: 1.68 (95% CI: 1.48–1.91)). Survival was better when the recurrence was found by mammography instead of physical examination or in patients without symptoms as compared to those with symptoms (HR: 2.44 (95% CI: 1.78–3.35); HR: 1.56 (95% CI: 1.36–1.79), respectively). If all breast cancer recurrences would be detected earlier, that 5–8 deaths (i.e. an absolute reduction in mortality of 17–28%) would be avoided by performing routine follow-up during a 10 year-period for 1,000 breast cancer patients. *Conclusion* These data support the hypothesis that detection of isolated loco-regional or contra-lateral breast cancer recurrences in patients without symptoms has beneficial impact on survival of breast cancer patients when compared to late symptomatic detection.

Keywords Breast neoplasm · Survival · Recurrence · Early detection · Meta-analysis

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Introduction

Screening for breast cancer has resulted in increasing numbers of patients diagnosed with early breast cancer. The combined effect of early diagnosis and improved treatment for breast cancer has led to a significant decrease in breast cancer-related mortality. As a consequence, the prevalence of breast cancer survivors rises. After curative treatment for breast cancer it is common practice to enter patients in a surveillance program for many years**.** There will be more breast cancer survivors followed by more need for long-term surveillance [1]. At the same time, there is an increasing pressure on breast services from new referrals and urgent cases [2]. It is predicted that there will be a 48% increased need for cancer services by 2020. This puts an increasing burden on follow-up oncology clinics [3]. There is a need to quantify the benefits of follow-up to organise the follow-up more efficiently.

One of the important goals of surveillance is improvement of survival. The surveillance program can extend survival when two assumptions are made: (1) most recurrences are detected at an early stage (i.e. are without symptoms at diagnosis) during the surveillance visits and (2) the early treatment of recurrences leads to better survival [4]. About 40% of loco-regional recurrences were asymptomatic at diagnosis in an earlier systemic review and meta-analysis that involved 5,045 patients and 378 isolated loco-regional recurrences [5]. The risk of breast carcinoma-related death is increased for patients with a local recurrence compared to those without local recurrence [6, 7]. Still, the effect of early detection of curable recurrence on overall survival remains questionable and controversy remains on the benefits of regular follow-up [8]. The aim of this study is to perform a meta-analysis of the impact of early detection of loco-regional or contralateral breast cancer recurrence on survival.

Methods

Search strategy

Pubmed Medline, CancerLit, Cochrane, Web of sciences and Embase were searched for relevant studies. Studies in any language were examined published between 1966 and 2006. MESH words used were "Breast Neoplasms", "Follow-Up Studies", "Mammography", "Physical Examination" and "Survival". Title and abstract were searched for the words: "breast cancer", "follow-up", "detection", "survival" and "recurrence". Reference lists and reviews were searched by hand.

Selection of papers

Studies were included in the meta-analysis when they met the following inclusion criteria. *Target population*: Studies were included if women were treated for primary breast cancer without evidence of distant metastasis at primary diagnosis. *Follow-up*: Studies were included if they concerned routine follow-up strategies or tests focusing on the early detection of curable recurrence (loco-regional recurrence and contralateral recurrence). *Contrast*: Studies were included if they focused on comparing early detection (recurrences without symptoms) versus late detection (recurrences with symptoms). *Outcome*: Studies were included when they presented survival data. *Data presentation:* Studies were included when they presented hazard ratios expressing the risk of death or when they presented information for calculating these hazard ratios (number of deaths and exact p-values).

Two researchers (GHdeB and LWL) independently examined titles ($n = 1{,}369$) and abstracts ($n = 413$) to decide if the full text articles should be obtained. Cases of disagreement were resolved by discussing the titles and abstracts ($n = 14$). Six studies fulfilled the inclusion criteria regarding follow-up, contrast and outcome, but did not present hazard ratios or information for calculating these hazard ratios. For two of these six studies, the number of deaths among the patients with recurrences was not available [9, 10]. For two studies, no (exact) *P*-value was available [11, 12]. For two studies, the number of deaths among the patients with recurrences was not available, nor the (exact) *P*-value was available [13, 14]. As a consequence 13 of 68 full-text articles that were examined could be included in the analysis. For an overview of studies included in the analysis, see Table 1.

Data extraction and definition

Data were extracted independently by the two researchers (GHdeB and LWL), by means of a predefined form. For an overview of the topics, see Table 1. Loco-regional recurrences were defined as the presence of cancer in the breast or axilla on the same side. Contra-lateral recurrences were defined as cancer in the other breast after the primary treatment of the first breast cancer. Distant metastases were defined as the evidence of breast cancer in any part of the body except breast and axilla. It was registered whether follow-up time was measured from the time of primary treatment or from the time of recurrence. A follow-up scheme was considered as standard when patients received regular mammography with or without physical examination. A follow-up scheme was considered as intensive when patients received additional blood tests and bone scans regularly and independent of symptoms. A recurrence was considered as being detected early when it was mammographically detected during a routine clinic visit in a patient without symptoms. A recurrence was considered as being detected late when it was detected by patient themselves.

Assessment of methodological quality and publication bias

Methodological quality was assessed independently by the investigators (GHdeB and LWL) by means of a predefined form. Because there is no generally accepted standard for measuring methodological quality in prognostic studies, this form was derived from the work of Altman and Laupacis and is presented in Table 2 [15, 16]. A score six or of higher was considered as a high quality score. The cut-off point was based on the median.

Table 1 Characteristics of the papers that met the inclusion criteria

Author	Patients with primary breast cancer (*N*)	Type of recurrence (*N*)	Starting point for computation of follow-up time	Type of follow-up scheme	Comparison made	Type of outcome	Age of the women under study[a]	Stage of primary tumour[a] (*N*)	Primary surgical treatment[a] (*N*)
Ciatto S, 2004/ 1990	–	339 CLR	Primary treatment	Standard	Asympt versus sympt	Death	Mean(range): 54.7(30–90)	pN0 (152/55) pT1 (197/61) pN + (40/31) pT2 + (39/40) pNx (42/19) pTx (4/8)	–
Imoto S, 1998	550	29LRR	Primary treatment	Intensive	Asympt versus sympt	Death	Age < 36 years:$n = 5$	Stage I (8)	Total mastectomy (59)
		36DM					$50 \geq$ Age ≥ 36 years:$n = 32$	Stage II (37)	Partial mastectomy (6)
							Age > 36 years:$n = 28$	Stage III (20)	
Kindler M, 1989	1,004	175 LRR + DM	Primary treatment	Intensive	Asympt versus sympt	Death	–	_	_
Perrone MA, 2004	408	104 LRR 98 DM 9 (LRR + DM)	Primary treatment	Intensive	Asympt versus sympt	Death	_	_	_
Stierer M, 1989	676	40LR	Primary treatment	Intensive	Asympt versus sympt	Death	Mean(Range): Group Asympt 59(33–82)	_	Modified Radical masctomy (76)
		93DM					Group Sympt 61(30–80)		Quadrantectomy(76) Simple mastectomy(3)
Te Boekhorst S, 2001	–	68 LRR	Primary treatment	Standard	Asympt versus sympt	Death	Mean(SD): 53(13)/54(13)	Stage I (12/14)	Breast conservation (58/81)
		181 DM+ 21 (LRR + DM)						Stage II (52/94) Stage III (36/62)	Mastectomy (42/89)
Tomin R, 1987	1,230	248 LRR + DM	Recurrence	Intensive	Asympt versus sympt	Death	_	_	Radical mastectomy(123) Modified radical masctomy (105) Simple mastectomy(18) Surgical mental resection(2)

Table 1 continued

Author	Patients with primary breast cancer (*N*)	Type of recurrence (*N*)	Starting point for computation of follow-up time	Type of follow-up scheme	Comparison made	Type of outcome	Age of the women under study[a]	Stage of primary tumour[a] (*N*)	Primary surgical treatment[a] (*N*)
Wagman LD, 1991	–	13CLR + 51DM	Primary treatment	Intensive	Routine versus interval	Death	_	Stage I (11) Stage II (45) Stage III (8)	_
Doyle T, 2001	–	112 LRR	Primary treatment	Standard	Mammo versus clinic %	Death/ DM	Age < 40 years:26 Age ≥ 40 years:67	–	–
Hussain ST, 1995	354	33LRR	Primary treatment	Standard	Mammo versus clinic %	Death	–	Stage I (13/3) Stage II (15/2)	–
Kaas R, 2001	–	275 CLR	Recurrence	Standard	Mammo versus clinic %	Death	Mean(SE) (Recurrence): 52(13)(LR) 58(13)(CLRR)	–	–
Orel SG, 1993	1,636	72 LRR	Primary treatment	Standard	Mammo versus clinic %	Death	Age < 36 years:$n = 11$ 51 ≥ Age ≥ 36 years:$n = 27$ Age > 51 years:$n = 34$	Stage Tis (11) Stage I (41) Stage II (9) Stage IV (3)	Salvage mastectomy (72)
Voogd AC, 1999	7,000	266 LRR	Recurrence	Standard	Mammo versus clinic %	Death/ DM	Mean(Range): 45(16–81)	Stage I(150) Stage II (111) Stage III (4)	Breast conservation therapy (all)

[a] Age of the women under study, stage of primary tumour and primary surgical treatment as presented in the study

% Clinically assessed implies by physical examination of based on symptoms

Table 2 Quality rating of included studies

No.	Item	Ciatto S 2004	Imoto S 1998	Kindler M 1989	Perrone MA 2004	Stierer M 1989	Te Boekhorst S 2001	Tomin R 1987	Wagman LD 1991	Doyle T 2001	Hussain ST 1995	Kass R 2001	Orel SG 1993	Voogd AC 1999
1	Is the population under study defined with inclusion and exclusion criteria?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Were all patients with a diagnosis of breast cancer included (also those without recurrences)?	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes
3	Were patients included within the context of any clinical trial?	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No
4	Were the patients included from more than one center or hospital?	Yes	No	No	No	No	No	Yes	No	No	No	Yes	Yes	Yes
5	Are the main prognostic patient and disease characteristics presented (at least: age at onset of primary diagnosis and stage of tumour)?	Yes	Yes	No	No	No	Yes	No	No	No	No	No	Yes	Yes
6	Is the treatment for the first tumor specified (at least: primary surgical treatment)?	No	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
7	Is the time of follow-up long enough (mean or meadian 5 years or more)?	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
8	Is the loss during follow-up specified?	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
9	Is the follow-up scheme (including mammography scheme) specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
10	Are the outcomes prospectively assessed?	No	No	No	No	No	No	No	No	No	No	No	No	No
	Quality scores	7	5	4	5	5	6	7	3	2	5	6	8	7

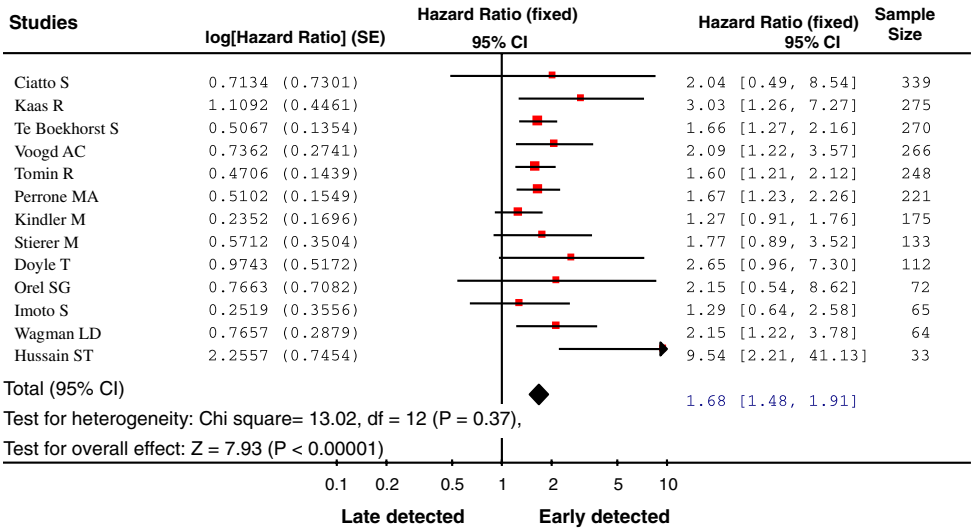

Fig. 1 Impact on survival of early detection of recurrences after the primary treatment for breast cancer. *Note*: Early detected recurrences versus late detected recurrences

To investigate publication bias, in Fig. 1 studies are presented based on sample size to get an impression of a potential relationship between sample size and effect size. To quantify this relation, Kendall's tau coefficient was calculated [17]. To estimate whether publication bias is likely to be a problem in this meta-analysis, the fail-safe number was assessed to calculate how many studies are needed to counterbalance the results [18].

Statistical analysis

The main outcome in this analysis was the hazard ratio (HR) and its standard error (SE). If these data were not directly available, these were estimated based on the total number of events in both groups and the two-sided *P*-value by using the method described by Parmar [19]. Based on the SE, 95% confidence intervals (CIs) were calculated. HRs were directly presented in only one study [20].

In the next step, HRs were combined by using Review Manager Version 4.2. By using the Generic Inverse Variance method, logHRs and SErs were entered. The pooled result was expressed as combined HRs with fixed effects with a 95% CI, and an overall test on heterogeneity was performed using the Chi-square test. Despite non significant results, we still explored heterogeneity because of the small number of studies. The following potential sources of heterogeneity were explored: the type of recurrences considered, the starting point for computation of follow-up time, type of follow-up scheme, comparisons made, quality score, and type of outcome. For each potential source of heterogeneity, a multilevel model was developed with the logHR as dependent variable and the source of heterogeneity as well as the SE as independent variables. To quantify the theoretical extent of survival improvement, if the loco-regional or contra-lateral recurrence would be early detected, the population attributable risk was calculated [21].

Results

Study characteristics

In the analysis, 2,263 patients from 13 studies were included having 724 loco-regional recurrences, 627 contra-lateral recurrences, 459 distant metastases, 30 loco-regional recurrences with distant metastases combined and 423 not specified recurrences (see Table 1). Fifty-eight percent (1,223) of these patients had a recurrence detected early and 42% were with late detection. The included studies were comparable regarding the distribution of age, primary tumour stage and primary surgical treatment. In the majority of studies, the time of follow-up was measured from date of primary diagnosis ($n = 10$; 77 %). In seven studies (54%) patients were offered routine follow-up, including regular mammography and physical examination, and in six studies patients were offered intensive follow-up including routine additional tests. Seven studies (54%) focused on patients diagnosed with recurrences without symptoms as compared to patients diagnosed with recurrences with symptoms. One study focused on recurrences found during routine follow-up or outside routine follow-up. Five studies focused on recurrences diagnosed by mammography or symptoms. Eleven studies had death as primary outcome, and two studies had a mixed outcome (death of distant metastases).

Quality score and publication bias

Seven studies had a quality score of 5 or lower (Table 2). There were no indications of publication bias because increasing sample size was not related to increasing effect size (Kendall's tau coefficient: -0.194 ($P = 0.36$)). The fail-safe number was 210, which means 210 contrary

Table 3 Outcomes in the papers that met the inclusion criteria

Author	Time of follow-up	Number of death among early detected patients	Number of death among late detected patients	Log-rank *P*-value	HR	SE
Ciatto S, 2004/1990	1–31 years	-/234	-/105	0.008	2.0408	0.7301
Imoto S, 1998	Median: 878 days (196–1806)	14.57/30△	17.25/35△	0.48	1.2865	0.3556
Kindler M, 1989	-	109/121△	54/54△	0.2	1.2652	0.1696
Perrone MA, 2004	Median: 94.7 month (9.7–198.3)	87/101	80/110	0.001	1.6656	0.1549
Stierer M, 1989	Median:41 month	8/37△	26/56△	0.1105	1.7705	0.3504
Te Boekhorst S, 2001	0–16 years	153/170	81/100	0.0003	1.6599	0.1354
Tomin R, 1987	0–16 years	67/89△	143/159△	0.0017	1.6010	0.1439
Wagman LD, 1991	5 years+	26/26△	24/38△	0.009	2.1505	0.2879
Doyle T, 2001	0–20 years	11/42	4/47	0.06	2.6493	0.5172
Hussain ST, 1995	0–11years	14/28	0/5	0.03	9.5421	0.7454
Kaas R, 2001	Median:82.5(10–166)	51/166	16/109	0.015	3.0320	0.4461
Orel SG, 1993	0–13 years	6/38	2/34	0.28	2.1517	0.7082
Voogd AC, 1999	2–4 years	61/141	10/47	0.02	2.0881	0.2741

△ Estimated from survival curve

studies would need to be included to counterbalance the result in this meta-analysis at a significance level 0.05.

Survival

Overall, survival was significantly better with early detection of the recurrence (HR: 1.68 (95% CI: 1.48–1.91, $P < 0.0001$; see Fig. 1). In all 13 studies, the HR showed a trend for better survival with early detection, but five out of the 13 included studies presented no significant result (Table 3). There was no significant heterogeneity among the studies (Chi-square = 13.12, $P = 0.37$; Fig. 1).

The chance of benefit of early detection was statistically significant higher in the studies that presented the data regarding loco-regional recurrence and contra-lateral recurrence separately from distant metastases (HR: 2.55 (95% CI: 1.76–3.70) as compared to the studies that did not (HR: 1.59 (95% CI: 1.38–1.82; $P = 0.02$); see Table 4).

Table 4 Comparison of HRs for six sources of heterogeneity

Sources of heterogeneity	Number of studies	Combined HR	95% CI	*P*-value[b]
Type of recurrence				
Only loco-regional or contra-lateral recurrences	6	2.55	1.76–3.70	
LRR, CLR and DM	7	1.59	1.38–1.82	0.02
Starting point for computation of follow-up time				
Primary treatment	9	1.64	1.41–1.91	
Recurrence	3	1.77	1.39–2.25	0.62
Type of follow-up scheme				
Standard	7	1.92	1.55–2.38	
Intensive	6	1.56	1.33–1.83	0.12
Comparison made				
Patient reported symptoms (no versus yes)	7	1.56	1.36–1.79	
Mammographically only versus clinically assessed[a]	6	2.44	1.78–3.35	0.01
Quality scores				
>5	6	1.73	1.45–2.06	
≤5	7	1.81	1.45–2.27	0.61
Type of outcome				
Death or distant metastases	2	2.20	1.37–3.54	
Death	11	1.64	1.44–1.88	0.24

[a] Assessed clinically, during interval or routine visit

[b] Based on estimations of the multilevel model

When analyzing the studies that calculated follow-up time from the date of primary treatment separately from the studies that calculated follow-up time from the date of recurrences, we observed that the HR for the studies excluding lead-time bias were comparable for the studies that calculated time to follow-up from the date of recurrence. (HR: 1.64 (95% CI: 1.41–1.91), HR: 1.77 (95% CI: 1.39–2.25), respectively). Studies focusing on the impact of an intensive regimen for follow-up gave a HR for survival comparable to studies focusing on a standard regimen for follow-up (HR: 1.56 (95% CI: 1.33–1.83), HR: 1.92 (95% CI: 1.55–2.38), respectively; $P = 0.12$). Recurrences assessed in patients without symptoms were related to a higher probability of survival than when symptoms were present (HR: 1.56 (95% CI: 1.36–1.79)). Survival was better in studies where recurrences were found by mammography instead of studies where recurrences were being assessed clinically (HR: 2.44 (95% CI: 1.78–3.35)). This advantage is significantly higher for studies mammographically assessed than for tumours clinically assessed ($P = 0.01$). Studies with a higher quality score were not related to a different HR than studies with a lower quality score (HR: 1.73 (95% CI: 1.45–2.06), HR: 1.81 (95% CI: 1.45–2.27), respectively; $P = 0.61$). Studies focusing on death or distant metastases had a non-significant higher HR for survival than studies focussing on death only (HR: 2.20 (95% CI: 1.37–3.54), HR: 1.64 (95% CI: 1.44–1.88), respectively; $P = 0.24$).

Absolute effects

There would be an absolute reduction in mortality of 17–28% of breast cancer patients with recurrences, if all recurrences would be early detected, given the pooled HR of 1.68 (95% CI: 1.48 to 1.91) and the proportion of the early detected recurrences (40%) [5]. Given the fact that nowadays nearly all patients in Western countries are in follow-up, the incidence of recurrence (10%) during a 10 year-period and the survival rate at 10 years (70%) of breast cancer patients with recurrence [22], 5–8 deaths would be avoided by performing routine follow-up during a 10 year-period for 1,000 breast cancer patients.

Discussion

This meta-analysis shows that early detection of isolated recurrences in patients without symptoms by routine follow-up or mammography improves survival of patients with breast cancer recurrences (HR = 1.68; 95% CI: 1.48–1.91). Given the proportion of early detected loco-regional recurrences is 40%, there would be an absolute reduction in mortality of 17–28% of breast cancer patients with recurrences, if all loco-regional recurrences would be detected early. Individual studies have been inconclusive in answering the question whether early detection of breast cancer recurrences is related to longer life. Five studies included did not show a significant difference in improving survival between early detection versus late detection of loco-regional recurrence [23–27]. One explanation might be that these studies had too small sample sizes. The meta-analysis allowed us to include the observations of more than 2,000 patients, and yields a far more precise estimate of the effect on survival of early detection of loco-regional or contra-lateral breast cancer recurrences.

A topic of debate in follow-up of breast cancer is the role of mammography and physical examination. Several studies concluded that the early detection of local disease recurrence require both clinical examination and mammography [28–30]. One study reported that the tumour size of local recurrences detected by mammography alone were smaller than those detected by physical examination [29]. Several studies [20, 31, 32] suggested that breast cancer patients who received regular mammograms were less likely to die than breast cancer patients who did not, and that recurrences found by mammography are associated with a better survival [33, 34]. A similar effect was seen in this meta-analysis. Our findings suggested that survival is better when the recurrence is found by mammography instead of physical examination (HR: 2.44 (95% CI: 1.78–3.35)). There were insufficient data to study the contribution of yearly mammogram as compared to 6 month mammogram. In this meta-analysis, late detected recurrences included those recurrences detected by breast self-examination or by symptoms. Recurrences assessed in patients without symptoms are also related to a higher probability of survival than when symptoms are present (HR: 1.56 (95% CI: 1.36–1.79)). This advantage is higher for tumours assessed by mammography ($P = 0.01$). These findings indicate that the actual survival benefit of early detection of a local recurrence by mammography may be higher than the pooled overall data reported in this meta-analysis. In the absence of related studies, the contribution of breast self-examination is not clear. According to the favorable effect size of early detection of curable recurrence by mammography, the result is in line with ASCO guideline that women should be made aware that monthly BSE does not replace mammography as a breast cancer screening tool to early detect isolated breast recurrences after a primary treatment for breast cancer [35].

In this meta-analysis, some studies were included that did not present data for loco-regional recurrence and contralateral recurrence separately from distant metastases, although the primary focus was loco-regional recurrence or contralateral recurrence [8, 24–26, 36, 37]. We found that the chance of benefit of early detection is significantly

higher in the studies that presented the data regarding loco-regional recurrence and contralateral recurrence separately from distant metastases (HR: 2.55 (95% CI: 1.76–3.70) as compared to the studies that did not (HR: 1.59 (95% CI: 1.38–1.82; $P = 0.02$)). The combined HR was attenuated in the studies which included distant metastasis because the early detection of distant metastasis unlikely had benefit on survival [38, 39].These findings may indicate that the actual survival benefit of early detection of a local recurrence is even higher than found in this meta-analysis.

There was no statistically significant difference in HR for survival between studies in this meta-anlaysis that used an intensive regimen compared to a standard regimen for follow-up (HR: 1.92 (95% CI: 1.55–2.38; HR: 1.56 (95% CI: 1.33–1.83), respectively). This is in line with previous publications in which it is found that intensive follow-up schemes focusing on the early detection of distant metastases does not improve the chances of survival [38, 39].

Lead time bias may have influenced the outcome of an analysis like we did [37, 40]. Lead time bias means that patients with disease detected by early diagnosis survive longer than those whose disease is detected on the occurrence of new signs or symptoms, even when treatment is without effect. When analyzing the ten studies that calculated follow-up time from the date of primary treatment separately from the three studies that calculated follow-up time from the date of recurrences we observed that the HR for the studies excluding lead-time bias is comparable with the HR for the studies that calculated time to follow-up from the date of recurrence. (HR: 1.64 (95% CI: 1.41–1.91), HR: 1.77 (95% CI: 1.39–2.25, respectively). Studies focusing on death or distant metastases had a non-significant higher HR for survival than studies focussing on death only (HR: 2.20 (95% CI: 1.37–3.54), HR: 1.64 (95% CI: 1.44–1.88), respectively; $P = 0.24$). This means that in this analysis, the effect of lead-time bias does not explain the effect of early detection that we found.

Studies with a higher quality score were not related to better outcome than studies with a lower quality score (HR: 1.73 (95% CI: 1.45–2.06), HR: 1.81 (95% CI: 1.45–2.27), respectively; $P = 0.24$). Identical benefits were presented in studies with high quality scores and studies with low quality scores. Increasing sample size was not related to increasing effects size (Kendall's tau coefficient: -0.194 ($P = 0.36$)). The fail-safe number of 210 indicates that 210 contrary studies would be needed to counterbalance the result in this meta-analysis at a significance level 0.05. So even if publication bias existed, it is not a problem that weakened the results of this meta-analysis.

A limitation of this meta-analysis is that all included studies were retrospective. The optimal design would be a clinical trial in which patients are randomized to follow-up versus no-follow-up. Such a study is not feasible for ethical and psychological reasons. Besides the early detection of recurrence, there are many other factors that have impact on breast cancer patients' survival. Due to the incomplete information on some important prognostic factors like age of the women, tumour stages or surgical treatment, we were not able to analyze the impact of these factors on the survival related to early detection of recurrences.

These data support the hypothesis that detection of breast cancer loco-regional or contra-lateral recurrences in asymptomatic patients during routine follow-up or assessed by mammography improves survival, when compared to late symptomatic detection and give an indication of the absolute effect. Further studies should focus on improvement of follow-up strategies aiming at early detection of loco-regional or contra-lateral recurrences and on cost-effectiveness of these strategies.

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