Systematic review

Meta-analysis of the oncological safety of autologous fat transfer after breast cancer

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Background: **Autologous fat transfer, also known as lipofilling, is a minimally invasive technique that uses the patient's own fat to correct disfiguring sequelae after breast cancer surgery. Despite its obvious clinical benefits, experimental research has demonstrated that autologous fat transfer inherently stimulates angiogenesis and tissue regeneration, which is feared to increase the risk of locoregional recurrence of breast cancer. This meta-analysis is founded on recently completed large cohort studies on this highly relevant topic.**

Methods: **A literature search was performed in PubMed, Embase and the Cochrane Library on 1 September 2017, adhering to the PRISMA guidelines, to identify all relevant studies of patients with breast cancer exposed to autologous fat transfer. The difference in incidence rate of locoregional recurrence between patients who had autologous fat transfer and controls was the primary outcome in the meta-analysis.**

Results: **Fifty-nine studies and a total of 4292 patients were included. These consisted of seven matched cohorts, 12 cohorts and 40 case series. Mean follow-up was 5·7 years from the date of primary cancer surgery and 2·7 years after autologous fat transfer. Meta-analysis of matched cohorts revealed an incidence rate difference of −0·15 (95 per cent c.i. −0·36 to 0·07) per cent per year, which was not statistically significant ($P = 0·419$). This finding was confirmed in the pooled results of the remaining cohorts and case series.**

Conclusion: **This meta-analysis of all oncological data from the published literature demonstrated that autologous fat transfer did not result in an increased rate of locoregional recurrence in patients with breast cancer. Autologous fat transfer can therefore be performed safely in breast reconstruction after breast cancer.**

An early and outdated version of this meta-analysis was presented to the Sixth European Association of Plastic Surgeons Research Council Meeting, Pisa, Italy, May 2017

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Introduction

Breast cancer is the most common malignancy in women worldwide, with 1·7 million new cases annually and a global burden that surpasses that of all other cancers[1]. Through improved early detection and treatment, the number of women surviving is gradually increasing, thereby shifting the focus towards improving quality of life and reducing cancer-related morbidity. As a result, an organ-saving surgical approach in the form of breast-conserving surgery (BCS) has been established as the standard of care for the majority of patients. Although current oncoplastic and breast reconstructive surgical techniques can restore the original breast contours successfully after oncological surgery, they fall short in their ability to eliminate remaining smaller deformities, which in some instances can be equally disfiguring and stigmatizing for the patient.

Autologous fat transfer (AFT) is a minimally invasive technique that excels in correcting various soft tissue deformities using liposuctioned fat tissue (*Fig. 1*). In essence, AFT involves harvesting fat tissue by means of liposuction and reinjecting it into an area of the breast

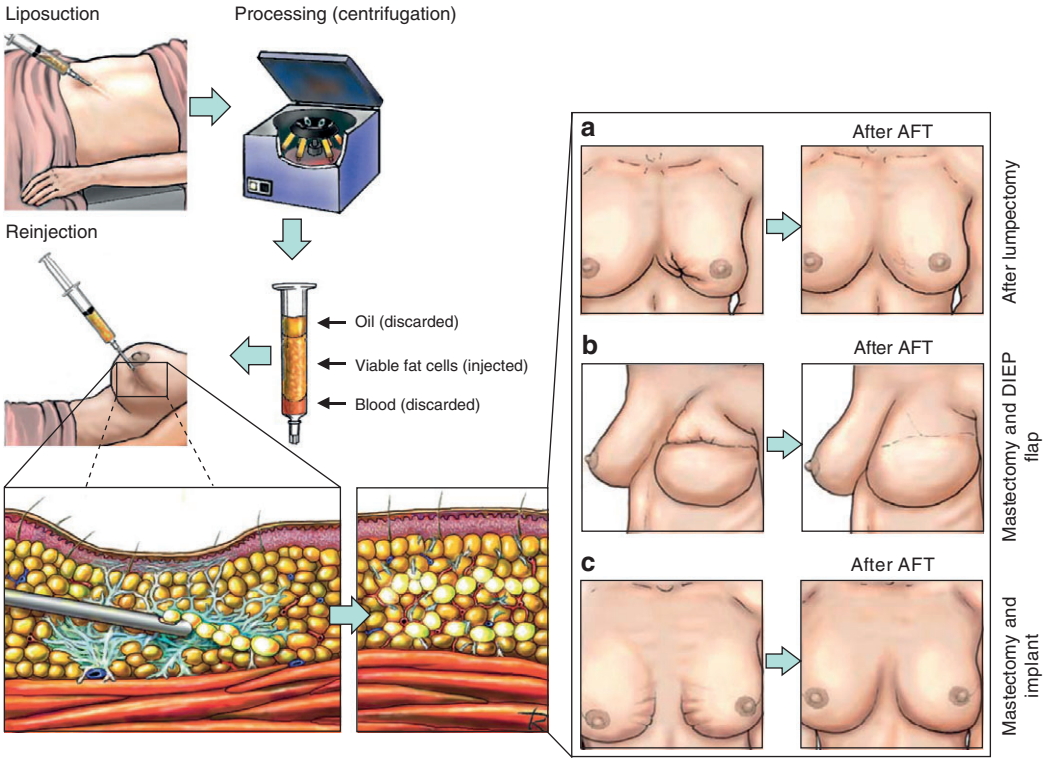

Fig. 1 Schematic overview of the autologous fat transfer (AFT) technique. It comprises three steps: harvesting using liposuction; processing (centrifugation); and reinjection into an area with soft tissue deformity. **a–c** Examples of the spectrum of indications that could profit from AFT treatment. **a** Deformities after lumpectomy with visible retraction of the scars, often exacerbated by irradiation. Such defects are normally too small to warrant reconstruction with implants or flaps and AFT remains the only reconstructive option. **b** Flap-based reconstruction (such as the deep inferior epigastric perforator (DIEP flap) with visible step-off deformities between the native tissue and the flap. **c** Implant reconstruction with visible implant rippling and volume deficiency in the cleavage area. (The left part of the figure has been published previously by Krastev *et al.*[2])

with a deformity, hence the popular term 'lipofilling'. Angiogenesis facilitates the survival of a major part of the injected fat cells resulting in a successful transplantation. Its low morbidity, and the prospect of achieving autologous breast reconstruction without relying on invasive pedicled or free-flap transfer, makes AFT an attractive procedure within the process of breast reconstruction.

Unfortunately, a major drawback to the widespread application of AFT after breast cancer has been the uncertainty regarding its oncological safety. Research in the field of stem cells and tissue engineering has led to the discovery of a previously underappreciated population of mesenchymal stem cells residing in adipose tissue, referred to as adipose-derived stem cells (ADSCs)[3]. ADSCs are thought to play a key role in the survival of adipocytes after AFT by stimulating angiogenesis and tissue regeneration through the secretion of a variety of cytokines and growth factors[4]. This has raised concerns that the intentional placement of regenerative cells in a previous tumour bed could potentially increase the risk of locoregional recurrence (LRR). Experiments in immunodeficient nude mice have shown that ADSCs co-injected with active tumour cells display an increased rate of cancer growth and proliferation[5–7]. It is questionable whether the interactions between human ADSCs and cancer cells that were modelled in immunodeficient mice can be extrapolated to the clinical setting. Nearly a decade later, however, clinical research has not been able to answer this question, while the use of AFT is gradually increasing in clinical practice.

Evaluating the oncological safety of AFT has posed unprecedented challenges for both the oncological and plastic surgical communities. AFT represents a novel treatment that is fundamentally different from conventional reconstructive techniques and therefore lacks an acceptable alternative to use in a control group. As this renders setting up RCTs unpractical and even unethical, researchers have approached this topic through retrospective case series and (matched) cohort studies. Although

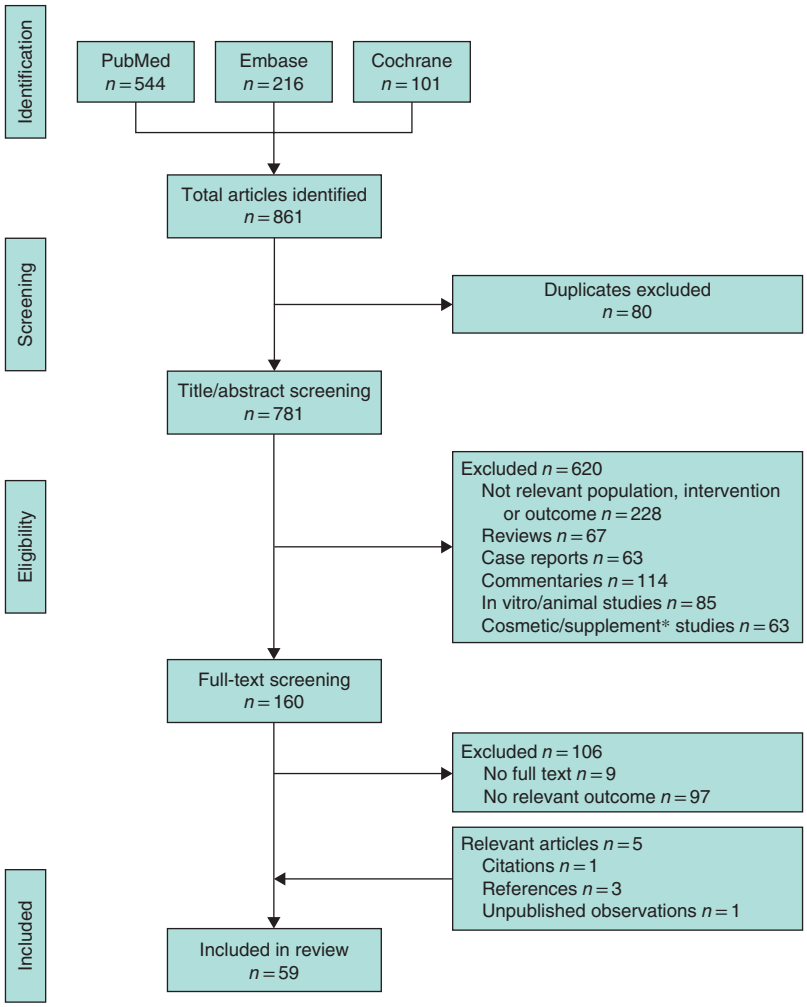

Fig. 2 Flow diagram showing selection of articles for review. *For example, platelet-rich plasma, stem-cell enrichment

the majority of these studies have consistently reported no increased rate of LRR after AFT, they are individually underpowered to provide conclusive evidence. Published systematic reviews[2,8–12] so far have consisted chiefly of descriptive summaries of results from individual studies. A meta-analysis was attempted on only one occasion[8], ultimately pooling data from three cohort studies, two of which consisted of overlapping populations with high heterogeneity ($I^2 = 56$ per cent). Therefore, the oncological safety of AFT in breast reconstruction after breast cancer surgery remains a topic of much debate.

With the increased rate of AFT in breast reconstruction worldwide, there is an urgent need to determine whether this treatment could potentially compromise oncological safety in patients with breast cancer, before a false sense of security engenders wide adoption in clinical practice. A meta-analysis on the oncological safety of AFT after breast cancer was undertaken, which aimed to address this highly controversial topic by integrating all relevant evidence and to provide a more reliable answer than the results of each individual study.

Methods

The research objectives were to identify, evaluate and synthesize the evidence examining the risk of LRR in patients treated with AFT after breast cancer surgery.

Search strategy and selection criteria

This systematic review adhered to the standards of the PRISMA statement[13]. A comprehensive, reproducible electronic search was conducted in PubMed, EMBASE and the Cochrane Library to identify all published studies of women receiving AFT for breast reconstruction after surgery for breast cancer (*Table S1*, supporting

Table 1 Summary of included studies

Reference	Study design	Treatment group	No. of patients	Type of surgery (no. of breasts)		Histology (no. of breasts)		Locoregional recurrence rate	
				Mastectomy	BCS	Invasive	*in situ*	Period B	Period C
Amar *et al.*[17]	CS	AFT	15	0	15	–	–	0 of 15	–
Bayti *et al.*[18]	CS	AFT	68	58	10	55	9	2 of 68	2 of 68
Beck *et al.*[19]	CS	AFT	10	0	10	–	–	0 of 10	–
Biazus *et al.*[20]	CS	AFT	20	0	20	20	0	0 of 20	–
Bonomi *et al.*[21]	CS	AFT	31	31	0	22	8	1 of 31	–
Brenelli *et al.*[22]	CS	AFT	158	96	62	–	–	0 of 158	–
Brenelli *et al.*[23]	CS	AFT	59	0	59	52	7	3 of 59	4 of 59
Brown *et al.*[24]	CS	AFT	88	69	19	–	–	2 of 88	–
Chirappapha *et al.*[25]	CS	AFT	137	85	52	–	–	0 of 137	–
Cohen *et al.*[26]	CH	AFT	162	162	0	111	51	4 of 162	4 of 162
		Control	414	414	0	331	83	–	8 of 414
Constantini *et al.*[27]	CS	AFT	22	14	8	–	–	1 of 22	–
Delaporte *et al.*[28]	CS	AFT	15	15	0	–	–	0 of 15	–
Delay *et al.*[29]	CS	AFT	42	0	42	39	3	1 of 42	–
Doren *et al.*[30]	CS	AFT	278	278	0	–	–	6 of 278	–
Fertsch *et al.*[31]	MCH	AFT	100	100	0	91	9	5 of 100	5 of 100
		Control	100	100	0	91	9	2 of 100	2 of 100
Gale *et al.*[32]	MCH	AFT	211	176	35	184	27	4 of 211	4 of 211
		Control	422	358	64	368	54	8 of 422	8 of 422
Helme *et al.*[33]	CS	AFT	29	0	29	–	–	0 of 29	–
Hitier *et al.*[34]	CS	AFT	150	130	20	127	23	0 of 150	–
Hoppe *et al.*[35]	CS	AFT	28	28	0	–	–	1 of 28	–
Ihrai *et al.*[36]	CS	AFT	64	50	14	–	–	2 of 64	2 of 64
Kaoutzanis *et al.*[37]	CS	AFT	108	108	0	–	–	0 of 108	–
Kaoutzanis *et al.*[38]	CS	AFT	108	97	0	61	36	0 of 97	0 of 97
Khan *et al.*[39]	CH	AFT	35	0	35	–	–	0 of 35	0 of 35
		Control	64	0	39	–	–	–	–
Kim *et al.*[40]	CH	AFT	102	102	0	60	42	1 of 102	1 of 102
		Control	449	449	0	–	–	–	9 of 449
Komorowska-Timek *et al.*[41]	CH	AFT	26	26	0	26	0	0 of 26	–
		AFT	53	53	0	40	13	0 of 53	–
Krastev *et al.* (unpublished results)	MCH	AFT	282	161	139	254	46	8 of 300	8 of 300
		Control	300	150	150	259	41	11 of 300	11 of 300
Kronowitz *et al.*[42]	CH	AFT	660	581	79	552	108	9 of 660	9 of 660
		Control	609	536	73	548	61	–	16 of 609
Langlands and McManus[43]	CS	AFT	224	–	–	–	–	5 of 224	5 of 224
Laporta *et al.*[44]	CH	AFT	20	20	0	–	–	–	0 of 20
		Control	20	20	0	–	–	–	0 of 20
Longo *et al.*[45]	CH	AFT	11	11	0	–	–	0 of 11	–
		AFT	10	10	0	–	–	0 of 10	–
Manconi *et al.*[46]	CS	AFT	12	12	0	–	–	0 of 12	–
Masia *et al.*[47]	CH	AFT	100	107	0	91	16	3 of 107	6 of 107
		Control	107	107	0	93	14	–	6 of 107
Mestak *et al.*[48]	CS*	AFT	30	0	30	–	–	0 of 30	–
Mestak *et al.*[49]	CH	AFT	32	0	32	28	4	0 of 32	0 of 32
		Control	45	0	45	42	3	2 of 45	2 of 45
Mirzabeigi *et al.*[50]	CS	AFT	20	0	20	–	–	0 of 20	0 of 20
Missana *et al.*[51]	CS	AFT	69	60	9	–	–	0 of 69	–
Missana and Germain[52]	CS	AFT	110	–	–	–	–	2 of 110	–
Moltó García *et al.*[53]	CS	AFT	37	0	37	37	0	0 of 37	0 of 37
Noor *et al.*[54]	CS	AFT	90	58	32	–	–	0 of 90	–
Parikh *et al.*[55]	CS	AFT	286	286	0	–	–	1 of 286	–
Petit *et al.*[56]	CS	AFT	513	370	143	405	108	13 of 513	13 of 513
Petit *et al.*[57]	MCH	AFT	321	196	125	284	37	8 of 321	8 of 321
		Control	642	392	250	568	74	19 of 642	19 of 642
Petit *et al.*[58]	MCH	AFT	59	47	12	0	59	6 of 59	6 of 59
		Control	118	94	24	0	118	3 of 118	3 of 118

Table 1 Continued

Reference	Study design	Treatment group	No. of patients	Type of surgery (no. of breasts)		Histology (no. of breasts)		Locoregional recurrence rate	
				Mastectomy	BCS	Invasive	*in situ*	Period B	Period C
Petit *et al.*[59]	MCH	AFT	322	0	322	322	0	17 of 322	17 of 322
		Control	322	0	322	322	0	22 of 322	22 of 322
Pierrefeu-Lagrange *et al.*[60]	CS	AFT	30	30	0	–	–	0 of 30	–
Pinell-White *et al.*[61]	CH	AFT	46	46	0	–	–	3 of 46	3 of 46
		Control	51	51	0	–	–	–	4 of 51
Rietjens *et al.*[62]	CS	AFT	158	81	77	–	–	0 of 158	–
Riggio *et al.*[63]	CS	AFT	60	60	0	58	2	2 of 60	3 of 60
Rigotti *et al.*[64]	CS	AFT	137	137	0	102	31	5 of 137	9 of 137
Sarfati *et al.*[65]	CS	AFT	28	28	0	–	–	0 of 28	–
Sarfati *et al.*[66]	CS	AFT	68	68	0	–	–	0 of 68	–
Semprini *et al.*[67]	CS	AFT	151	0	151	–	–	0 of 151	0 of 151
Seth *et al.*[68]	CH	AFT	67	67	0	50	17	0 of 67	0 of 67
		Control	763	763	0	587	176	–	17 of 763
Silva-Vergara *et al.*[69]	CS	AFT	195	132	63	137	31	6 of 195	6 of 195
Silva-Vergara *et al.*[70]	MCH	AFT	205	147	58	161	44	7 of 205	7 of 205
		Control	410	286	124	335	75	16 of 410	16 of 410
Stumpf *et al.*[71]	CH	AFT	27	–	27	27	0	0 of 27	0 of 27
		Control	167	–	167	167	0	4 of 167	4 of 167
Tissiani and Alonso[72]	CS	AFT	9	9	0	7	2	0 of 9	0 of 9
van Turnhout *et al.*[73]	CS	AFT	114	–	114	–	–	0 of 114	0 of 114
Zhu *et al.*[74]	CS	AFT	10	10	–	–	–	0 of 10	–

*Originally an RCT with two treatment arms receiving autologous fat transfer (AFT). BCS, breast-conserving surgery; LRR, locoregional recurrence; CS, case series; CH, cohort; MCH, matched cohort.

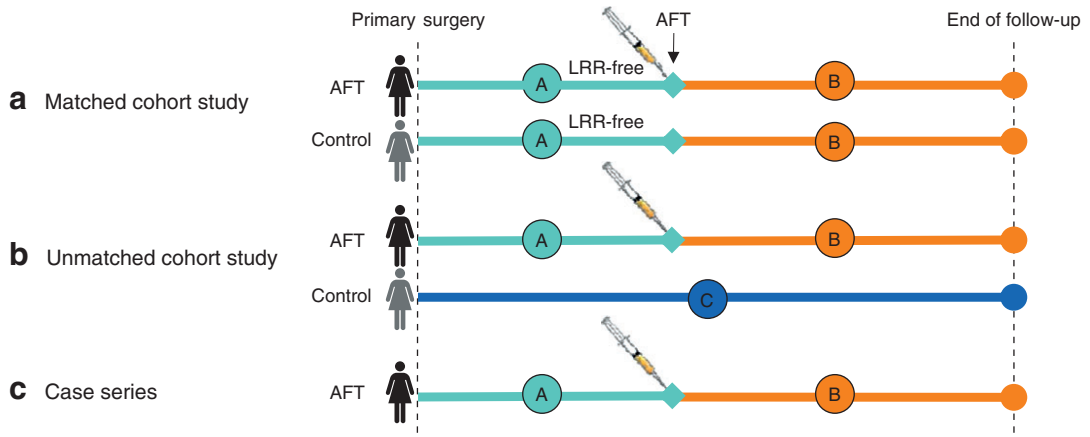

Fig. 3 Oncological follow-up in relation to study type. Oncological follow-up was subdivided into three distinct phases: period A, interval between primary surgery and autologous fat transfer (AFT); period B, interval between AFT and end of follow-up; and period C, total oncological follow-up (A + B). **a** Matched cohort studies comprised patients who underwent AFT and were subsequently matched with controls from the same institution based on relevant baseline characteristics. Patients were included only if they were disease-free before AFT (period A) to be matched with controls who had the same disease-free period. **b** In unmatched cohort studies, the AFT group was compared with controls with similar baseline characteristics from the same institution, who did not undergo AFT. **c** Case series typically investigated the incidence of locoregional recurrence (LRR) in a group of consecutive patients who had AFT (period B)

information). The search was last performed on 1 September 2017. The retrieved articles were screened by two independent reviewers based on the title and abstract using predefined inclusion and exclusion criteria (*Fig. 2*). Only studies focusing on evaluating oncological events in patients treated with AFT were considered for inclusion. Potentially relevant articles, as well as those with insufficient information in the title and abstract, were selected for full-text review. Disagreements were resolved through discussion until consensus was reached.

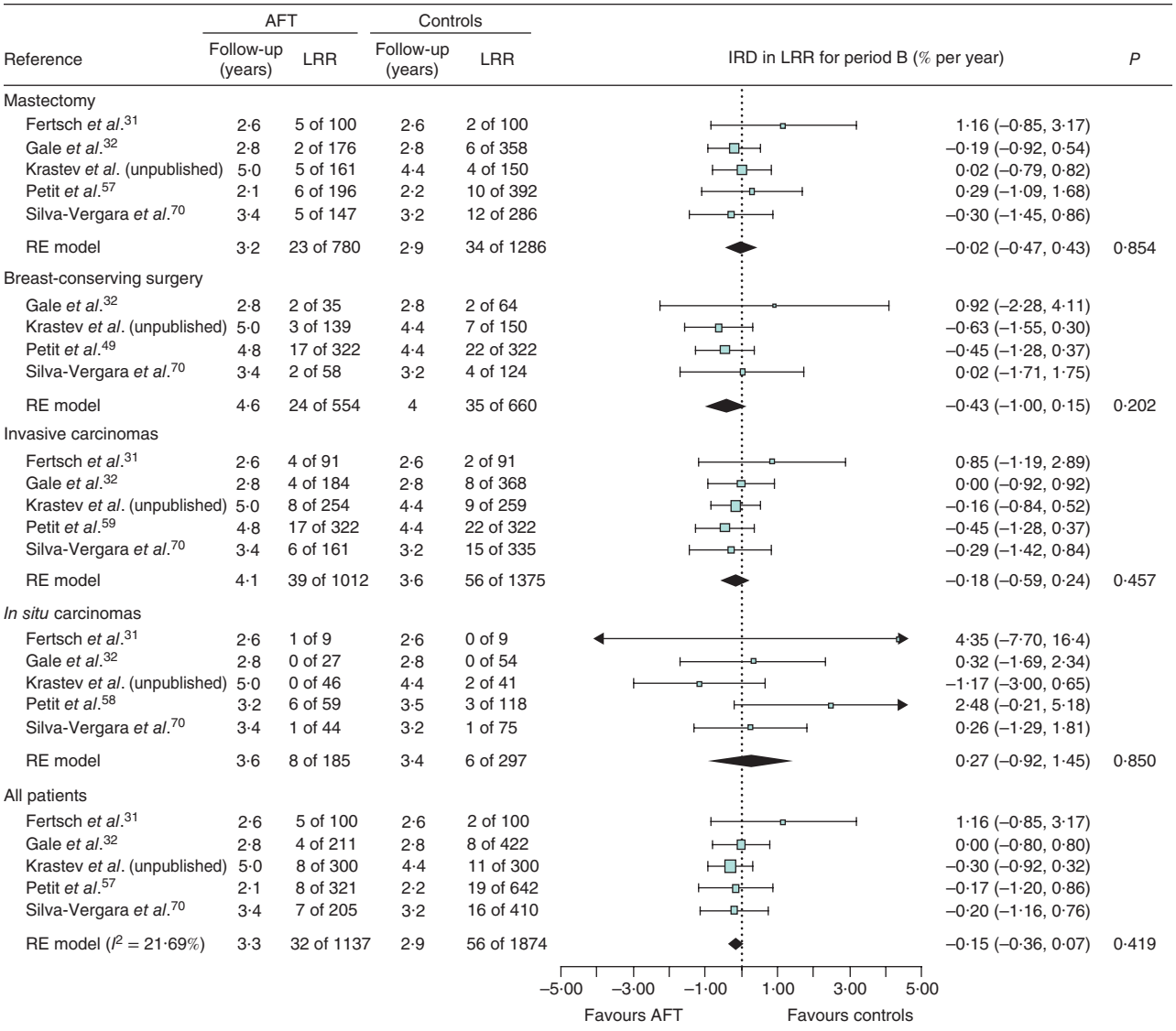

Fig. 4 Forest plot showing incidence rate difference (IRD) in locoregional recurrence (LRR) in period B between the autologous fat transfer (AFT) and control groups in matched cohort studies. Analyses were carried out for all patients, and for subgroups of patients who underwent mastectomy or breast-conserving surgery, and subgroups with invasive or *in situ* carcinomas. IRDs are shown with 95 per cent confidence intervals. A random-effects (RE) model was used for all meta-analyses

Data analysis

A data extraction sheet was developed in Excel® (Microsoft, Redmond, Washington, USA), pilot-tested and refined accordingly (*Table S2*, supporting information). Both reviewers performed a thorough data extraction for all relevant outcomes. In addition, studies were assessed for the risk of overlap and bias according to methodological standards of the *Cochrane Handbook of Systematic Reviews of Interventions*[14]. On some occasions, authors were contacted to provide additional data. Whenever necessary, units were standardized to ensure comparability and allow pooling of data. For continuous variables reported using median (range) values, corresponding mean(s.d.) values were estimated using the standard equations used for meta-analyses[15].

The incidence rate of LRR was the primary outcome of interest, as it corrects for the variable length of follow-up between studies. It is defined as the percentage of patients experiencing LRR events per year of follow-up

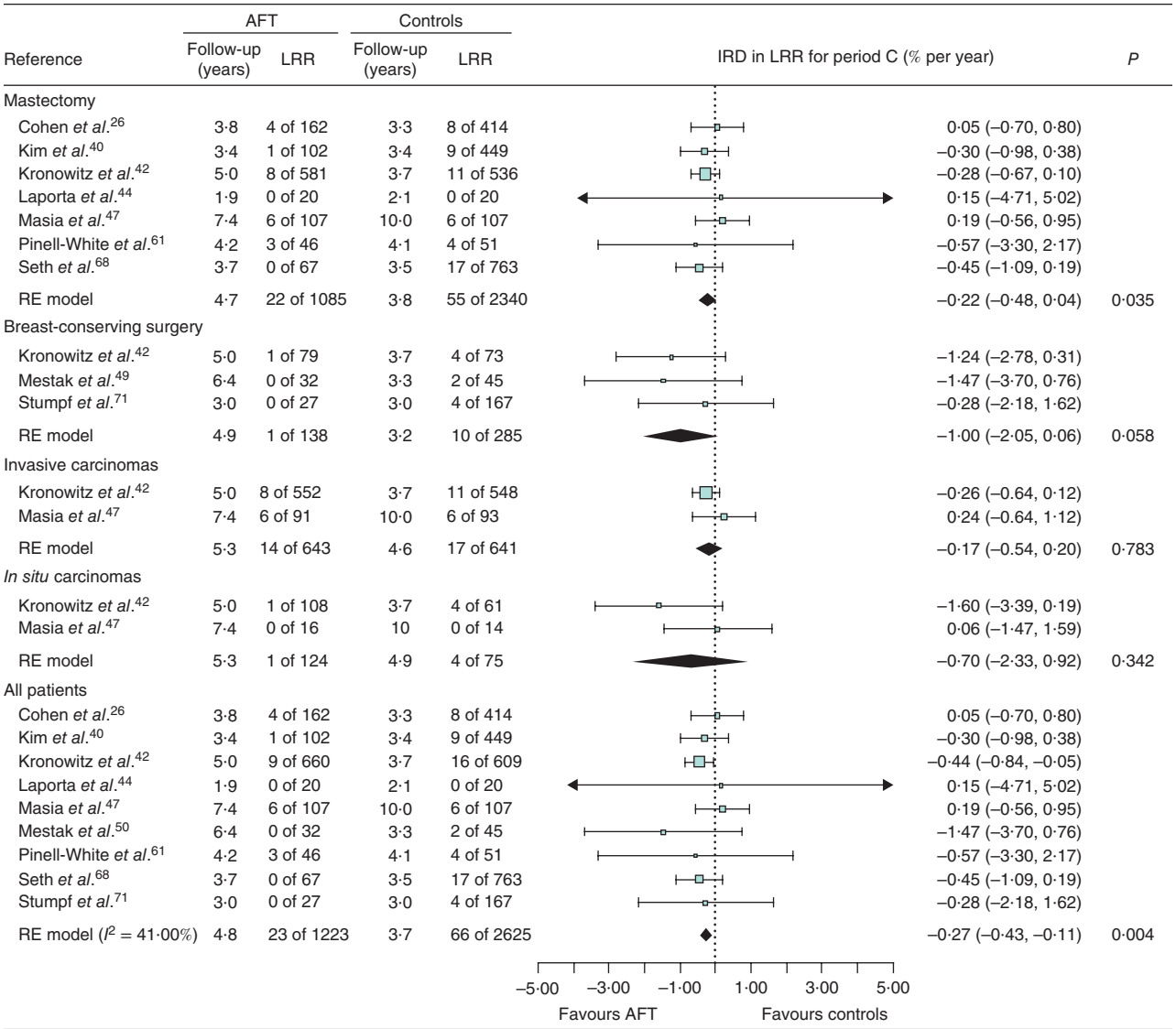

Fig. 5 Forest plot showing incidence rate difference (IRD) in locoregional recurrence (LRR) in period C between the autologous fat transfer (AFT) and control groups in unmatched cohorts. Analyses were carried out for all patients, and for subgroups of patients who underwent mastectomy or breast-conserving surgery, and subgroups with invasive or *in situ* carcinomas. IRDs are shown with 95 per cent confidence intervals. A random-effects (RE) model was used for all meta-analyses

as represented by the following formula:

$$\text{Incidence rate } (\%\text{ per year}) = \frac{\text{no. of events}}{\text{total patient-years}}$$

$$= \frac{\text{no. of events}}{(\text{number of patients}) \times (\text{mean follow-up})}$$

To deal with differences in the methodology and measurement of outcomes, two different summary measures were applied in this meta-analysis. The incidence rate difference (IRD) was used for cohort studies that provided data on the LRR rate for both AFT and control groups. A Wald-type test was used to test for significance between the groups (and subgroups). Owing to the absence of control groups, only the raw incidence rate could be computed in the remaining case series. To place the measured pooled effect estimate in context for the general breast cancer population, it was compared with the reported incidence rates in large historical cohorts.

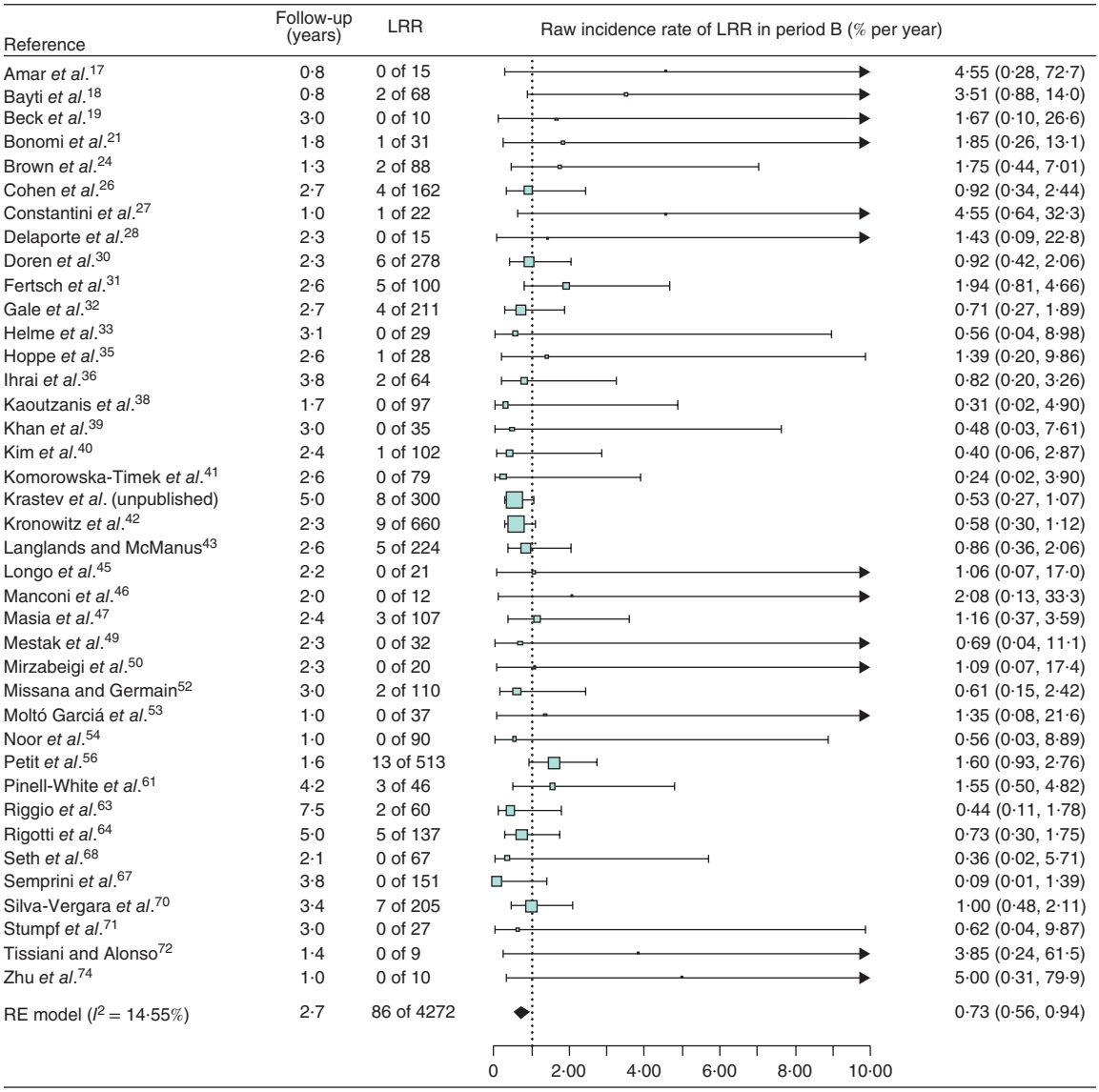

Fig. 6 Forest plot showing raw incidence rate of locoregional recurrence (LRR) in period B in case series and the autologous fat transfer (AFT) groups in cohort studies. Incidence rates are shown with 95 per cent confidence intervals. The dotted line indicates the expected LRR rate. A random-effects (RE) model was used for meta-analysis

The meta-analysis was performed using the metafor package[16] of RStudio software, version 1.0.136 (R Foundation for Statistical Computing, Vienna, Austria). Summary measures (incidence rates) were pooled in a Poisson–normal random-effects model and presented as forest plots. Heterogeneity was assessed using the I^2 statistic, which was tolerable if the I^2 value was below 40 per cent. Publication bias was considered acceptable if the distribution of studies was approximately symmetrical on visual inspection of funnel plots.

Results

Study characteristics

The electronic search yielded a total of 861 articles (*Fig. 2*). Screening of titles and abstracts resulted in the inclusion of 160 studies for further evaluation. A total of 59 clinical trials were selected through further screening of the full text (*Table 1*; an expanded version is available as *Table S3*, supporting information) (References 17–74 and T. Krastev *et al.*, unpublished results). These consisted of 40 case series

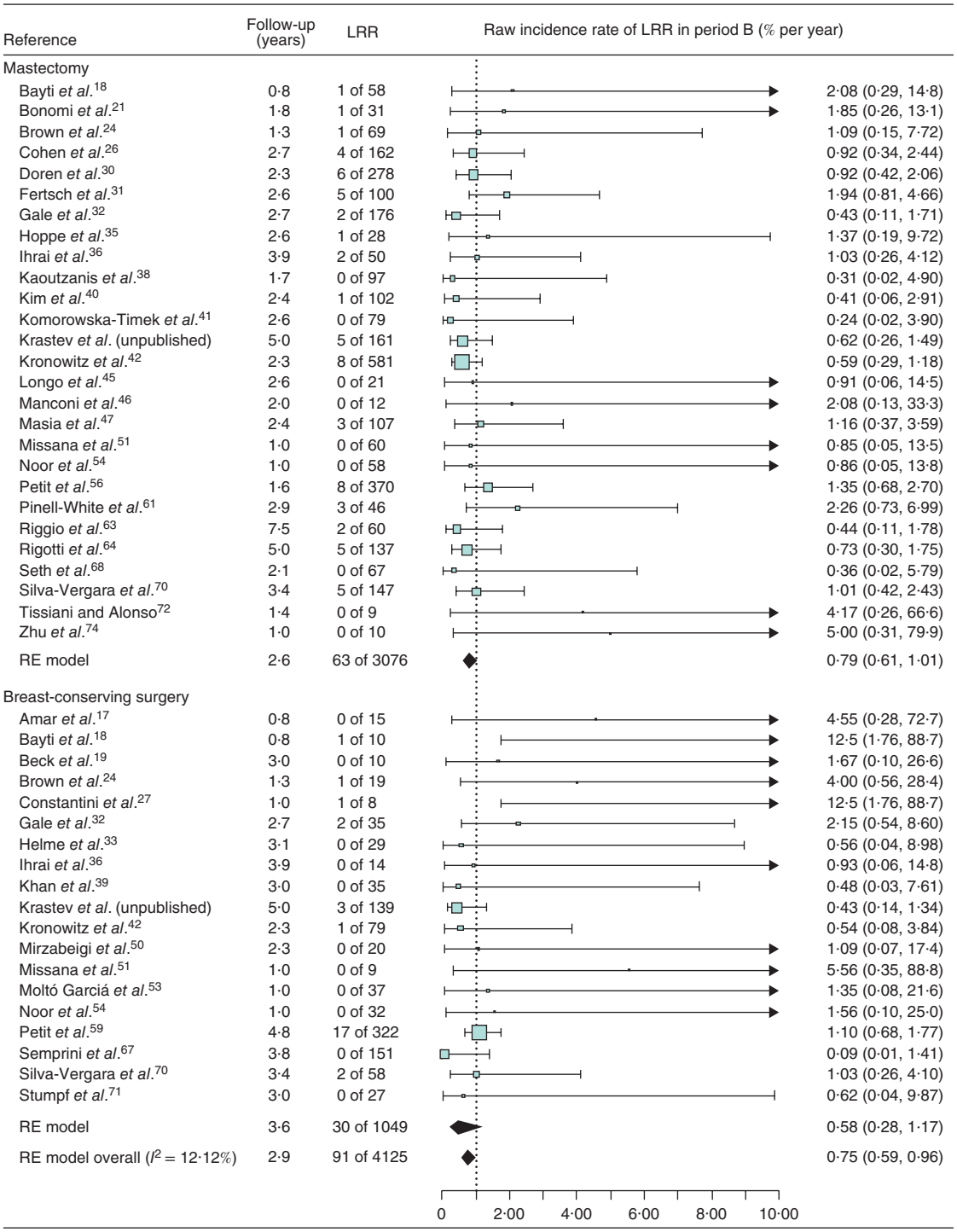

Fig. 7 Forest plot showing raw incidence rate of locoregional recurrence (LRR) in period B in case series and the autologous fat transfer groups in cohort studies, according to type of surgery. Incidence rates are shown with 95 per cent confidence intervals. The dotted line indicates the expected LRR rate. A random-effects (RE) model was used for all meta-analyses

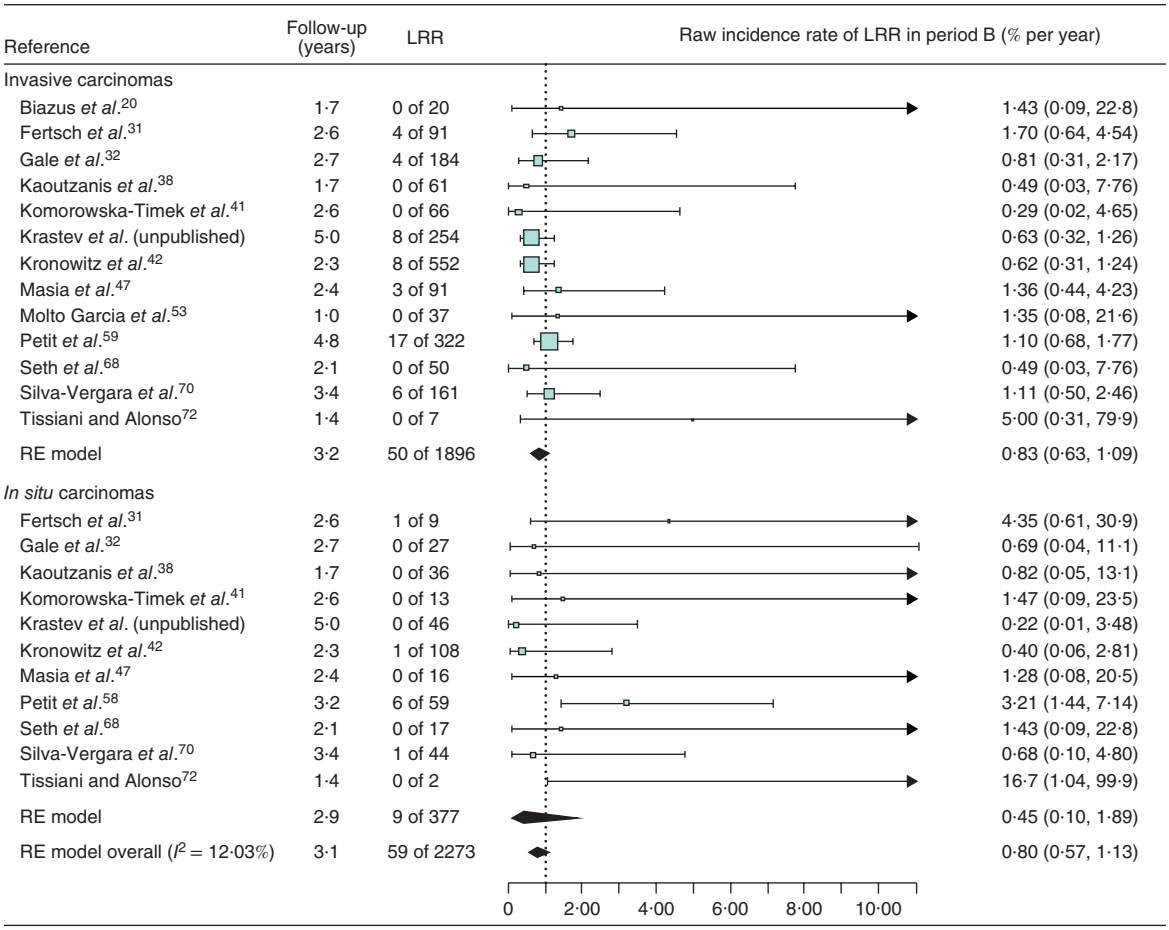

Fig. 8 Forest plot showing raw incidence rate of locoregional recurrence (LRR) in period B in case series and the autologous fat transfer (AFT) groups in cohort studies, according to histology of carcinoma. Incidence rates are shown with 95 per cent confidence intervals. The dotted line indicates the expected LRR rate. A random-effects (RE) model was used for all meta-analyses

and 19 cohort studies, undertaken between 1983 and 2016. Trials conducted by the same authors or institutions over the same treatment period were assessed for the possibility of overlap, and only the latest or largest study was used in the meta-analysis.

After excluding overlapping studies, the remaining 40 studies comprised 4292 unique patients with breast cancer, with a mean age of 50 (95 per cent c.i. 48 to 51) years, who subsequently underwent AFT for the purpose of correcting breast deformities. In 3076 women (71·7 per cent), it involved defects after mastectomy and breast reconstruction (autologous or implant-based), whereas in 1049 (24·4 per cent) AFT was performed for the correction of disfiguring sequelae after BCS (*Fig. 1*). In the remaining 167 (3·9 per cent), the type of oncological surgery was not specified. Histopathological characteristics of the primary tumour were reported in 2214 patients; there were 1896 (85·6 per cent) invasive and 318 (14·4 per cent) *in situ* carcinomas. The Bloom and Richardson classification was reported in 897 patients, consisting of 170 grade 1 (19·0 per cent), 383 grade 2 (42·7 per cent) and 344 grade 3 (38·4 per cent) tumours. Breast cancer stage was specified in 2103 patients; 453 patients had stage 0 disease (21·5 per cent), 800 stage I (38·0 per cent), 637 stage II (30·3 per cent), 207 stage III (9·8 per cent) and six stage IV (0·3 per cent). With respect to studies that provided adequate data on (neo)adjuvant treatment, 1631 of 3095 patients (52·7 per cent) were treated with radiotherapy, 914 of 1988 (46·0 per cent) with chemotherapy, and 391 of 753 (51·9 per cent) with endocrine therapy and immunotherapy.

Relevant control groups from the 14 cohort studies included patients who had undergone surgery for breast cancer who did not have AFT for the purpose of breast reconstruction during oncological follow-up. They

comprised 4499 patients with a mean age of 51 (95 per cent c.i. 48 to 53) years, of whom 3626 (80·6 per cent) and 873 (19·4 per cent) were treated with mastectomy and BCS respectively. Of the 3967 patients with specified histological characteristics of the tumours, 3377 (85·1 per cent) had invasive and 590 (14·9 per cent) *in situ* carcinomas. The Bloom and Richardson classification in 1972 patients was grade 1 in 340 (17·2 per cent), grade 2 in 932 (47·3 per cent) and grade 3 in 700 (35·5 per cent). Tumour stage was specified in 2826 patients, and was stage 0 in 482 (17·1 per cent), stage I in 1012 (35·8 per cent), stage II in 1016 (36·0 per cent), stage III in 313 (11·1 per cent) and stage IV in three (0·1 per cent). Regarding (neo)adjuvant treatment, 1385 of 3288 patients (42·1 per cent) received radiotherapy, 1477 of 2429 (60·8 per cent) chemotherapy and 735 of 1353 (54·3 per cent) endocrine therapy.

In each of the seven matched-cohort studies (References 31, 32, 57–59, 70 and T. Krastev *et al.*, unpublished results), each individual patient who underwent AFT was matched to one or more control subjects based on relevant prognostic factors such as age, date of cancer surgery, type of cancer surgery, tumour histology, tumour size, lymph node involvement, Bloom and Richardson grade, disease stage, oestrogen receptor status, progesterone receptor status and human epidermal growth factor receptor 2 overexpression. This was done to minimize the possibility of confounding resulting from differences in baseline characteristics between the groups.

Oncological follow-up

To allow comparison between the included studies, the oncological follow-up in each study was subdivided into three intervals for the purpose of this meta-analysis (*Fig. 3*). Period A was defined as the interval between the primary oncological intervention (mastectomy or BCS) and the first AFT procedure, with a mean of 2·9 (range 0–6·5) years. In matched cohort studies, this interval represented a required LRR-free period for both AFT and control subjects, and was a mean of 3·3 (2·1–4·7) years. Period B represented the interval between the first AFT procedure and the end of oncological follow-up (censoring time), and was a mean of 2·7 (0·8–7·5) years for all studies. The sum of the two, representing the total oncological follow-up after primary surgery (period C), was a mean of 5·7 (1·0–12·1) years for all patients treated with AFT and 5·1 (3·0–10·0) years for controls from cohort studies.

Results of meta-analysis

The IRD was used to compare the LRR rate between patients who had AFT and corresponding controls from cohort studies. Meta-analysis of the seven matched cohorts (References 31, 32, 57–59, 70 and T. Krastev *et al.*, unpublished results), investigating the incidence of LRR for period B, showed an IRD of −0·15 (95 per cent c.i. −0·36 to 0·07) per cent per year, indicating a 0·15 per cent per year lower raw incidence rate of LRR in patients who underwent AFT compared with the controls (*Fig. 4*). This difference was, however, not statistically significant ($P = 0·419$). Similarly, no significant differences were identified within subgroups based on the type of cancer surgery (mastectomy or BCS) and tumour histology (invasive or *in situ*).

Additional meta-analysis of the remaining unmatched cohorts[26,40,42,44,47,49,61,68,71] was possible only for the IRD of LRR for period C, as control subjects did not have a disease-free interval (period A) equivalent to that in the AFT group. The overall IRD was −0·27 (−0·43 to −0·11) per cent per year, with a significantly lower overall LRR rate among patients who had AFT ($P = 0·004$). The difference was also significant in the mastectomy subgroup ($P = 0·035$) (*Fig. 5*).

Finally, data from all non-overlapping populations in case series[17–19,21,24,27,28,30,33,35,36,38,43,46,50,52–54,56,63,64,67,72,74] as well as AFT treatment arms of cohort studies (References 26, 31, 32, 39–42, 45, 47, 49, 61, 68, 70, 71 and T. Krastev *et al.*, unpublished results) were pooled to provide an estimate of the combined incidence rate of LRR after exposure to AFT (period B). The raw incidence rate for all patients was 0·73 (0·56 to 0·94) per cent per year (*Fig. 6*). Subgroup meta-analyses revealed raw incidence rates of 0·79 (0·61 to 1·01) per cent per year in patients who underwent mastectomy and 0·57 (0·23 to 1·40) per cent per year among those who had BCS (*Fig. 7*). Likewise, raw incidence rates were 0·83 (0·63 to 1·09) per cent per year for patients with invasive carcinomas and 0·45 (0·10 to 1·89) per cent per year for those with *in situ* carcinomas (*Fig. 8*).

Discussion

Over the past decade, AFT has gained increasing popularity among both clinicians and patients, owing to its distinct advantages over conventional treatments, offering an autologous reconstruction using a minimally invasive approach. The high demand is being dampened only by uncertainty regarding its oncological safety, which has restricted its application in recent years. To date, no RCTs have been completed to investigate this matter and such trials are unlikely to be initiated in the near future because of practical and ethical concerns. Therefore, the best evidence regarding the oncological safety of AFT after breast cancer surgery is retrieved from matched cohort studies and retrospective case series.

A number of previous systematic reviews[2,8–12] and one small meta-analysis[8] have attempted to evaluate the oncological safety of AFT, but these studies were hindered by the low quality and the small number of studies. Moreover, none of them accounted for possible study overlap or differentiated between BCS and mastectomy procedures.

With a large number of relevant studies published over the past few years, the present systematic review and meta-analysis identified 60–94 per cent more relevant, non-overlapping studies than its predecessors[2,8–12]. This meta-analysis therefore delivers an up-to-date overview of the current evidence and facilitates intuitive interpretation by clinicians, guidelines committees and policymakers. In addition, it provides the foundation upon which evidence-based recommendations can be made regarding the oncological safety of AFT in breast reconstruction.

The present review incorporated data from 41 non-overlapping studies that reported LRR events in patients with breast cancer. They comprised a total of 4292 unique patients with AFT and 4499 controls. The first meta-analysis of exclusively matched cohorts (*Fig. 4*) forms the essence of the present results and recommendations. In the absence of high-quality data from randomized trials, these studies remain the best available evidence to date. Typically, authors employed propensity score matching techniques to pair each patient undergoing AFT with one or more control subjects not exposed to AFT with matching demographic and oncological characteristics. In this way, matched cohort studies were able to select control groups with matching baseline characteristics, thereby reducing the risk of confounding and allowing more accurate assessment of the absolute effect of AFT on the LRR rate. Pooled data from 1137 patients who had AFT and 1874 matched controls revealed no significant IRD in LRR events overall, or in the subgroups treated with either mastectomy or BCS, and among patients with invasive or *in situ* carcinomas.

The second meta-analysis (*Fig. 5*) included oncological data from the remaining (unmatched) cohorts, where patients from the same institution not treated with AFT were selected as a control group. As these studies reported the rate of LRR in controls for the whole oncological follow-up, the meta-analysis was limited to the evaluation of LRR events for the total follow-up, and served to assess only whether alarming overall rates of LRR could be detected in the AFT group. Remarkably, this analysis revealed a significantly lower overall incidence rate in the AFT group compared with controls, as well as among patients who had AFT in the mastectomy subgroup. Apart from selection bias, for example resulting from differences in baseline characteristics in the absence of matching, it can be argued that preselection could have taken place if patients undergoing breast reconstruction with AFT were more likely to be disease-free before the treatment. This could ultimately result in underestimation of the overall rate of LRR after AFT compared with controls if patients with early recurrence did not qualify for AFT. Therefore, although high rates of LRR were not observed in patients exposed to AFT compared with controls, the methodological shortcomings of these studies undermine their validity in assessing the outcome of interest.

The raw incidence rate of LRR after AFT in all 4272 patients with breast cancer was 0·73 (95 per cent c.i. 0·56 to 0·94) per cent per year, which falls within the range reported in the literature (0·73–1·25 per cent per year)[75–78]. Similarly, the mastectomy and BCS subgroups, as well patients with invasive carcinomas and those with *in situ* carcinomas, did not show high rates of LRR. Although these results confirm the findings of cohort studies, data from case series can be subject to important methodological flaws. As with unmatched cohorts, it is possible that preselection could result in populations with more favourable prognosis than the typical patient with breast cancer. In addition, the small sample sizes and relatively short follow-up could have been insufficient to detect cancer recurrences in many of the case series. As a result of these factors, it is possible that case series grossly underestimate the true incidence rate of LRR and therefore cannot reliably measure this outcome. As with results from unmatched cohorts, these findings merely served as an extra check that LRR rates were not alarmingly high when the scope of the meta-analysis was broadened to include all patients treated with AFT in published studies.

The main limitation of this meta-analysis is that it is restricted to retrospective studies. Although RCTs on this subject are lacking for practical and ethical reasons, the publication of several matched cohort studies over the past few years has offered a viable alternative to assessing the LRR rate in patients with breast cancer treated with AFT. Another limitation is the use of summary measures from included studies such as the raw incidence rate or IRD, derived from the number of LRR events per total patient-years of follow-up, to correct for differences in follow-up between the included studies. Unfortunately, this method does not take into account the exact timing of censoring in the follow-up of each subject, which is best assessed by the Kaplan–Meier method. As only a small fraction of cohorts reported hazard ratios, it was not possible to pool these in a separate meta-analysis. In addition, the use of summary measures as opposed to raw study data does not allow reliable assessment of confounders and can mask their effect in an individual

patient. These issues can be resolved only by analysing the raw study data, ideally in the form of an individual-patient data meta-analysis.

Most studies reported a follow-up of around 3 years after AFT exposure and 6 years in total. Theoretically, regenerative effects from activated ADSCs should take effect during the first few months up to a year after fat transfer. However, it is unclear whether LRRs developing more than 5 years after treatment can be attributed to AFT as opposed to the natural history of breast cancer. Future studies should assess the safety of AFT over a follow-up of at least 5 years after initial exposure. Last but not least, it is not known whether the timing of AFT has an influence on the rate of LRR, considering that cancers of various histopathological stages and receptor status show distinct recurrence patterns, typically peaking between the first and fifth year of oncological follow-up[79].

The present meta-analysis did not demonstrate an increased LRR rate among more than 4000 unique patients across 59 studies. This confirms the results of individual studies that AFT can be performed safely in breast reconstruction after breast cancer surgery.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.