Original Article

Breast cancer recurrence after immediate and delayed postmastectomy breast reconstruction—A systematic review and meta-analysis

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BACKGROUND: Oncological safety of different types and timings of PMBR after breast cancer remains controversial. Lack of stratified risk assessment in literature makes current clinical and shared decision-making complex. This is the first systematic review and meta-analysis to evaluate differences in oncological outcomes after immediate versus delayed postmastectomy breast reconstruction (PMBR) for autologous and implant-based PMBR separately. **METHODS:** A systematic literature search was performed in MEDLINE, Cochrane Library, and Embase. The Cochrane Collaboration Handbook and Meta-analysis Of Observational Studies in Epidemiology checklist were followed for data abstraction. Variability in point estimates attributable to heterogeneity was assessed using I^2-statistic. (Loco)regional breast cancer recurrence rates, distant metastasis rates, and overall breast cancer recurrence rates were pooled in generalized linear mixed models using random effects. **RESULTS:** Fifty-five studies, evaluating 14,217 patients, were included. When comparing immediate versus delayed autologous PMBR, weighted average proportions were: 0.03 (95% confidence interval [CI], 0.02–0.03) versus 0.02 (95% CI, 0.01–0.04), respectively, for local recurrences, 0.02 (95% CI, 0.01–0.03) versus 0.02 (95% CI, 0.01–0.03) for regional recurrences, and 0.04 (95% CI, 0.03–0.06) versus 0.01 (95% CI, 0.00–0.03) for locoregional recurrences. No statistically significant differences in weighted average proportions for local, regional and locoregional recurrence rates were observed between immediate and delayed autologous PMBR. Data did not allow comparing weighted average proportions of distant metastases and total breast cancer recurrences after autologous PMBR, and of all outcome measures after implant-based PMBR. **CONCLUSIONS:** Delayed autologous PMBR leads to similar (loco)regional breast cancer recurrence rates compared to immediate autologous PMBR. This study highlights the paucity of strong evidence on breast cancer recurrence after specific types and timings of PMBR. ***Cancer* 2022;0:1-21**.

LAY SUMMERY:

- Oncologic safety of different types and timings of postmastectomy breast reconstruction (PMBR) remains controversial.
- Lack of stratified risk assessment in literature makes clinical and shared decision-making complex.
- This meta-analysis showed that delayed autologous PMBR leads to similar (loco)regional recurrence rates as immediate autologous PMBR. Data did not allow comparing weighted average proportions of distant metastases and total breast cancer recurrence after autologous PMBR, and of all outcome measures after implant-based PMBR.
- Based on current evidence, oncological concerns do not seem a valid reason to withhold patients from certain reconstructive timings or techniques, and patients should equally be offered all reconstructive options they technically qualify for.

KEYWORDS: autologous, breast cancer, breast neoplasm, breast reconstruction, implant, metastasis, oncological safety, recurrence.

INTRODUCTION

Advances in early detection and treatment of breast cancer have improved breast cancer survival and shifted focus toward optimizing quality of life.[1] In this context, an increase in requests for postmastectomy breast reconstruction (PMBR) has been observed to preserve breast contour and function.[2] Autologous tissue, breast implants, or a combination, can be used

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The PROSPERO registration number is CRD42020141137.

This study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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for PMBR, either in an immediate or delayed fashion.[2] Because of logistical challenges, concerns about delays in adjuvant treatment, and concerns of impaired outcomes of PMBR in combination with adjuvant radiotherapy, breast reconstruction is often performed in a delayed fashion.[2,3] Still, immediate PMBR is considered superior in terms of patient satisfaction, costs, hospitalization and psychological benefits,[2,4–6] and as such, hospitals are increasingly offering immediate PMBR.[7]

The growing application of PMBR has raised new concerns regarding long-term oncological safety.[8] According to the concept of tumor dormancy, breast cancer patients might harbor dormant micrometastases that can be activated by stressors, such as extensive (reconstructive) surgery,[8,9] thereby inducing recurrence and metastasis.[10,11] Also, reconstructed breasts might mask recurrent tumors on radiological imaging.[12]

In the absence of well-known landmark studies, the oncological safety of different types and timings of PMBR remains controversial. Isern and colleagues[11] reported higher breast cancer recurrence rates after delayed PMBR than after mastectomy only, whereas others were not able to confirm this increased risk.[8,12,13] Moreover, different relapse patterns were described, such as a higher 18-month peak in relapses following delayed versus no reconstruction, and after autologous versus implant-based reconstruction.[9] There is a paucity of studies comparing differences in oncological outcomes after immediate versus delayed PMBR for autologous and implant-based reconstructions separately. Making this distinction is important, because surgical impact, indications, and patient selection differ between autologous and implant-based reconstructions, and the same applies to immediate versus delayed reconstructions.

The abundance of inconclusive literature on breast reconstructive surgery makes current clinical decision-making and clear patient education complex.[14] As such, contemporary decision-making remains based on expert consensus rather than scientific clinical evidence, subsequently leading to unequal access to reconstructive options. A well conducted up-to-date systematic review and meta-analysis (SR/MA) may provide more insight into this much-debated issue and support clinical and shared decision-making. Therefore, with this SR/MA, we aim to investigate whether delayed PMBR leads to different (loco)regional recurrence, distant metastasis, and overall recurrence rates than immediate PMBR in patients with primary breast cancer. Because of differences in nature and indications of implant-based and autologous breast reconstructive techniques,[5] this question was evaluated separately for autologous and implant-based breast reconstruction.

MATERIALS AND METHODS

This SR/MA was registered in PROSPERO (CRD42020141137).

Search strategy

A comprehensive systematic literature search was performed following the Cochrane Collaboration Handbook[15] and the Meta-analysis Of Observational Studies in Epidemiology checklist in MEDLINE (via PubMed), Embase and the Cochrane Library from inception to November 19, 2020 (Fig. 1). The search strategy was designed by three authors (C.A.B., A.D., and A.B.) and two hospital librarians (Nienke van der Werf and Carla Sloof-Enthoven), and included three components: "breast cancer," "breast reconstruction," and "oncological outcome" (Table S1). Duplicate articles were removed.

Study selection

Two authors (C.A.B. and M.I.) independently screened all articles for title and abstract. If title and abstract were ambiguous, the full-text article was reviewed. Authors were blinded for each other's results until the screening process was completed. Subsequently, two independent authors (C.A.B. and M.I.) screened full-texts to select articles for inclusion in the SR/MA.

Original articles including patients >18 years old and reporting oncological outcomes (i.e., "local," "regional," "locoregional" or "total breast cancer recurrences," and "distant metastasis") after PMBR in patients with breast cancer were included. Because of the scarcity of randomized controlled trials, prospective and retrospective observational studies were included. Comparative studies with only one study arm meeting in- and exclusion criteria were included. Exclusion criteria included (1) other publication types (i.e., isolated abstracts, case reports, preclinical studies, reviews, meta-analyses, practical summary's, guidelines, editorials, communications, correspondence, discussions, unrelated, duplicated, conference, overlapping data, authors response theses, books, and letters), (2) animal studies, (3) non-English or non-Dutch language articles, (4) studies published before 2000, (5) studies including cohorts with <50 patients, (6) studies with a mean follow-up <24 months or unknown follow-up, (7) studies including patients with PMBR after initial breast-conserving surgery or prophylactic mastectomy, and (8) studies including patients with distant metastasis at time of diagnosis or PMBR, and breast cancer recurrence before PMBR. Nonavailable full-text articles (9) were also excluded. In case of overlapping cohorts,

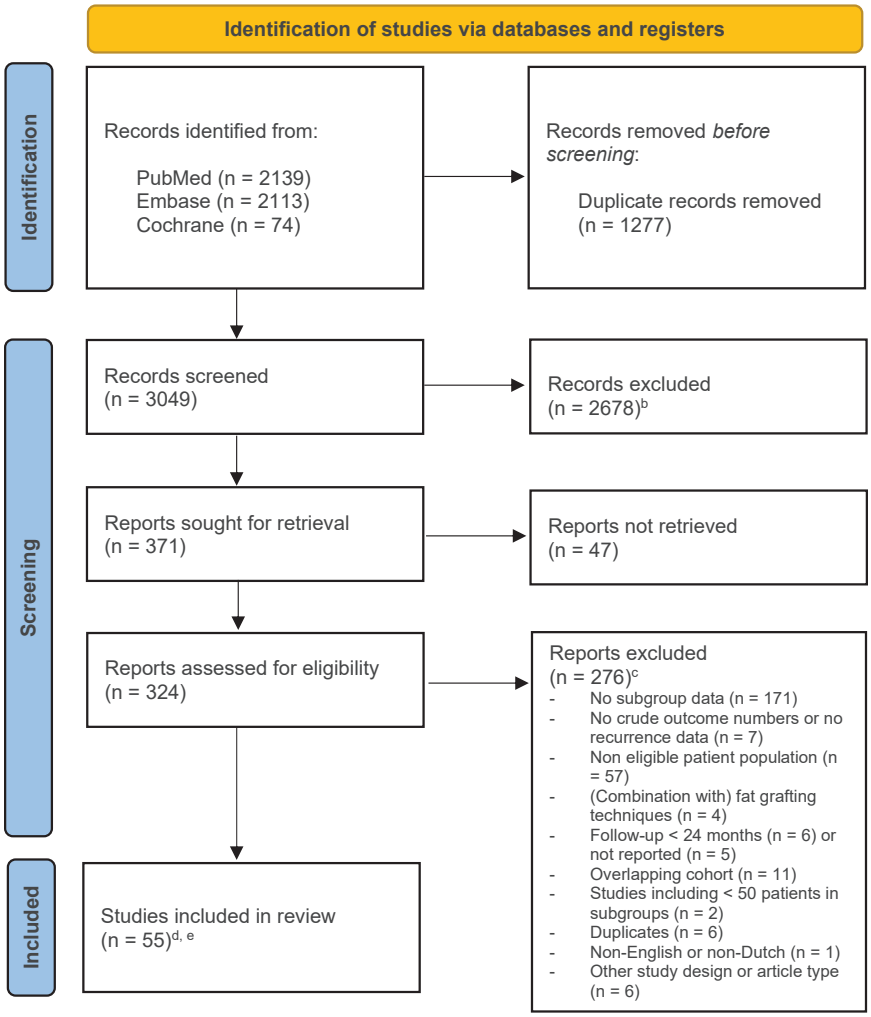


Figure 1. Flow diagram of literature search and screening following the PRISMA 2020 Flow Diagram. (A) The format for this flowchart was retrieved from the PRISMA 2020 statement as published by Page et al.[76] (B) Inclusion criteria included mastectomy with breast reconstruction, first breast cancer episode, age > 18 years old, randomized controlled trials, prospective and retrospective observational studies, and original articles published after 1999. (C) Exclusion criteria included prophylactic mastectomy, breast-conserving surgery, prior breast surgery, distant recurrence at time of diagnosis, studies <50 patients, follow-up <24 months, animal studies, non-English or non-Dutch studies, and other design or article types (i.e., isolated abstracts, case reports, preclinical studies, reviews, meta-analyses, practical summary's guidelines, editorials, communications, correspondence, discussions and letters). (D) A cross-reference check yielded zero additional articles. After exclusion of 276 studies, 48 were left for inclusion. However, of an additional seven studies that were originally excluded more detailed data was provided by the corresponding authors. (E) Of the 55 included studies, 37 were included in quantitative synthesis (meta-analysis) for autologous breast reconstruction and 28 for implant-based reconstruction.

either the largest cohort or the cohort with the most suitable study design was included. A cross-reference check was performed among included articles and excluded reviews for additional studies meeting the inclusion criteria.

Missing data

All corresponding authors of articles reporting aggregated data on recurrences or metastases for immediate and delayed or implant-based and autologous PMBR were contacted to request data for each group separately.

Quality assessment and data extraction

The quality of studies and risk of bias was evaluated with the Methodological Index for NOn-Randomized Studies, which is designed to critically appraise prospective and retrospective studies, as well as comparative and noncomparative studies.[16] The maximum score for noncomparative studies is 16 and 24 for comparative studies. A higher total score corresponds with less risk of bias.

Data extraction was performed by two independent authors (C.A.B. and M.I.) using a standardized form that was pilot-tested and optimized accordingly. Extracted

FIGURE 2. Forest plots of local, regional, locoregional, distant, and total breast cancer recurrences after immediate and delayed autologous breast reconstruction. The first column shows the included studies by year of publication and first author. The second and third columns show the total number of recurrences and the total study population, respectively. The fourth column shows the recurrence rates with 95% CIs of each study. On the right, each study corresponds to a red square centered at the point estimate (i.e., recurrence rate) with black horizontal lines indicating the 95% CI. Powerful studies (i.e., studies with more participants) have a narrower 95% CI. The overall weighted recurrence rates are represented by the black diamonds. The width of the diamond represents the 95% CI for the overall weighted recurrence rate. The vertical lines highlight study-specific deviations from the overall weighted recurrence rates. 95% CI indicates 95% confidence interval; 95% CIGLMM, 95% confidence interval generalized linear mixed models; DBR, delayed breast reconstruction; df, degrees of freedom; GLMM, generalized linear mixed models; IBR, immediate breast reconstruction; P, *p* value. (A) Forest plot of local recurrences after immediate and delayed autologous breast reconstruction. (B) Forest plot of regional recurrence after immediate and delayed autologous breast reconstruction. (C) Forest plot of locoregional recurrence after immediate and delayed autologous breast reconstruction. (D) Forest plot of distant metastasis after immediate and delayed autologous breast reconstruction. (E) Forest plot of total breast cancer recurrence after immediate and delayed autologous breast reconstruction.

data included study design, patient characteristics, interventions, and outcomes (Tables 2–4). Outcomes of interest were local, regional, locoregional, distant and overall breast cancer recurrence and expressed as the proportion of patients experiencing recurrence. Overall breast cancer recurrence was defined as the sum of all (loco)regional recurrences and distant metastases.

Discordances in study selection, quality assessment, and data extraction were resolved by discussion by two authors (C.A.B. and M.I.). In case of disagreement, a third author (D.A.Y.-A.) was involved in reaching consensus.

Data analysis

For all studies, one or more of the primary outcomes of interest were reported. Proportions of recurrence and distant metastasis were pooled in a generalized linear mixed model (GLMM) and presented as forest plots. Publication bias was considered acceptable if the distribution of studies was symmetrical on visual inspection of the funnel plots. The variability in point estimates attributable to heterogeneity was assessed using the Higgin's and Thompson's I^2-statistic, which was tolerable if I^2 values were low or moderate (<75%).[17] Based on I^2 values, analyses for the primary outcomes were conducted using random effects models. Weighted averages were reported as proportions with 95% confidence intervals (95% CI). Variances of distribution of true proportions among subgroups (between-study variances) were reported using the maximum-likelihood estimator for tau^2 (T^2). T^2 reflects the absolute value of true heterogeneity across the population of studies included in the subgroup analyses. When no variance between studies is observed, T^2 is low or 0.[18] Differences in weighted average proportions after delayed versus immediate breast reconstruction were evaluated among subgroups by comparing 95% CIs. In case of overlapping 95% CIs, differences were not considered statistically significant. Statistical analyses were performed in the R software environment (R Foundation of Statistical Computing).

RESULTS

Search results and synthesis of evidence

After removing 1277 duplicates, the literature search yielded 3049 unique studies (Fig. 1). After title and abstract screening, full texts of 371 studies were assessed for eligibility. Finally, 48 studies[4,9,11,13,19–62] met the inclusion criteria. Additional data was requested for 65 studies (Table S2) of whom seven (10.8%)[8,60,63–68] provided data, enabling inclusion of these studies in analyses. In total, 55 studies[4,8,9,11,13,19–68] were selected for qualitative synthesis (Tables 2–4). Quantitative synthesis included 37 studies[4,8,9,11,13,19,21–30,39–47,50–52,56,58,59,62–65,67,68] on autologous PMBR (Figs. 2A-E; Table S3a) and 28 studies[20,31–38,41–43,46–49,53–55,57–61,64,66–68] on implant-based PMBR (Figs. 3A–E; Table S3b).

Study characteristics and quality of evidence

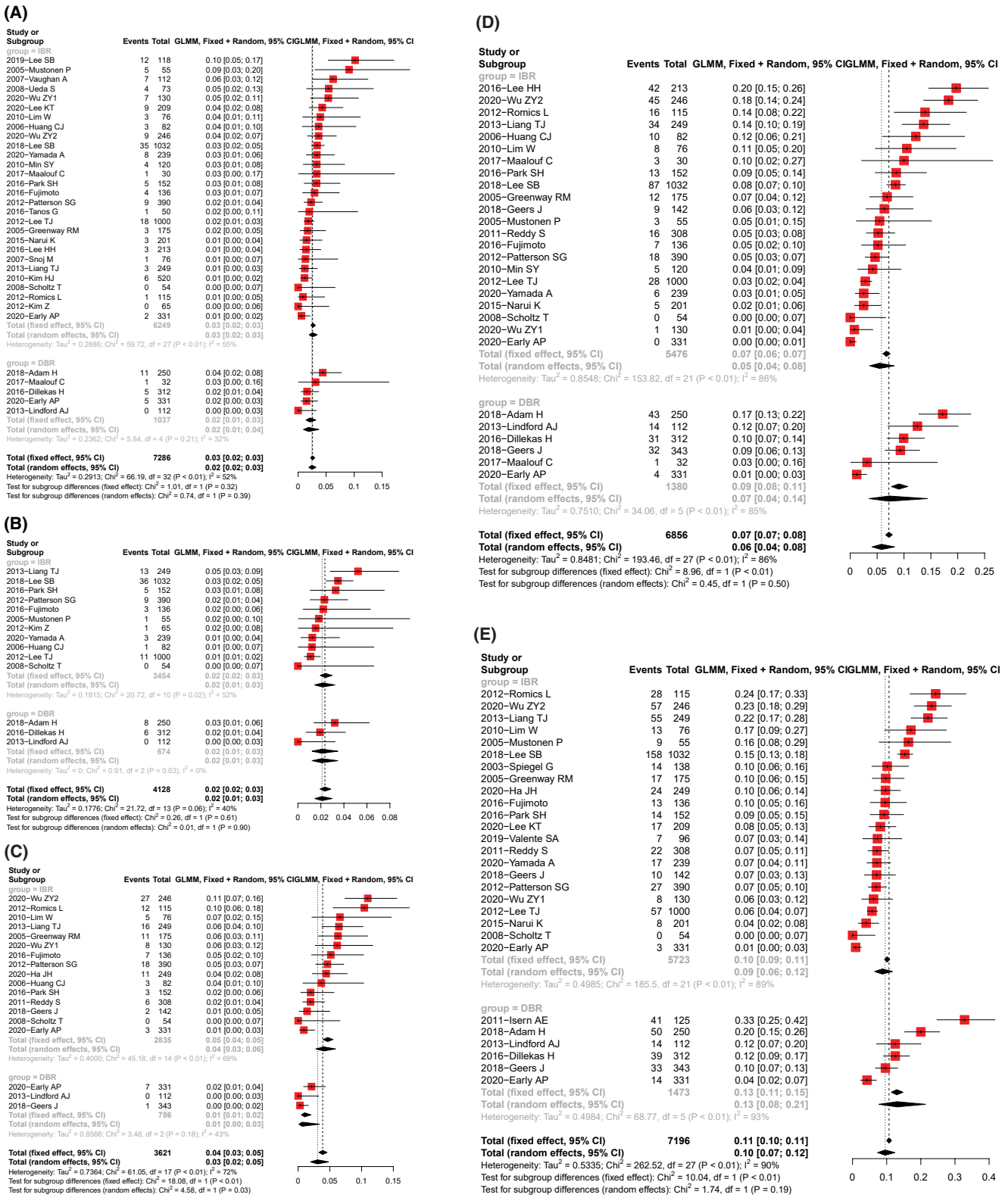
All included studies were published between February 2003[43] and October 2020[68] (Table 2). Among the 55 studies, 48 studies (87.3%)[4,8,9,11,13,19–23,25–32,34,36,38–41,43–54,56–58,60–68] were retrospective and seven (12.7%)[24,33,35,37,42,55,59] were prospective. The quality of included studies ranged from 6 to 12 points for noncomparative studies, and from 10 to 20 points for comparative studies (Table 1).

Study population

The 55 studies evaluated 14,452 patients, including 12,480 PMBRs performed in an immediate setting, 1852 in a delayed setting, and for 337,[65] the setting was unclear (Tables 2–4). Median sample size per study was 138 patients (interquartile range, 77–249). Mean/median age ranged from 33 to 53 years old. Mean/median follow-up time ranged from 27 to 146 months. The majority of patients (n = 11,429, 80.4%) were diagnosed with invasive breast cancer.

Immediate versus delayed autologous PMBR

A total of 31 studies[4,9,13,19,21–30,39,40,42,44,45,47,50–52,56,59,62–65,67,68] included local recurrence as an outcome



(Fig. 2A, I^2 = 51.7% [95% CI, 27.9%–67.6%]), 28 of which [4,21–30,39,40,42,44,45,47,50–52,56,59,62–65,67,68] (T^2 = 0.29) reported on immediate autologous post-mastectomy breast reconstruction (I-ABR) and five studies[9,13,19,50,65] (T^2 = 0.24) on delayed autologous post-mastectomy breast reconstruction (D-ABR). In the I-ABR group, 163

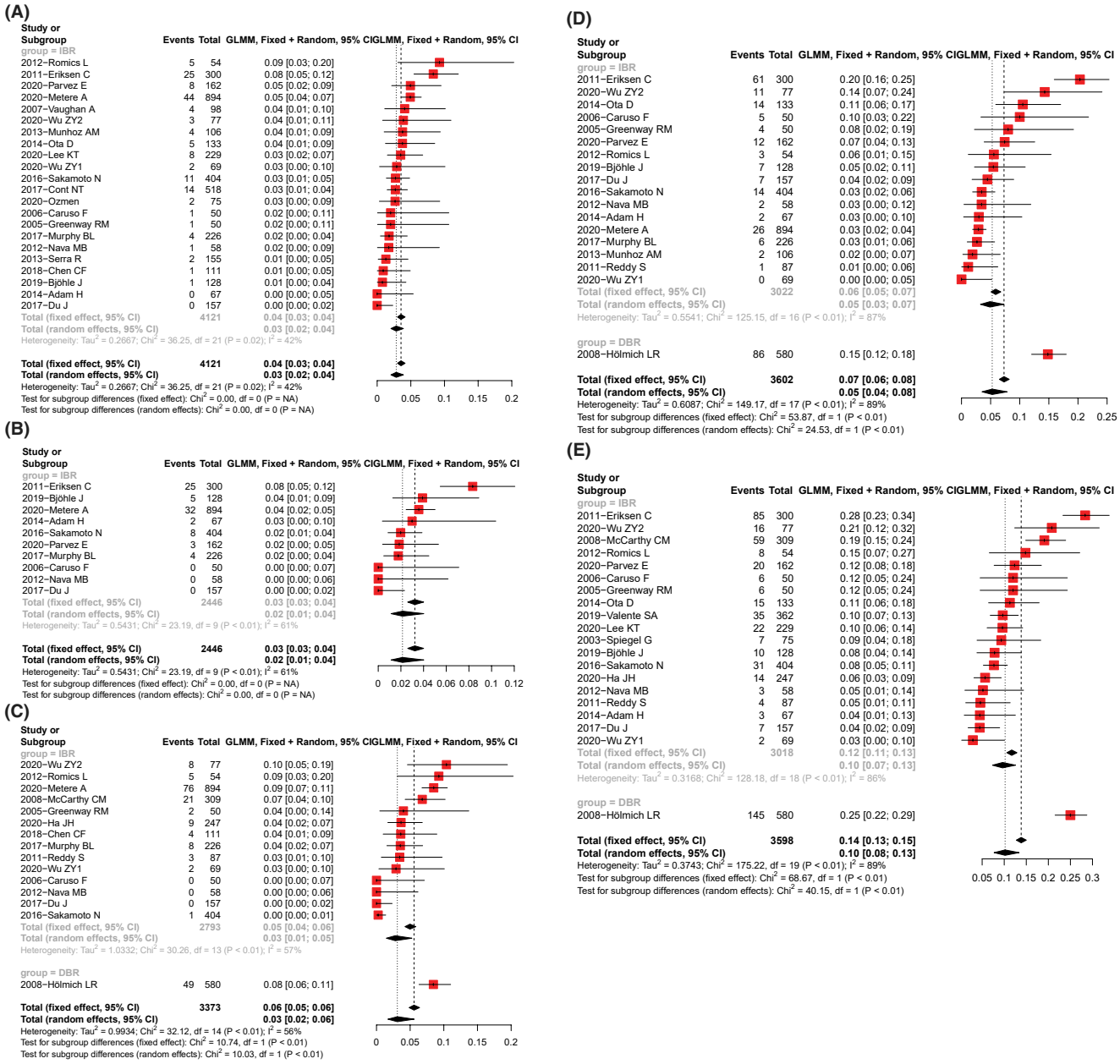


FIGURE 3. Forest plots of local, regional, locoregional, distant and total breast cancer recurrences after immediate and delayed implant-based breast reconstruction. The first column shows the included studies by year of publication and first author. The second and third columns show the total number of recurrences and the total study population, respectively. The fourth column shows the recurrence rates with 95% CIs of each study. On the right, each study corresponds to a red square centered at the point estimate (i.e., recurrence rate) with black horizontal lines indicating the 95% CI. Powerful studies (i.e., studies with more participants) have a narrower 95% CI. The overall weighted recurrence rates are represented by the black diamonds. The width of the diamond represents the 95% CI for the overall weighted recurrence rate. The vertical lines highlight study-specific deviations from the overall weighted recurrence rates. 95% CI indicates 95% confidence interval; 95% CIGLMM, 95% confidence interval generalized linear mixed models; DBR, delayed breast reconstruction; df, degrees of freedom; GLMM, generalized linear mixed models; IBR, immediate breast reconstruction; P, *p* value. (A) Forest plot of local recurrences after immediate implant-based breast reconstruction. No studies were available on local recurrences after delayed implant-based breast reconstruction. (B) Forest plot of regional recurrences after immediate implant-based breast reconstruction. No studies were available on regional recurrences after delayed implant-based breast reconstruction. (C) Forest plot of locoregional recurrence after immediate and delayed implant-based breast reconstruction. (D) Forest plot of distant metastasis after immediate and delayed implant-based breast reconstruction. (E) Forest plot of total breast cancer recurrences after immediate and delayed implant-based breast reconstruction.

TABLE 1. Risk Of Bias Appraisal Following The Methological Index For Non-Randomized Studies (Minors) Criteria

	A stated aim of the study	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the study aim	Unbiased evaluation of endpoint	Follow-up period appropriate to the major endpoint	Loss to follow-up <5%	Prospective sample size calculation	Gold standard for control group	Contemporary groups	Baseline equivalence	Statistical analysis for study design	Total score
Adam H, 2014[48]	2	2	0	2	2	2	0	0	2	2	2	2	18
Adam H, 2018[19]	2	2	0	2	2	2	0	0	1	2	2	1	16
Björle J, 2019[38]	1	2	0	2	2	2	0	0	2	2	1	2	16
Caruso F, 2006[31]	0	1	0	2	2	2	2	0					9
Chen CF, 2018[32]	1	2	0	1	2	2	0	0	2	2	1	2	15
Cont NT, 2017[49]	1	2	0	0	2	2	0	0					7
Dillekas H, 2016[9]	1	2	0	1	2	2	0	0	2	2	1	2	15
Du J, 2017[33]	0	2	2	1	2	2	0	0	0	2	1	1	13
Early AP, 2020[65]	1	1	0	2	2	2	0	0					8
Eriksen C, 2011[34]	2	2	0	2	2	2	0	0	2	2	1	2	17
Fujimoto H, 2016[21]	1	2	0	1	2	2	0	0					8
Geers J, 2018[8]	2	2	0	1	2	2	2	0	2	2	0	2	18
Greenway RM, 2005[64]	0	1	0	1	2	2	0	0	2	2	0	0	10
Ha JH, 2020[58]	2	2	0	2	2	2	0	0	1	2	2	2	17
Hölmich LR, 2008[20]	0	2	0	1	2	2	0	0	2	2	0	2	13
Huang CJ, 2006[22]	2	2	0	2	2	2	0	0	2	2	1	2	17
Isern AE, 2011[11]	2	2	0	1	2	2	0	0	2	2	1	1	15
Kim HJ, 2010[23]	1	2	0	2	2	2	0	0	2	2	0	2	15
Kim Z, 2012[39]	2	1	0	1	2	2	1	0					8
Lee HH, 2016[25]	1	2	0	2	2	2	0	0	2	2	1	2	16
Lee KT, 2020[59]	2	2	2	2	2	2	0	0					12
Lee SB, 2018[26]	2	2	0	2	2	2	0	0	2	2	0	2	16
Lee SB, 2019[27]	2	2	0	1	2	2	0	0	2	2	1	2	16
Lee TJ, 2012[24]	1	1	2	2	2	2	0	0	2	2	0	2	16
Liang TJ, 2013[28]	2	2	0	2	2	2	0	0					10
Linford AJ, 2013[13]	2	2	0	2	2	2	0	0	2	2	1	1	16
Lim W, 2010[63]	2	1	0	1	2	2	0	0	2	2	1	2	15
Maalouf C, 2017[50]	2	2	0	1	2	2	0	0	2	2	2	2	17
McCarthy CM, 2008[53]	2	2	0	1	2	2	0	0	2	2	1	2	16
Metere A, 2020[60]	2	2	0	2	2	1	0	0					9
Min SY, 2010[4]	2	2	0	2	2	2	0	0	1	2	0	2	15
Munhoz AM, 2013[54]	0	1	0	1	2	2	0	0					6
Murphy BL, 2017[55]	1	0	0	1	2	2	0	0					6
Mustonen P, 2005[56]	1	1	0	1	2	2	0	0					7
Narui K, 2015[29]	2	2	0	2	2	2	0	0	2	2	0	2	16
Nava MB, 2012[35]	0	0	2	2	2	2	0	0					8
Ota D, 2014[36]	0	1	0	2	2	2	0	0	2	2	1	2	14
Ozmen V, 2020[61]	2	2	0	2	2	2	0	0	1	2	0	2	15
Park SH, 2016[40]	2	2	0	2	2	2	0	0	2	2	1	2	17
Parvez E, 2020[66]	1	2	0	2	2	1	0	0					8
Patterson SG, 2012[30]	2	2	0	2	2	2	0	0					10
Reddy S, 2011[41]	0	2	0	1	2	2	0	0	2	2	0	2	13
Romics L, 2012[42]	2	2	2	2	2	2	0	0					12
Sakamoto N, 2016[57]	2	1	2	1	2	2	0	0					10
Scholz T, 2008[52]	0	1	0	1	2	2	0	0					6
Serra R, 2013[37]	0	1	2	1	2	2	0	0					8
Snoj M, 2007[51]	1	2	0	2	2	2	0	0	2	2	2	2	17
Spiegel G, 2003[43]	0	1	0	1	2	2	0	0					6
Tanos G, 2016[44]	2	1	0	1	2	2	0	0	1	2	1	2	14
Ueda S, 2008[45]	0	2	0	2	2	2	0	0	2	2	1	1	14
Valente SA, 2019[46]	2	2	0	1	2	2	0	0					9
Vaughan A, 2007[47]	2	2	0	0	2	2	0	0					8
Wu ZY, 2020[67]	2	2	0	2	2	2	0	0					10
Wu ZY, 2020[68]	2	2	2	2	2	2	0	0	2	2	2	2	20
Yamada A, 2020[62]	2	2	0	2	2	2	0	0					10

Abbreviation: MINORS, methodological index for non-randomized studies.
Note: Each item was scored 0–2 points: 0 indicates that this item was not reported in the article, 1 indicates that it was reported, but inadequately, and 2 indicates that it was reported adequately. A higher total score corresponds with less risk of bias. Green, 2 points; yellow, 1 point; red, 0 points.

of 6,249 patients (2.6%) developed local recurrence, and in the D-ABR group 22 of 1037 patients (2.1%) developed local recurrence (Table S3a). The weighted average proportion for local recurrence in the I-ABR group was 0.03 (95% CI, 0.02–0.03), and 0.02 (95% CI, 0.01–0.04) in the D-ABR group.

TABLE 2. Study Characteristics And Baseline Characteristics Of Included Study Populations

Year	First author	Country	Journal	Study design	No. of patients	No. of breasts	Age (range), years	Follow-up (range), months	Reconstructive method
2014	Adam[48]	Sweden	*Eur J Surg Oncol*	Re	67	69	49[b] (24–74)	36[b] (4–162)	Immediate, implant-based
2018	Adam[19]	Sweden	*Br J Surg*	Re	250	254	48[b] (25–67)	89[b] (4–214)	Delayed, autologous
2019	Bjöhle[38]	Sweden	*Radiother Oncol*	Re	128	128	46[b] (21–68)	69.6[b] (1–90)	Immediate, implant-based
2006	Caruso[31]	Italy	*Eur J Surg Oncol*	Re	50	51	42[b] (28–68)	66[a] (9–140)	Immediate, implant-based
2018	Chen[32]	Taiwan	*Ann Plast Surg*	Re	111	111	40.5[a] (SD = 7.5)	85.3[a]/91.0[b] (NR)	Immediate, implant-based
2017	Cont[49]	Italy	*Breast Cancer Res Treat*	Re	518	518	NR	33[a] (NR)	Immediate, implant-based
2016	Dillekås[9]	Norway	*Breast Cancer Res Treat*	Re	312	312	48[b] (NR)	137[b] (NR)	Delayed, autologous
2017	Du[33]	China	*Sci Rep*	Pr	157	157	NR	74[b] (52–111)	Immediate, implant-based
2020	Early[65]	United States of America	*Clin Breast Cancer*	Re	337	337	NR (34–70)	45.4[a] (NR)	Immediate and delayed, autologous
2011	Eriksen[34]	Sweden	*Breast Cancer Res Treat*	Re	300	300	48[b] (23–70)	144[b] (48–216)	Immediate, implant-based
2016	Fujimoto[21]	Japan	*Eur J Plast Surg*	Re	136	144	42[a] (24–63)	75[b] (51–129)	Immediate, autologous
2018	Geers[8]	Belgium	*BMC Cancer*	Re	485	485	47[b] (24–71)	76[b] (4–152)	Immediate and delayed, autologous
2005	Greenway[64]	United States of America	*Am J Surg*	Re	225	225	50[a] (25–76)	49[a] (NR)	Immediate, autologous and implant-based
2020	Ha[58]	South-Korea	*BMC Cancer*	Re	496	496	Implant: 41[a] (SD = 8.73) Autologous: 43[a] (SD = 6.99)	Implant: 57.3[b] (NR) Autologous: 58.3[b] (NR)	Immediate, autologous and implant-based
2008	Hölmich[20]	Denmark	*Ann Plast Surg*	Re	580	580	47[b] (24–72)	121[b] (12–155)	Delayed, implant-based
2006	Huang[22]	China	*Plast and Reconstr Surg*	Re	82	83	42.7[a] (27–58)	40[b] (24–74)	Immediate, autologous
2011	Isern[11]	Sweden	*Br J Surg*	Re	125	125	45.4[a] (SD = 7.8)	146[b] (NR)	Delayed, autologous
2010	Kim[23]	South-Korea	*Ann of Surg*	Re	520	520	42[b] (35–50)	63[b] (NR)	Immediate, autologous
2012	Kim[39]	South-Korea	*World J Surg Oncol*	Re	65	65	48.4[a] (21–74)	34[a] (1.6–89.9)	Immediate, autologous
2016	Lee[25]	Taiwan	*PLoS ONE*	Re	213	213	44.8[b] (26–60)	85.2[a]/80[b] (11–189)	Immediate, autologous
2020	Lee[59]	South-Korea	*Br J Surg*	Pr	438	438	43.1[a] (SD = 7.4)	82[b] (13–131)	Immediate, autologous and implant-based
2018	Lee[26]	South-Korea	*Medicine (Baltimore)*	Re	1032	1032	48.1[a] (23–90)	94.4[b] (8.1–220.2)	Immediate, autologous
2019	Lee[27]	South-Korea	*Asia J Med*	Re	118	118	33.0[b] (23 –35)	86.7[b] (NR)	Immediate, autologous
2012	Lee[24]	South-Korea	*Arch Plast Surg*	Pr	1000	1000	42.2[a] (22–68)	56.4[a] (3–93)	Immediate, autologous
2013	Liang[28]	Taiwan	*World J Surg Oncol*	Re	249	249	41[b] (22–62)	53[b] (24–181)	Immediate, autologous
2013	Lindford[13]	Finland	*World J Surg*	Re	112	125	53[b] (24–69)	64[b] (5–111)	Delayed, autologous
2010	Lim[63]	South-Korea	*J Surg Oncol*	Re	87	87	38.41[a] (SD = 7.07)	62.52[a] (8.07–156.73)	Immediate, autologous and implant-based
2017	Maalouf[50]	Canada	*Ann Chir Plast Est*	Re	62	62	Immediate: 50[a] (SD = 9.5) Delayed: 47[a] (SD = 8)	Immediate: 32[b] (11–67) Delayed: 92[b] (26–240)	Immediate and delayed, autologous
2008	McCarthy[53]	United States of America	*Plast Reconstr Surg*	Re	309	309	46.8[b] (25.6–73.3)	68.4[b] (2.4–111.6)	Immediate, implant-based
2020	Metere[60]	Italy	*Medicina (Kaunas)*	Re	894	894	47.5[a] (22–76)	41.2[a] (15.7–101)	Immediate, implant-based
2010	Min[4]	South-Korea	*Breast J*	Re	120	120	40.7[a] (26–61)	39.2[a] (SD = 15.8)	Immediate, autologous
2013	Munhoz[54]	Brazil	*Breast Canc Res Treat*	Re	106	114	51.4[a] (33–78)	65.6[a] (6–130)	Immediate, implant-based
2017	Murphy[55]	United States of America	*Am J Surg*	Pr	226	240	48.5[b] (43–54)	34[b] (NR)	Immediate, implant-based
2005	Mustonen[56]	Finland	*Scand J Surg*	Re	56	56	SSM = 46.8[a] (SD = 6.2) SCM = 47.2[a] (SD = 8.0)	SSM = 43.2[a] (SD = 9.6) SCM = 46.8[a] (SD = 13.2)	Immediate, autologous
2015	Narui[29]	Japan	*Eur J Surg Oncol*	Re	201	205	42.2[b] (23-64)	36[b] (NR)	Immediate, autologous

TABLE 2. *Continued*

Year	First author	Country	Journal	Study design	No. of patients	No. of breasts	Age (range), years	Follow-up (range), months	Reconstructive method
2012	Nava[35]	Italy	*Breast*	Pr	58	59	NR	36[a] (24–84)	Immediate, implant-based
2014	Ota[36]	Japan	*Clin Breast Cancer*	Re	133	133	46[b] (27–49)	47[b] (NR)	Immediate, implant-based
2020	Ozmen[61]	Turkey	*World J Surg Oncol*	Re	75	75	42[b] (24–78)	56[b] (14–116)	Immediate, implant-based
2016	Park[40]	South-Korea	*J Breast Cancer*	Re	189	189	41.98[a] (SD = 80.8)	65.6[b] (10–132)	Immediate, autologous and implant-based
2020	Parvez[66]	Canada	*Clin Breast Cancer*	Re	162	173	47.9[a] (SD = 11.2)	27[b] (5–68)	Immediate, implant-based
2012	Patterson[30]	United States of America	*Ann Surg Oncol*	Re	390	390	49.5[a] (SD = 8.3)	69.2[b] (24.1–134.4)	Immediate, autologous
2011	Reddy[41]	United States of America	*Ann Plast Surg*	Re	494	494	47.8[b] (23.9–72.2)	54[a] (NR)	Immediate, autologous and implant-based
2012	Romics[42]	Scotland	*Br J Surg*	Pr	207	207	49[b] (26–68)	119[b] (14–163)	Immediate, autologous and implant-based
2016	Sakamoto[57]	Japan	*Breast Cancer*	Re	404	421	≥40 years: 92 < 40 years: 329	61[b] (7.2–139)	Immediate, implant-based
2008	Scholz[52]	United States of America	*Plast Reconstr Surg*	Re	54	54	51.5[b] (31–69)	42[b] (12–108)	Immediate, autologous
2013	Serra[37]	Italy	*Plast Surg Int*	Pr	155	155	37.5[a] (20–52)	47[a] (12–96)	Immediate, implant-based
2007	Snoj[51]	Slovenia	*Eur J Surg Oncol*	Re	156	157	45.9[b] (26–68)	66[b] (18–277)	Immediate and delayed, autologous
2003	Spiegel[43]	United States of America	*Plast Reconstr Surg*	Re	221	221	42[1] (24–81)	117.6[a] (72–156)	Immediate, autologous and implant-based
2016	Tanos[44]	United Kingdom	*Plast Reconstr Surg Glob Open*	Re	88	88	Implant-based: 48[b] (29–75) Autologous: 50[b] (25–70)	Implant-based: 28.2[b] (NR) Autologous: 27.9[b] (NR)	Immediate, autologous and implant-based
2008	Ueda[45]	Japan	*Surgery*	Re	74	74	45.7[a] (NR)	50[a] (NR)	Immediate, autologous and implant-based
2019	Valente[46]	United States of America	*Am J Surg*	Re	458	586	49[b] (26–85)	90.48[b] (65.64–144.96)	Immediate, autologous and implant-based
2007	Vaughan[47]	United States of America	*Am J Surg*	Re	206	210	Local recurrence: 41[a] (31–56) No recurrence: 43[a] (18–75)	58.6[a] (13.1–132.5)	Immediate, autologous and implant-based
2020	Wu[67]	South-Korea	*Ann Surg Oncol*	Re	199	199	43[b] (20–65)	97[b] (39–186)	Immediate, autologous and implant-based
2020	Wu[68]	South-Korea	*JAMA Surg*	Re	323	323	42[b] (23–72)	67[b] (17–125)	Immediate, autologous and implant-based
2020	Yamada[62]	Japan	*J Surg Res*	Re	239	239	44[b] (23–65)	73[b] (NR)	Immediate, autologous

Abbreviations: NR, not reported; Pr, prospective; Re, retrospective; SCM, subcutaneous mastectomy; SD, standard deviation; SSM, skin-sparing mastectomy.
[a]Mean.
[b]Median.

TABLE 3. Oncological Characteristics Of Included Study Populations

Year	First author	AJCC stage (*n*)	T classification (*n*)	Histology (*n*)	ER (*n*)	PR (*n*)	Her2Neu (*n*)
2014	Adam[48]	NR	Tis: NR T1: 37 T2: 14 T3: 3 T4: 1 Missing: 14	In situ: 14 Invasive: 55 Missing: 0	Positive: 44 Negative: 14 Missing: 11	Positive: 40 Negative: 17 Missing: 12	Positive: 44 Negative: 7 Missing: 18
2018	Adam[19]	NR	Tis: 9 T1: 65 T2: 140 T3: 40 T4: 0 Missing: 0	In situ: 9 Invasive: 219 Missing: 19	Positive: 176 Negative: 61 Missing: 17	Positive: 148 Negative: 75 Missing: 31	Positive: 31 Negative: 89 Missing: 134
2019	Bjöhle[38]	NR	Tis: 0 T1: 65 T2: 45 T3: 13 T4: 0 Missing: 5	In situ: 0 Invasive: 128 Missing: 0	Positive: 95 Negative: 32 Missing: 1	NR	Positive: 30 Negative: 98 Missing: 0
2006	Caruso[31]	0: 8 I: 24 II: 18 III: 1 Missing: 0	NR	In situ: 21 Invasive: 30 Missing: 0	Positive: 37 Negative: 9 Missing: 5	Positive: 32 Negative: 14 Missing: 5	NR
2018	Chen[32]	0: 0 I: 6 II: 63 III: 42 Missing: 0	T0–T1: 32 T2: 70 T3: 8 T4: 1 Missing: 0	NR	Positive: 78 Negative: NR Missing: NR	Positive: 74 Negative: NR Missing: NR	Positive: 23 Negative: 66 Null: 1 Missing: 21
2017	Cont[49]	NR	NR	NR	Positive: 442 Negative: NR Missing: 11	Positive: 404 Negative: NR Missing: 13	Positive: 76 Negative: NR Missing: 100
2016	Dillekås[9]	NR	Tis: 0 T1: 190 T2: 91 T3: 22 T4: 2 Missing: 7	In situ: 0 Invasive: 312 Missing: 0	Positive: 218 Negative: 61 Missing: 33	NR	NR
2017	Du[33]	0: 0 I: 36 II: 97 III: 24 Missing: 0	NR	In situ: 0 Invasive: 157 Missing: 0	Positive: 113 Negative: 44 Missing: 0	NR	Positive: 53 Negative: 104 Missing: 0
2020	Early[65]	NR	NR	NR	NR	NR	NR
2011	Eriksen[34]	NR	Tis: 0 T1: 191 T2: 99 T3: 10 T4: 0 Missing: 0	In situ: NR Invasive: 291 Missing: 9	Positive: 219 Negative: NR Missing: 26	Positive: 179 Negative: NR Missing: 49	NR
2016	Fujimoto[21]	0: 48 I: 35 II: 44 III: 7 Missing: 2	Tis: 48 T1: 42 T2: 36 T3: 8 Missing: 2	In situ: 48 Invasive: 88 Missing: 0	Positive: 82 Negative: 26 Missing: 28	NR	Positive: 20 Negative: 101 Missing: 15
2018	Geers[8]	I: 45 II: 206 III: 225 Missing: 9	NR	In situ: NR Invasive: 485 Missing: 0	Positive: 374 Negative: 103 Missing: 8	Positive: 374 Negative: 103 Missing: 8	Positive: 92 Negative: 375 Missing: 18
2005	Greenway[64]	0 - II	Tis: 27 T1: 123 T2: 75 T3–T4: 0 Missing: 0	NR	NR	NR	NR

TABLE 3. *Continued*

Year	First author	AJCC stage (*n*)	T classification (*n*)	Histology (*n*)	ER (*n*)	PR (*n*)	Her2Neu (*n*)
2020	Ha[58]	Implant-based/ autologous: 0: 47/57 I: 100/82 II: 73/79 III: 27/31 Missing: 0	NR	NR	Implant-based/ autologous: Positive: 198/206 Negative: 49/43 Missing: 0/0	Implant-based/ autologous: Positive: 171/173 Negative: 76/76 Missing: 0/0	Implant-based/ autologous: Positive: 56/44 Negative: 174/193 Missing: 17/12
2008	Hölmich[20]	NR	T1: 370 T2–T4: 188 Missing: 22	In situ: NR Invasive: 548 Missing: 32	NR	NR	NR
2006	Huang[22]	0: 0 I: 4 II: 64 III: 14	NR	In situ: NR Invasive: 82 Missing: 0	Positive: 36 Negative: 37 Missing: 9	Positive: 28 Negative: 48 Missing: 9	NR
2011	Isern[11]	NR	Tis: 0 T1: 60 T2: 60 T3: 5 T4: 0 Missing: 0	In situ: 0 Invasive: 125 Missing: 0	Positive: 105 Negative: 20 Missing: 0	Positive: 90 Negative: 34 Missing: 1	Positive: 23 Negative: 101 Missing: 1
2010	Kim[23]	0: 84 I: 220 II: 176 III: 40	NR	NR	Positive: 324 Negative: 180 Missing: 10	NR	0–2: 341 3: 158 Missing: 21
2012	Kim[39]	0: 15 I: 29 II: 20 III: 1	Tis: 15 T1: 30 T2: 20 T3–T4: 0 Missing: 0	In situ: 15 Invasive: 50 Missing: 0	NR	NR	NR
2016	Lee[25]	0: 0 I: 0 II: 121 III: 92	Tis: 0 T1: 48 T2: 134 T3: 24 T4: 7 Missing: 0	In situ: 0 Invasive: 213 Missing: 0	Positive: 113 Negative: 83 Missing: 17	Positive: 95 Negative: 99 Missing: 19	NR
2020	Lee[59]	0: 116 I–III: 332	Tis: 116 T1–T4: NR	In situ: 116 Invasive: 332 Missing: 0	Positive: 341 Negative: 97 Missing: 0	Positive: 320 Negative: 118 Missing: 0	Positive: 169 Negative: 269 Missing: 0
2018	Lee[26]	0: 164 I: 382 II: 399 III: 87	NR	NR	Positive: 656 Negative: 338 Missing: 38	Positive: 616 Negative: 378 Missing: 38	Positive: 332 Negative: 644 Missing: 56
2019	Lee[27]	0: 0 I: 54 II: 50 III: 14	NR	In situ: 0 Invasive: 118 Missing: 0	Positive: 72 Negative: 47 Missing: 0	Positive: 61 Negative: 58 Missing: 0	Positive: 47 Negative: 72 Missing: 0
2012	Lee[24]	0: 173 I: 362 II: 371 III: 93	NR	NR	NR	NR	NR
2013	Liang[28]	0: 0 I: 32 II: 132 III: 85	Tis: 0 T1: 110 T2: 130 T3: 6 T4: 3 Missing: 0	In situ: 0 Invasive: 249 Missing: 0	Positive: 162 Negative: 22 Missing: 65	Positive: 137 Negative: 112 Missing: 0	NR
2013	Lindford[13]	NR	Tis: 0 T1: 46 T2: 56 T3: 6 T4: 3 Missing: 1	In situ: 0 Invasive: 112 Missing: 0	Positive: 92 Negative: 20 Missing: 0	Positive: 73 Negative: 39 Missing: 0	Positive: 20 Negative: 80 Missing: 12

(Continued)

TABLE 3. *Continued*

Year	First author	AJCC stage (*n*)	T classification (*n*)	Histology (*n*)	ER (*n*)	PR (*n*)	Her2Neu (*n*)
2010	Lim[63]	0: 0 I: 0 II: 8 III: 79	T1: 13 T2: 48 T3: 26	In situ: NR Invasive: 87 Missing: 0	"Hormone receptor": Positive: 65 Negative: 22 Missing: 0	"Hormone receptor": Positive: 65 Negative: 22 Missing: 0	Positive: 26 Negative: 57 Missing: 4
2017	Maalouf[50]	Immediate/delayed: 0: 1/0 I: 5/9 II: 16/12 III: 8/11 Missing: 0	NR	Immediate/delayed: In situ: 1/0 Invasive: 29/32 Missing: 0/0	Immediate/delayed: Positive: 20/24 Negative/missing: NR/NR	Immediate/delayed: Positive: 17/22 Negative/missing: NR/NR	Immediate/delayed: Positive: 5/3 Negative/missing: NR/NR
2008	McCarthy[53]	0: 0 I: 98 II: 164 III: 47	NR	In situ: 0 Invasive: 309 Missing: 0	Positive: 189 Negative: 77 Missing: 43	Positive: 157 Negative: 106 Missing: 46	NR
2020	Metere[60]	0: NR I–II: 75.2% III: NR	NR	In situ: 232 Invasive: 662 Missing: 0	Positive: 779 Negative: 115 Missing: 0	Positive: 729 Negative: 165 Missing: 0	Positive: 71 Negative: 823 Missing: 0
2010	Min[4]	0: 22 I: 48 II: 31 III: 13 Missing: 0	NR	In situ: 22 Invasive: 98 Missing: 0	"Hormone receptor": Positive: 76 Negative: 40 Missing: 4	"Hormone receptor": Positive: 76 Negative: 40 Missing: 4	NR
2013	Munhoz[54]	NR	Tis: 0 T1: 78 T2: 28 T3–T4: 0 Missing: 0	NR	NR	NR	NR
2017	Murphy[55]	NR	T0–Tis: 73 T1: 109 T2: 47 T3: 11 T4: 0 Missing: 0	DCIS: 63 Invasive: 168 Other: 9	Positive: 205 Negative: 30 Missing: 5	NR	Positive: 18 Negative: 147 Missing: 15
2005	Mustonen[56]	NR	NR	NR	NR	NR	NR
2015	Narui[29]	0: 83 I: 45 II: 63 III: 10 Missing: 0	NR	DCIS: 83 Invasive: 120 Other: 2	Positive: 107 Negative: 13 Missing: 85	NR	Positive: 14 Negative: 106 Missing: 85
2012	Nava[35]	0: 8 I: 24 II: 18 III: 9 Missing: 0	Tis: 8 T1: 35 T2: 12 T3: 1 T4: 0 Missing: 3	In situ: 8 Invasive: 51 Missing: 0	Positive: 38 Negative: 10 Missing: 11	Positive: 38 Negative: 10 Missing: 11	Positive: 12 Negative/missing: NR
2014	Ota[36]	NR	Tis–T3: 128 T4: 5 Missing: 0	In situ: 20 Invasive: 113 Missing: 0	"Hormone receptor": Positive: 114 Negative: 19 Missing: 0	"Hormone receptor": Positive: 114 Negative: 19 Missing: 0	NR
2020	Ozmen[61]	0: 0 I–III: NR	Tis: 0 T1: 44 T2: 27 T3: 4 T4: 0 Missing: 0	In situ: 0 Invasive: 75 Missing: 0	Positive: 64 Negative: 11 Missing: 0	Positive: 57 Negative: 18 Missing: 0	Positive: 15 Negative: 57 Missing: 0
2016	Park[40]	0: 0 I: 101 II: 66 III: 22 Missing: 0	Tis: 0 T1: 121 T2: 52 T3: 13 T4: 3 Missing: 0	In situ: 0 Invasive: 189 Missing: 0	Positive: 129 Negative: 60 Missing: 0	Positive: 100 Negative: 89 Missing: 0	Positive: 55 Negative: 113 Missing: 21

TABLE 3. *Continued*

Year	First author	AJCC stage (*n*)	T classification (*n*)	Histology (*n*)	ER (*n*)	PR (*n*)	Her2Neu (*n*)
2020	Parvez[66]	NR	Tis: 31 T1: 83 T2: 51 T3: 10 T4: 0 Missing: 0	In situ: NR Invasive: 144 Missing: 31	"Hormone receptor": Positive: 103 Negative: 41 Missing: 31	"Hormone receptor": Positive: 103 Negative: 41 Missing: 31	Positive: 24 Negative: 120 Missing: 31
2012	Patterson[30]	0–II: 312 III: 70 Missing: 0	NR	In situ: 100 Invasive: 254 Missing: 36	Positive: 215 Negative: 88 Missing: 87	Positive: 193 Negative: 110 Missing: 87	NR
2011	Reddy[41]	0: 119 I: 183 II: 114 III: 43	NR	NR	Positive: 295 Negative: 90 Missing: 109	Positive: 128 Negative: 74 Missing: 292	Positive: 83 Negative: 209 Missing: 202
2012	Romics[42]	0: 54 I: 57 II: 83 III: 13	Tis: 54 T1: 94 T2: 52 T3: 6 T4: 1 Missing: 0	In situ: 54 Invasive: 153 Missing: 0	Positive: 119 Negative: 34 Missing: 54	NR	NR
2016	Sakamoto[57]	0: 117 I: 149 II: 141 III: 14	NR	In situ: 117 Invasive: 304 Missing: 0	Positive: 333 Negative: 71 Missing: 17	NR	Positive: 57 Negative: 231 Missing: 133
2008	Scholz[52]	0: 23 I: 17 II: 14 III: 0 Missing: 0	NR	In situ: 23 Invasive: 31 Missing: 0	NR	NR	NR
2013	Serra[37]	NR	Tis: 23 T1: 36 T2: 96 T3–T4: 0 Missing: 0	In situ: 23 Invasive: 132 Missing: 0	NR	NR	NR
2007	Snoj[51]	NR	Tis: 0 T1: 78 T2: 61 T3: 15 Missing: 3	In situ: 0 Invasive: 157 Missing: 0	Positive: 99 Negative: 53 Missing: 5	Positive: 84 Negative: 67 Missing: 6	NR
2003	Spiegel & Butler[43]	NR	NR	In situ: 44 Invasive: 177 Missing: 0	NR	NR	NR
2016	Tanos[44]	0–I: 0 III: 88 Missing: 0	NR	In situ: 0 Invasive: 88 Missing: 0	NR	NR	NR
2008	Ueda[45]	NR	Tis: 7 T1: 32 T2: 33 T3: 2 T4: 0 Missing: 0	In situ: 7 Invasive: 67 Missing: 0	NR	NR	NR
2019	Valente[46]	0: 0 I: 208 II: 189 III: 61 Missing: 0	Tis: 0 T1: 272 T2: 151 T3: 27 T4: 8 Missing: 0	In situ: 0 Invasive: 458 Missing: 0	Positive: 350 Negative: 106 Missing: 2	NR	Positive: 87 Negative/missing: NR
2007	Vaughan[47]	0: 40 I: 41 II: 65 III: 64 Missing: 0	Tis/T1: 107 T2: 80 T3: 13 T4: 10 Missing: 0	NR	NR	NR	NR
2020	Wu[67]	0: 199 Missing: 0	Tis: 199 Missing: 0	In situ: 199 Missing: 0	Positive: 173 Negative: 21 Missing: 5	Positive: 155 Negative: 39 Missing: 5	Positive: 47 Negative: 147 Missing: 5

(Continued)

TABLE 3. *Continued*

Year	First author	AJCC stage (*n*)	T classification (*n*)	Histology (*n*)	ER (*n*)	PR (*n*)	Her2Neu (*n*)
2020	Wu[68]	NR	Tis/T0: 44 T1: 122 T2: 115 T3: 42 T4: 0 Missing: 0	In situ: NR Invasive: 316 Other: 7	"Hormone receptor": Positive: 234 Negative: 89 Missing: 0	"Hormone receptor": Positive: 234 Negative: 89 Missing: 0	Positive: 114 Negative: 209 Missing: 0
2020	Yamada[62]	0: 101 I: 54 II: 73 III: 11 Missing: 0	NR	In situ: 65 Invasive: 174 Missing: 0	Positive: 153 Negative: 21 Missing: 65	NR	Positive: 26 Negative: 148 Missing: 65

Abbreviations: AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; NR, not reported; PR, progesterone receptor.

Fourteen studies[9,13,19,21,22,24,26,28,30,39,40,52,56,62] reported on regional recurrence (Fig. 2B, $I^2 = 40.1\%$ [95% CI, 0.0%–68.2%]). Eleven studies[21,22,24,26,28,30,39,40,52,56,62] ($T^2 = 0.19$) included 3454 patients with I-ABR, and three studies[9,13,19] ($T^2 = 0$) included 674 patients with D-ABR (Table S3a). In the I-ABR group, 83 (2.4%) regional recurrences occurred, and 14 (2.1%) in the D-ABR group. Their weighted average proportions were 0.02 (95% CI, 0.01–0.03) and 0.02 (95% CI, 0.01–0.03), respectively.

Locoregional recurrence after autologous PMBR was reported by 16 studies[8,13,21,22,28,30,40–42,52,58,63–65,67,68] (Fig. 2C, $I^2 = 72.2\%$ [95% CI, 55.3%–82.6%]). Of those, 15 studies[8,21,22,28,30,40–42,52,58,63–65,67,68] reported on I-ABR ($T^2 = 0.40$), and the weighted average proportion of locoregional recurrences was 0.04 (95% CI, 0.03–0.06). In the three studies that reported on D-ABR[8,13,65] ($T^2 = 0.86$), the weighted average proportion of locoregional recurrence was 0.01 (95% CI, <0.01–0.03).

Twenty-five studies[4,8,9,13,19,21,22,24–26,28–30,40–42,50,52,56,62–65,67,68] (Fig. 2D, $I^2 = 86.0\%$ [95% CI, 80.9%–89.8%]) reported occurrence of distant metastasis after autologous PMBR, of which 22 studies[4,8,21,22,24–26,28–30,40–42,50,52,56,62–65,67,68] ($T^2 = 0.85$) included 5476 patients with I-ABR, and 6 studies[8,9,13,19,50,65] ($T^2 = 0.75$) included 1380 patients with D-ABR (Fig. 1D). In total, 368 of 5476 patients (6.7%) developed distant metastasis after I-ABR, and 125 of 1380 patients (9.1%) developed distant metastasis after D-ABR (Table S3a). The heterogeneity among these studies was too high to pool the results. Therefore, no weighted average proportion is reported.

Finally, 26 studies[8,9,11,13,19,21,24,26,28–30,40–43,46,52,56,58,59,62–65,67,68] reported total breast cancer recurrence in autologous PMBR (Fig. 2E, $I^2 = 89.7\%$ [95% CI, 86.6%–92.5%]). Twenty-two studies[8,21,24,26,28–30,40–43,46,52,56,58,59,62–65,67,68] ($T^2 = 0.50$), representing 5723 patients after I-ABR, reported 578 recurrences (10.1%, Table S3a). Six studies[8,9,11,13,19,65] ($T^2 = 0.50$), including 1473 patients after D-ABR, reported 191 recurrences (13.0%). Again, the high heterogeneity among these studies did not allow pooling of the data.

In conclusion, delayed autologous PMBR did not lead to different local, regional, and locoregional breast cancer recurrence rates than immediate autologous PMBR. Although it seems that there are no statistically significant differences in distant metastasis or overall breast cancer recurrence rates between immediate and delayed autologous PMBR, we could not calculate reliable weighted average proportions for these outcome measures due to a too high heterogeneity among the studies. Therefore, it was not possible to draw a solid conclusion on whether delayed autologous PMBR leads to higher distant metastasis and total breast cancer recurrence rates than immediate autologous PMBR.

Immediate versus delayed implant-based PMBR

In total, 22 studies[31–38,42,47–49,54,55,57,59–61,64,66–68] reported local recurrence after immediate implant-based post-mastectomy breast reconstruction (I-IBR) (Fig. 3A, $I^2 = 42.1\%$ [95% CI, 3.8%–65.1%]). These studies ($T^2 = 0.27$) included 4121 patients, of whom 146 (3.5%) developed local recurrences (Table S3b). The weighted average proportion of local recurrences was 0.03 (95% CI, 0.02–0.04).

Proportions of regional recurrences after I-IBR were reported in 10 studies[31,33–35,38,48,55,57,60,66] ($I^2 = 61.2\%$ [95% CI, 22.6%–80.5%]), including 79 regional recurrences in 2446 patients (3.2%) (Fig. 3B; Table S3b). The weighted average proportion of regional recurrences was 0.02 (95% CI, 0.01–0.04).

Fifteen studies[20,31–33,35,41,42,53,55,57,58,60,64,67,68] ($I^2 = 56.4\%$ [95% CI, 22.4%–75.5%]) reported locoregional recurrences after implant-based PMBR (Fig. 3C).

TABLE 4. Treatment Characteristics Of Included Study Populations

Year	First author	Mastectomy type	Chemotherapy[a]	Radiotherapy[a]	Hormone therapy[1]
2014	Adam[48]	Skin- and nipple-sparing: 69 Missing: 0	Neo-adjuvant/adjuvant: Yes: 6/19 No/missing: NR/NR	Yes: 22 No/missing: NR	Yes: 41 No/missing: NR
2018	Adam[19]	NR	Neo-adjuvant/adjuvant: Yes: 94/157 No: 160/96 Missing: 0/1	Yes: 209 No: 44 Missing: 1	Yes: 191 No: 63 Missing: 1
2019	Bjöhle[38]	NR	Neo-adjuvant/adjuvant: Yes: 31/79 No: 97/48 Missing: 0/1	Yes: 128 No: 0 Missing: 0	Yes: 95 No: 32 Missing: 1
2006	Caruso[31]	Skin- and nipple-sparing: 51 Missing: 0	Yes: 12 No: 39 Missing: 0	Yes: 3 No: 48 Missing: 0	Yes: 21 No: 30 Missing: 0
2018	Chen[32]	NR	Yes: 110 No: NR Missing: 0	Yes: 111 No: NR Missing: 0	Yes: 77 No: NR Missing: 0
2017	Cont[49]	Skin- and nipple-sparing: 518 Missing: 0	Yes: 253 No/missing: NR	Yes: 94 No/missing: NR	Yes: 420 No/missing: NR
2016	Dillekås[9]	NR	Yes: 143 No: 144 Missing: 25	NR	Yes: 136 No: 117 Missing: 59
2017	Du[33]	Skin- and nipple-sparing: 157 Missing: 0	NR	Yes: 18 No/missing: NR	NR
2020	Early[65]	Conventional mastectomy, skin-sparring mastectomy, and nipple-areola skin-sparing mastectomy: NR	NR	NR	NR
2011	Eriksen[34]	NR	Neo-adjuvant/adjuvant: Yes: 39/132 No: NR/NR Missing: 0/8	Yes: 99 No: NR Missing: 11	Yes: 209 No: NR Missing: 17
2016	Fujimoto[21]	Skin- and nipple-sparing: 136 Skin-sparing: 36 Missing: 0	Neo-adjuvant: Yes: 25 No/missing: NR	NR	NR
2018	Geers[8]	NR	NR	NR	NR
2005	Greenway[64]	Skin-sparing: 225 Missing: 0	NR	NR	NR
2020	Ha[58]	Implant-based/autologous: Skin- and nipple-sparing: 68/58 Skin-sparing: 64/84 Total/conventional mastectomy: 115/107 Missing: 0/0	Implant-based/autologous: Yes: 136/132 No: 111/117 Missing: 0/0	Implant-based/autologous: Yes: 51/48 No: 195/200 Missing: 1/1	NR
2008	Hölmich[20]	NR	Yes: 165 No/M: NR Missing: NR	Yes: 116 No: 464 Missing: 0	Yes: 24 No: NR Missing: NR
2006	Huang[22]	Modified radical mastectomy: 82 Missing: 0	Yes: 82 No: 0 Missing: 0	Yes: 82 No: 0 Missing: 0	"All patients with ER- or PR-positive receptor"
2011	Isern[11]	NR	Yes: 48 No: 77 Missing: 0	Yes: 109 No: 16 Missing: 0	Yes: 33 No: 92 Missing: 0
2010	Kim[23]	Skin- and nipple-sparing: 152 Skin-sparing: 368 Missing: 0	NR	Yes: 38 No/missing: NR	NR
2012	Kim[39]	Skin-sparing: 65 Missing: 0	Yes: 29 No: 36 Missing: 0	Yes: 1 No: 64 Missing: 0	Yes: 50 No: 15 Missing: 0
2016	Lee[25]	Modified radical mastectomy: 213 Missing: 0	Yes: 213 No: 0 Missing: 0	Yes: 213 No: 0 Missing: 0	"All hormonal receptor-positive patients"
2020	Lee[59]	Skin- and nipple-sparing: 111 Skin-sparing: 327 Missing: 0	Neo-adjuvant/adjuvant: Yes: 29/182 No: NR Missing: NR	Yes: 52 No/missing: NR	NR

(Continued)

TABLE 4. *Continued*

Year	First author	Mastectomy type	Chemotherapy[a]	Radiotherapy[a]	Hormone therapy[1]
2018	Lee[26]	Skin- and nipple-sparing: 1032 Missing: 0	Yes: 603 No: 423 Missing: 6	Yes: 87 No: 940 Missing: 5	Yes: 648 No: 377 Missing: 7
2019	Lee[27]	Skin-sparing: 118 Missing: 0	Yes: 93 No: 26 Missing: 0	Yes: 17 No: 102 Missing: 0	Yes: 80 No: 39 Missing: 0
2012	Lee[24]	Skin- and nipple-sparing: 361 Skin-sparing: 510 Modified radical mastectomy: 29 Missing: 100	NR	NR	NR
2013	Liang[28]	Skin-sparing: 249 Missing: 0	Neo-adjuvant/adjuvant: Yes: 16/196 No: NR/NR Missing: NR/0	Yes: 32 No/missing: NR	Yes: 126 No/missing: NR
2013	Lindford[13]	Nonskin-sparing: 112 Missing: 0	Yes: 91 No: 21 Missing: 0	Yes: 76 No: 36 Missing: 0	Yes: 83 No: 29 Missing: 0
2010	Lim[63]	Skin- and nipple-sparing: 14 Skin-sparing: 73 Missing: 0	Yes: 86 No: 1 Missing: 0	Yes: 49 No: 38 Missing: 0	Yes: 65 No: 22 Missing: 0
2017	Maalouf[50]	Skin-sparing: 40 Modified radical mastectomy: 22 Missing: 0	Immediate/delayed: Yes: 24/22 No/missing: NR/NR	Immediate/delayed: Yes: 30/32 No/missing: NR/NR	Immediate/delayed: Yes: 17/23 No/missing: NR/NR
2008	McCarthy[53]	NR	Yes: 238 No: 69 Missing: 2	Yes: 67 No: 236 Missing: 303	NR
2020	Metere[60]	Skin- and nipple-sparing: 894 Missing: 0	Neo-adjuvant/adjuvant: Yes: 215/264 No/missing: NR/NR	Yes: 87 No/missing: NR	NR
2010	Min[4]	NR	Neo-adjuvant: Yes: 9 No: 111 Missing: 0	Yes: 72 No: 48 Missing: 0	NR
2013	Munhoz[54]	Skin- and nipple-sparing: 106 Missing: 0	Yes: 28 No/missing: NR	Yes: 10 No/missing: NR	NR
2017	Murphy[55]	Skin- and nipple-sparing: 240 Missing: 0	NR	NR	NR
2005	Mustonen[56]	Skin- and nipple-sparing: 21 Subcutaneous: 34 Nonskin-sparing: 1 Missing: 0	NR	NR	NR
2015	Narui[29]	Skin- and nipple-sparing: 152 Skin-sparing: 53 Missing: 0	Yes: 43 No/missing: NR	Yes: 15 No/missing: NR	Yes: 120 No/missing: NR
2012	Nava[35]	Skin- and nipple-sparing: 59 Missing: 0	Yes: 26 No/missing: NR	Yes: 10 No/missing: NR	Yes: 38 No/missing: NR
2014	Ota[36]	Skin- and nipple-sparing: 2 Skin-sparing: 131 Missing: 0	Yes: 60 No: 73 Missing: 0	Yes: 2 No/missing: NR	Yes: 91 No: 42 Missing: 0
2020	Ozmen[61]	Skin- and nipple-sparing: 75 Missing: 0	NR	Yes: 23 No/missing: NR	NR
2016	Park[40]	Skin- and nipple-sparing: 36 Skin-sparing: 78 Total/conventional mastectomy: 75 Missing: 0	Yes: 136 No: 53 Missing: 0	Yes: 19 No: 170 Missing: 0	NR
2020	Parvez[66]	Skin- and nipple-sparing: 175 Missing: 0	Yes: 49 No/missing: NR	Yes: 40 No/missing: NR	NR
2012	Patterson[30]	Skin-sparing: 170 Modified radical mastectomy: 142 Total/conventional mastectomy: 78 Missing: 0	Yes: 105 No/missing: NR	Yes: 51 No/missing: NR	Yes: 65 No/missing: NR
2011	Reddy[41]	NR	Yes: 181 No: 313 Missing: 0	Yes: 135 No: 359 Missing: 0	Yes: 232 No: 262 Missing: 0
2012	Romics[42]	Skin-sparing: 207 Missing: 0	Yes: 100 No: 107 Missing: 0	Yes: 72 No: 81 Missing: 54	Yes: 126 No: 27 Missing: 54

TABLE 4. *Continued*

Year	First author	Mastectomy type	Chemotherapy[a]	Radiotherapy[a]	Hormone therapy[1]
2016	Sakamoto[57]	Skin- and nipple-sparing: 421 Missing: 0	Yes: 181 No: 240 Missing: 0	Yes: 54 No: 367 Missing: 0	Yes: 285 No: 136 Missing: 0
2008	Scholz[52]	Skin-sparing: 54 Missing: 0	NR	NR	NR
2013	Serra[37]	Skin-sparing: 155 Missing: 0	Yes: 87 No/missing: NR	NR	Yes: 68 No/missing: NR
2007	Snoj[51]	Skin-sparing: 25 Nonskin-sparing: 132 Missing: 0	Yes: 73 No/missing: NR	Yes: 36 No/missing: NR	Yes: 68 No/missing: NR
2003	Spiegel[43]	Skin-sparing: 221 Missing: 0	NR	NR	NR
2016	Tanos[44]	NR	NR	NR	NR
2008	Ueda[45]	Skin- and nipple-sparing: 33 Skin-sparing: 41 Missing: 0	Yes: 16 No/missing: NR	Yes: 2 No/missing: NR	Yes: 43 No/missing: NR
2019	Valente[46]	NR	Yes: 292 No/missing: NR	Yes: 103 No/missing: NR	NR
2007	Vaughan[47]	Skin-sparing: 210 Missing: 0	NR	Yes: 42 No/missing: NR	NR
2020	Wu[67]	Skin- and nipple-sparing: 199 Missing: 0	NR	Yes 0 No: 199 Missing: 0	Yes: 15 No: 184 Missing: 0
2020	Wu[68]	Skin- and nipple-sparing: 187 Skin-sparing: 136 Missing: 0	Yes: 44 No: 279 Missing: 0	"Chest wall": Yes: 191 No: 132 Missing: 0	Yes: 239 No: 84 Missing: 0
2020	Yamada[62]	Skin- and nipple-sparing: 172 Skin-sparing: 67 Missing: 0	Yes: 75 No: 164 Missing: 0	Yes: 16 No: 226 Missing: 0	Yes: 170 No: 69 Missing: 0

Abbreviations: ER, estrogen receptor; NR, not reported; PR, progesterone receptor.
[a]Neoadjuvant and/or adjuvant.

Fourteen studies[31–33,35,41,42,53,55,57,58,60,64,67,68] included 2793 patients in the I-IBR group, of whom 139 patients (5.0%) developed locoregional recurrences (Table S3b). Their weighted average proportion was 0.03 (95% CI, 0.01–0.05). One study[20] reported 49 locoregional recurrences in 580 patients (8.4%) after delayed implant-based post-mastectomy breast reconstruction (D-IBR), representing a proportion of 0.08 (95% CI, 0.06–0.11).

Eighteen studies[20,31,33–36,38,41,42,48,54,55,57,60,64,66,67,69] (Fig. 3D, I^2 = 88.6% [95% CI, 83.5%–92.1%) described the occurrence of distant metastasis after implant-based PMBR, of which 17[31,33–36,38,41,42,48,54,55,57,60,64,66,67,69] reported distant metastases after I-IBR (T^2 = 0.55); in total, 177 of 3022 patients (5.9%) developed distant metastases after I-IBR (Table S3b). However, the high heterogeneity among these studies did not allow pooling of the data. One study[20] reported 86 distant metastases in 580 patients (14.8%) after D-IBR, representing a proportion of 0.15 (95% CI, 0.12–0.18).

Twenty studies[20,31,33–36,38,41–43,46,48,53,57–59,64,66–68] (I^2 = 89.2% [95% CI, 84.7%–92.3%]) reported overall recurrences after implant-based PMBR, of which 19 studies[48,50–53,55,58–60,63,65,70,74–76,89,98,100,109] (T^2 = 0.32) reported data on a3018 patients after I-IBR (Fig. 3E) with 353 recurrences (11.7%) (Table S3b). High heterogeneity did not allow pooling of the data. One study[20] reported 145 (25.0%) overall recurrences among 580 patients after D-IBR (0.25 [95% CI, 0.22–0.29]).

In summary, the data were too heterogenous to calculate weighted average proportions for distant and total breast cancer recurrences after I-IBR. Moreover, none of the studies reported local or regional recurrence rates after D-IBR, and only one study[20] reported locoregional recurrence, distant metastasis, and total recurrence rates after D-IBR (Table S3b). Consequently, there were insufficient data to calculate weighted average proportions of local, regional, locoregional, distant, or total breast cancer recurrence rates after D-IBR. Therefore, it was not possible to compare local, regional, locoregional, distant, or total recurrence rates between I-IBR and D-IBR.

DISCUSSION

This SR/MA, including studies of moderate-level quality, showed that delayed autologous PMBR does not lead to different local, regional, and locoregional breast cancer recurrence rates compared to immediate autologous PMBR. Data of the included studies were either insufficient or too heterogeneous to evaluate whether delayed autologous

PMBR leads to different distant metastasis or overall breast cancer recurrence rates compared to immediate autologous PMBR, or whether delayed implant-based PMBR led to higher breast cancer recurrence and distant metastasis rates than immediate implant-based PMBR. This meta-analysis is the first to focus on the differences in oncological outcomes after immediate versus delayed PMBR for autologous and implant-based PMBR separately.

Consistent with our results, Shen and colleagues[6] (2020) observed no difference in recurrence rates after immediate and delayed PMBR in their systematic review. Similarly, in a meta-analysis by Gieni and colleagues[3] (2012), no difference was found in local recurrences between immediate PMBR and mastectomy only. However, both reviews were limited by the absence of stratified data on type of reconstruction (i.e., autologous and/or implant-based).[3,6] Similar limitations were present in a review by Tsoi and colleagues,[14] comparing implant-based with autologous PMBR while not considering the timing of reconstruction. Both distinctions are important for clinical decision-making, because surgical impact and postoperative complications differ greatly between implant-based and autologous breast reconstructive surgery and between immediate and delayed breast reconstructions.[6,14] Ha and colleagues[58] were the first to compare oncological safety between immediate reconstructive methods. To provide robust evidence that supports clinical and shared decision-making, prospective studies focusing on both surgical methods and both timings of reconstructive surgery separately are needed.[58]

Personalized health care is increasingly becoming standard of care for patients with breast cancer.[70] Ideally, each patients' treatment strategy is aligned with patients' genotypic, phenotypic and clinical characteristics, as well as patients' personal preferences. Subsequently, decision aids (DAs) to support shared decision-making (SDM) are gaining popularity.[71] However, breast reconstruction DAs are predominantly designed for general patient education about different reconstructive options and at best predict the risk of postoperative complications. Because of lack of detailed data on oncological outcomes after different methods and timings, it is not surprising that information on oncological outcomes is not included in current DAs. Moreover, due to various reasons (e.g., previous surgery or radiotherapy, body type), not all patients are eligible for all reconstructive options.[2] To support SDM and improve personalized patient information, patient education should be adjusted to the specific characteristics of the individual. This tailored information can only be achieved through better understanding of differences in oncological outcomes after PMBR.

Another important aspect of clinical decision-making in the field of breast reconstructive surgery concerns the potential influence of specific reconstructive types and timings on the overall breast cancer treatment strategy. Immediate PMBR does not delay time to adjuvant chemotherapy to a clinically relevant extent.[72] However, the timing of PMBR when radiotherapy is indicated, is still controversial.[7] To enhance personalized medicine, better understanding of oncological risks within subgroups will allow more profound assessments of individual risks in a multidisciplinary setting, thereby improving quality of care.

Better insight in recurrence rates and recurrence patterns after different reconstructive techniques may also improve postoperative surveillance strategies. To date, no consensus exists on routine imaging of the reconstructed breast.[73,74] Physical examination is mostly used to detect locoregional recurrences after PMBR, but deeper located recurrences (i.e., chest wall recurrences) may be missed.[73] Although Shammas and colleagues[73] did not find a difference in disease-free survival between reconstructed patients who received postoperative imaging for surveillance versus those who did not, routine imaging may still be of added clinical value after specific reconstructive techniques or in patients with certain risk profiles. In example, due to preservation of the skin envelope, immediate autologous PMBR might form a risk for developing local recurrences. Because approximately two thirds of all patients with locoregional recurrences will develop distant metastasis, larger studies are needed to define the role of routine mammography, ultrasound, and/or magnetic resonance imaging for early detection of locoregional recurrences.[75]

Most importantly, the low risk of locoregional breast cancer recurrence and distant metastasis after breast cancer treatment makes it hard to generate robust evidence-based conclusions about oncological outcomes after the various reconstructive timings and techniques, and recommendations for breast cancer surveillance after PMBR.[74] As a result, patient education on which type and timing of breast reconstruction patients qualify for remains highly sensitive to experts' beliefs (e.g., the tumor dormancy theory), preferences, resources, and experience. As such, breast reconstructive options that are offered vary widely, even on regional levels.

In addition to the generally low recurrence rates after breast cancer treatment, other challenges of many studies on PMBR are the heterogeneity in study populations and follow-up, and their susceptibility for confounding by indication. This was illustrated by the large variation

in recurrence rates found in our analyses. For example, recurrence rates for distant metastasis and overall breast cancer recurrences after D-IBR, as reported by Hölmich and colleagues[20] seem high in comparison to other subgroups. However, their high recurrence rates could be explained by the fact that only patients with invasive breast carcinoma were included, that patients were treated between 1978 and 1992, and by their long follow-up of 10 years. Although we recognize the challenges researchers are faced with when performing studies concerning PMBR, we would like to emphasize the need for larger, prospective long-term follow-up studies focusing on PMBR and oncological outcomes in order to increase equal education on, and access to various reconstructive options.[3] The use of prospectively maintained databases and intensive collaboration between existing registries such as oncological, pathological, and surgical registries (e.g., the Dutch Breast Implant Registry or the UK Flap registry) will help overcome these challenges. Transparent, uniform, and complete data collection can be improved by implementation of standardized reporting formats in electronic medical patient records.

This meta-analysis has several limitations inherent to the quality of the included studies. Despite efforts to minimize heterogeneity among the study populations by only including studies reporting outcomes per subgroup (i.e., autologous delayed and immediate, implant-based delayed and immediate) and applying strict in- and exclusion criteria, substantial heterogeneity was observed. Moreover, the definitions of local, regional, locoregional, and total recurrences were not always specified among studies and often one of these outcomes was not reported. However, we did not exclude studies lacking a detailed description of their outcome measure to ensure we could use all data of all available studies, given that they complied with our predefined level of quality, to support a data-driven conclusion. Because of the nonrandomized nature of the studies and lack of high-quality trials, the risk of selection bias and confounding in the included studies is substantial. However, performing randomized trials for breast reconstructive surgery and oncological safety is often considered unethical or unfeasible.[6] By requesting specified data of subgroups from authors who only reported outcomes for the entire groups, selection bias due to unavailability of studies was reduced. Subgroup or adjusted analyses based on tumor stage were not feasible due to incomplete and/or unstratified data. Last, considering that multiple different groups were compared, although formal testing was not performed, there could be an issue with multiple testing. However, the included data allowed for only few formal comparisons. Therefore, we believe this potential issue is minor. We believe this would not have affected the interpretation of the results. A strength of these aggregated patient data (APD) meta-analyses is that it overcomes potential bias of narrative literature reviews, whereas summarizing data of many studies that were each too small to provide valid evidence. Furthermore, generalizability was strengthened by the large number of studies including a wide range of patient demographics and origins (i.e., Asia, Europe, North and South America).

In conclusion, delayed autologous PMBR leads to similar (loco)regional breast cancer recurrence rates as compared to immediate autologous PMBR. Data of the included studies were unfit to reliably conclude whether delayed autologous PMBR leads to different distant metastasis or overall breast cancer recurrence rates compared to immediate autologous PMBR, or whether delayed implant-based PMBR leads to different breast cancer recurrence and distant metastasis rates than immediate implant-based PMBR. Based on current evidence, oncological concerns do not seem a valid reason to withhold patients from certain reconstructive timings or techniques, and patients should equally be offered all reconstructive options they technically qualify for.

However, these results are based on moderate-level quality studies and therefore do not allow firm conclusions regarding oncological outcomes after different types and timings of PMBR. As such, it remains challenging to define evidence-based recommendations. In support of equal access to care and better patient selection for breast reconstructions, prospective and sufficiently powered studies evaluating long-term oncological outcomes are needed to confirm oncological safety after different breast reconstructive timings and techniques in the treatment of patients with breast cancer.

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AUTHOR CONTRIBUTIONS

Claudia A. Bargon: Conception or design of the work, acquisition of data for the work, analysis of data for the work, interpretation of data for the work, drafting the work, critical revision of the work for important intellectual content, and responsibility for overall content as a guarantor. **Danny A. Young-Afat:** Conception or design of the work, analysis of data for the work, interpretation of data for the work, drafting the work, and critical revision of the work for important intellectual content. **Mehmet Ikinci:** Acquisition of data for the work, analysis of data for the work, interpretation of data for the work, and critical revision of the work for important intellectual content. **Assa Braakenburg:** Conception or design of the work, interpretation of data for the work, and critical revision of the

work for important intellectual content. **Hinne A. Rakhorst:** Conception or design of the work, interpretation of data for the work, and critical revision of the work for important intellectual content. **Marc A.M. Mureau:** Conception or design of the work, interpretation of data for the work, drafting the work, and critical revision of the work for important intellectual content. **Helena M. Verkooijen:** Conception or design of the work, acquisition of data for the work, interpretation of data for the work, and critical revision of the work for important intellectual content. **Annemiek Doeksen:** Conception or design of the work, acquisition of data for the work, analysis of data for the work, interpretation of data for the work, drafting the work, critical revision of the work for important intellectual content, and responsibility for overall content as a guarantor. All authors have given final approval for the version of this article to be published and have agreed to be accountable for all aspects of the work and thereby ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICTS OF INTEREST

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