Scientific Research Publishing

Advances in Breast Cancer Research, 2019, 8, 87-111
http://www.scirp.org/journal/abcr
ISSN Online: 2168-1597
ISSN Print: 2168-1589

The Keys to Optimising Breast Wounds: A Meta-Analysis

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How to cite this paper: Vincent, S.M.A., Gallagher, M., Johnston, A., Djohan, R., Varzgalis, M. and Sugrue, M. (2019) The Keys to Optimising Breast Wounds: A Meta-Analysis. *Advances in Breast Cancer Research*, **8**, 87-111.
https://doi.org/10.4236/abcr.2019.83007

Received: April 27, 2019
Accepted: June 25, 2019
Published: June 28, 2019

Abstract

Background: Breast disease and breast cancer management form a major part of healthcare delivery. Surgical site occurrence (SSO) poses septic and oncological risks to patients. This study undertook a meta-analysis to identify key risk factors and interventions that may alter the incidence of SSO in patients undergoing breast surgery. **Methods:** An ethically approved, PROSPERO-registered meta-analysis following PRISMA guidelines and Cochrane Handbook for Systematic Reviews was undertaken of all published English articles using electronic databases from 2010 to 2017 incorporating MeSH terms "risk factors", "surgical site infections", "breast surgery", and "interventions". Articles scoring > 10 for non-comparative studies and >15 for comparative studies, using MINORS criteria were included. The OR or RR using random-effects, Mantel-Haenszel method were computed for each risk factor and intervention respectively with RevMan 5. **Results:** The pre-operative factors affecting breast surgery SSO were diabetes mellitus (OR = 2.52, CI = 1.78 - 3.59, $p < 0.001$), smoking (OR = 2.39, CI = 1.57 - 3.63, $p < 0.001$), ASA ≥ III (OR = 2.37, CI = 1.51 - 3.74, $p < 0.001$), obese versus non-obese (OR = 1.84, CI = 1.52 - 2.24, $p < 0.001$), over-weight/obese versus normal BMI (OR = 1.70, CI = 1.36 - 2.13, $p < 0.001$), hypertension (OR = 1.63, CI = 1.39 - 1.90, $p < 0.001$), and antibiotics prophylaxis (RR = 0.58, CI = 0.36 - 0.95, $p = 0.03$). The intraoperative factors were surgical wound classifications 3 - 4 (OR = 6.16, CI = 2.52 - 15.02, $p < 0.001$), surgical drains (OR = 2.80, CI = 1.06 - 7.38, $p = 0.04$), and axillary lymph node dissection (OR = 1.46, CI = 1.18 - 1.80, $p < 0.001$). The post-operative factors were adjuvant radiotherapy (OR = 1.77, CI = 1.26 - 2.50, $p = 0.001$), re-operated patients (OR = 1.65, CI = 1.01 - 2.70, $p = 0.05$), post-operative antibiotics (RR = 0.57, CI = 0.33 - 0.98, $p = 0.04$), and drain antisepsis care (RR = 0.15, CI = 0.03 - 0.82, $p = 0.03$). **Conclusions:**

This study identified key factors associated with increased risk of breast surgery wound occurrence. It will facilitate the development of a peri-operative breast wound bundle to optimize outcomes.

Keywords

Breast Wound Care, Breast Wound Infection, Breast Surgical Site, Adverse Outcomes, Breast Implant Loss, Return to the Operating Theatre

1. Introduction

Breast disease and breast cancer management form a major part of healthcare delivery, constituting one of the most frequent elective surgeries performed globally [1]. Uncomplicated surgical outcomes are important in optimising functional, cosmetic and oncological outcomes. Surgical site occurrence (SSO) including wound infection, wound dehiscence and deep infection, with or without implant loss pose septic and oncological risks to patients [2] [3] [4]. There is a spectrum from minor wound infection to implant loss with increasing costs for the health care system [3] [5]. Reducing SSO will benefit patient's physical and psychological outcomes, facilitate adjuvant treatment, and optimise long term cosmetic and oncological outcomes [6] [7].

Wound infection and adverse wound events are multifactorial [8] [9] [10]. Identifying the relative importance of the contributing factors is challenging. A bundle approach to wound care has been shown to facilitate better outcomes [11] [12] [13]. There are few reports of the use of bundled approaches to reducing SSO in breast surgery [14]. The National Mastectomy Audit suggests that current rates of SSO are unacceptable [15].

The aim of this meta-analysis is to identify key risk factors and interventions that may alter the incidence of SSO in patients undergoing breast surgery.

2. Methods

2.1. Search Strategy and Study Eligibility

An ethically approved meta-analysis of the literature was undertaken to incorporate articles relating to breast wound care, breast wound infection, breast surgical site adverse outcomes, infected related implant loss, and return to the operating theatre. Existing research optimising wound care in surgery was reviewed to determine current strategies to improve wound outcomes. Key risk factors and interventions for SSO were identified in three keys phases of care, pre-, intra- and post-operative periods.

The methods of analysis and inclusion criteria were specified in advance to avoid selection bias and documented in a protocol which was registered and published with the International Prospective Register of Systematic Reviews (PROSPERO) (ID 42016039883). This meta-analysis adhered to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16] and Cochrane Handbook for Systematic Reviews of Interventions [17].

A systematic review and meta-analysis of all published English articles was conducted using PubMed, Scopus and Cochrane Library electronic databases from 2010 to 2017. Medical Subject Headings used terms which included risk factors ("risk factor*"), surgical site infections ("surgical site infection*", "wound infection*"), breast surgery ("breast surg*"), and interventions ("intervention*"). The following search strategies were used in our meta-analysis: ("risk factor*" AND "breast surg*" AND "infection*"), ("intervention*" AND "breast surg*" AND "infection*"), ("risk factor*" OR "intervention*" AND "breast surg*" AND "surgical site infection*"), and ("risk factor*" OR "intervention*" AND "breast surg*" AND "wound infection*"). Studies that were case studies or meta-analysis, not related to breast surgery, did not report key outcomes, or where data was inadequate for interpretation via meta-analysis, or duplicate studies were excluded.

Eligibility assessment was performed independently in a blinded standardised manner by two reviewers (SV and MG). Disagreements between reviewers were resolved by discussion between the two review authors and if no agreement could be reached, it was planned a third reviewer (AJ) would decide.

2.2. Data Extraction and Quality Assessment

We developed a standardised data extraction sheet and one reviewer (SV) extracted the following data from included studies and the second reviewer (MG) checked the extracted data. Discrepancies were resolved by discussion and consultation with another reviewer (AJ). Two reviewers (SV and MG) independently assessed each published study for the quality of study design by using the Methodological Index for Nonrandomised Studies (MINORS) score whereby the global ideal score is 16 for non-comparative studies and 24 for comparative studies [18]. Articles scoring > 10 for non-comparative studies and >15 for comparative studies, using MINORS criteria were included in the final analysis (**Table S1**). Risk of bias across studies was not assessed as there were too few included studies per outcome.

Information was extracted from each included study on: 1) Characteristics of participants 2) Inclusion and exclusion criteria 3) Risk factor or type of intervention 4) Well-reported outcome measurements (including a clear report of surgical site infections or breast wound infections).

2.3. Data Synthesis and Analysis

The odds ratio (OR) and risk ratio (RR) of surgical site infections (SSI) were the primary measure of risk factors and intervention effect respectively. The meta-analyses were performed by computing the OR or RR using Mantel-Haenszel method and random-effects model to combine variables of interest. OR or RR

and 95% Confidence Intervals (CI) for each risk factor and intervention were calculated. No additional analyses were done. The analysis was performed by using Review Manager Version 5 [19].

2.4. Definitions

The Centres for Disease Control and Prevention (CDC) definitions [5] [20] for surgical site infection were used. These are classified into superficial, deep or organ/space relating to implant/infection. The ASEPSIS (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, Stay duration as inpatient > 14 days) scoring system was also used to quantify surgical site infections [21].

WHO classification of nutritional status according to Body Mass Index (BMI) [22] was used to categorise underweight (BMI < 18.5), normal weight (BMI 18.5 - 24.9), pre-obesity (BMI 25.0 - 29.9), obesity class 1 (BMI 30.0 - 34.9), obesity class 2 (BMI 35.0 - 39.9), and obesity class 3 (BMI > 40). Patients were considered to have diabetes mellitus only if they were taking oral hypoglycaemic agents and/or on insulin. Patients were considered smokers if they were currently smokers or had smoked cigarettes in the year before admission for surgery. The tumour-node-metastasis (TNM) classification [23] for breast cancer was used to determine breast cancer staging. The American Society of Anesthesiology (ASA) Physical Status classification [24] was defined as follows: 1) normal healthy patient; 2) mild systemic disease; 3) patient with severe systemic disease; 4) severe systemic disease with constant threat to life; and 5) moribund patient not expected to survive without surgery. Neoadjuvant chemotherapy treatment was defined as administration of chemotherapeutic agents for cancer within 30 to 90 days prior to surgery [28] [33] [34] [40] [57] [61] [65]. Neoadjuvant radiotherapy included patients who had treatment within 90 days before surgery. Breast reoperations were defined as re-excision or mastectomy within 180 days of initial breast surgery.

To determine the level of risk, a number of classification systems were used in this study. These included the surgical wound classification [5] [20] and the National Nosocomial Infection Surveillance (NNIS) Risk Index [25].

3. Results

This meta-analysis reviewed 1606 articles for risk factors and interventions of SSI in breast surgery. 64 studies were found to be suitable after eligibility analysis and 49 studies were included for quantitative analysis of this meta-analysis (**Figure 1**). Characteristics of the studies included in this meta-analysis are listed in **Table S2**. Significant and insignificant factors affecting breast SSO that are not included in the quantitative meta-analysis are listed in **Table 1** and **Table 2** respectively.

A number of statistical significant causative factors and interventions for SSI in breast surgery in the key phases of care were identified; seven in pre-operative, three in intra-operative and four in post-operative.

Table 1. Significant factors for breast SSO not included in the quantitative meta-analysis.

Study ID	Significant factors	Odds Ratio	95% CI	p-value
	Pre-operative phase			
Angarita 2011 [26]	Active skin disorders	36.39	7.76 - 173.45	<0.001
Chung 2015 [30]	Hypertension	1.82	1.41 - 2.33	<0.001
	Pulmonary comorbidity	4.29	1.43 - 12.82	0.009
Olsen 2016 [57]	Depression	1.62	1.17 - 2.24	0.004
	Obesity	1.85	1.35 - 2.54	<0.001
	Liver disease	4.07	1.71 - 9.73	0.002
	Tobacco use disorder	1.29	1.00 - 1.67	0.05
	Smoking related disorder	2.22	1.52 - 3.24	<0.001
	Rheumatologic disease	1.86	1.10 - 3.13	0.02
Ota 2016 [60]	BMI ≥ 25	4.79	1.64 - 13.97	0.004
Pettke 2016 [87]	Age ≥ 80 years	0.66	0.57 - 0.78	<0.001
Tanner 2011 [67]	NNIS score 1	3.97	1.16 - 13.54	0.03
	NNIS score 2	33.75	4.34 - 262.28	<0.001
Teija-Kaisa 2012 [68]	AMP 30 - 60 mins before incision	2.64	1.05 - 6.65	0.04
	Intra-operative phase			
Angarita 2011 [26]	Radical vs BCS	17.62	5.13 - 60.47	<0.001
Chattha 2017 [75]	Mastectomy weight ≥ 500 g	2.98	1.78 - 5.01	<0.001
Cordeiro 2016 [77]	Overnight stay vs same-day stay	1.48	1.24 - 1.76	<0.001
	Stay ≥ 2 days vs same-day stay	2.16	1.79 - 2.61	<0.001
Franchelli 2012 [40]	Tumour stage II-IV	5.29	1.35 - 20.66	0.02
Gil-Londoño 2017 [80]	Radical mastectomy	2.73	1.43 - 5.19	0.002
Gülçelık 2017 [83]	IORT	12.97	1.57 - 107.18	0.02
Olsen 2015 [56]	Needle localisation	0.78	0.66 - 0.92	0.003
Parikh 2016 [85]	Ambulatory surgery centre vs outpatient	0.35	0.28 - 0.44	<0.001
Winocour 2015 [72]	Operative time ≥ 2.5 hours	2.19	1.72 - 2.80	<0.001
	Post-operative phase			
Franchelli 2012 [40]	Radiotherapy after surgery before infection	4.08	1.03 - 16.23	0.05
Leyngold 2012 [49]	Cellulitis	242.67	35.42 - 1662.23	<0.001
	Wound dehiscence	10.06	2.65 - 38.27	<0.001
	Wound necrosis	8.74	2.32 - 32.95	<0.001
Olsen 2016 [57]	Home healthcare	0.72	0.58 - 0.89	0.002
Olsen 2017 [58]	SSI after SR + Implant IR	4.58	3.23 - 6.50	<0.001
Ota 2016 [60]	Seroma aspiration	15.92	6.16 - 41.11	<0.001
Pellino 2014 [86]	NPWT	0.22	0.05 - 0.93	0.04

Table 2. Insignificant factors for breast SSO not included in the quantitative meta-analysis.

Study ID	Insignificant factors	Odds Ratio	95% CI	p-value
	Pre-operative phase			
Chung 2015 [30]	Alcohol use	1.71	0.39 - 7.41	0.48
Leyngold 2012 [49]	Age > 60 years	0.44	0.05 - 3.62	0.45
Olsen 2016 [57]	Age 51 - 64 years	1.05	0.89 - 1.24	0.57
	Rural vs urban residence	1.2	0.95 - 1.50	0.12
	0 - 50th income quartile	1.01	0.85 - 1.20	0.92
	Previous radiotherapy	1.17	0.82 - 1.68	0.38
	Inflammatory breast disease	1.57	0.88 - 2.83	0.13
Teija-Kaisa 2012 [68]	Age ≥ 65	0.64	0.36 - 1.12	0.12
	Pre-operative hospital stay ≥ 48 hrs	1.22	0.07 - 22.34	0.89
	Non-intact skin condition	0.67	0.38 - 1.19	0.17
	Intra-operative phase			
Cooney 2016 [76]	Matching procedure	1.37	0.97 - 1.95	0.08
Franchelli 2012 [40]	TNM cancer stage II-IV	2.77	0.69 - 12.71	0.19
Leyngold 2012 [49]	Mastectomy	1.72	0.09 - 32.72	0.72
Olsen 2015 [56]	Brachytherapy catheter placement	1.42	0.75 - 2.68	0.28
Olsen 2017 [58]	Implant vs autologous IR	0.9	0.76 - 1.07	0.24
Ota 2016 [60]	Excisional biopsy	1.05	0.37 - 2.98	0.92
	Simultaneous bilateral reconstruction	0.33	0.02 - 5.79	0.45
Tanner 2011 [67]	WLE + marker	1.84	0.52 - 6.52	0.35
Teija-Kaisa 2012 [68]	Invasive tumour marking	0.96	0.57 - 1.63	0.89
	Duration of operation ≥ 87 mins	1.5	0.88 - 2.55	0.14
Giordano 2013 [81]	Combination of povidone-iodine solution + antibiotic pocket irrigation	0.67	0.11 - 3.94	0.65
Golfam 2011 [82]	100% oxygen	0.2	0.01 - 4.08	0.3
Mittal 2017 [84]	Harmonic scalpel vs electrocautery	0.75	0.30 - 1.85	0.63
Williams 2011 [89]	Triclosan coated sutures	0.66	0.32 - 1.37	0.27
	Post-operative phase			
de Oliveira 2014 [78]	Active exercise	1.2	0.60 - 2.41	0.6
Dieterich 2013 [79]	Hydroxyethyl starch	0.89	0.46 - 1.73	0.73
Santosa 2016 [88]	Postmastectomy radiation therapy before exchange (TE radiotherapy) vs after permanent implant exchange	0.74	0.29 - 1.91	0.53

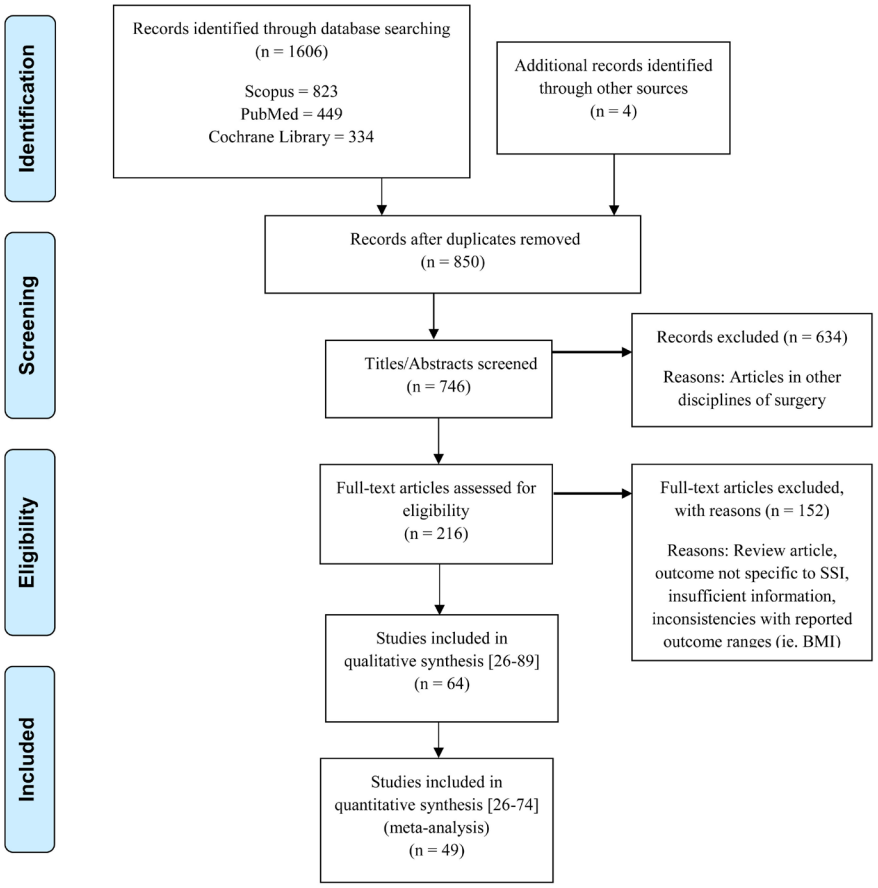
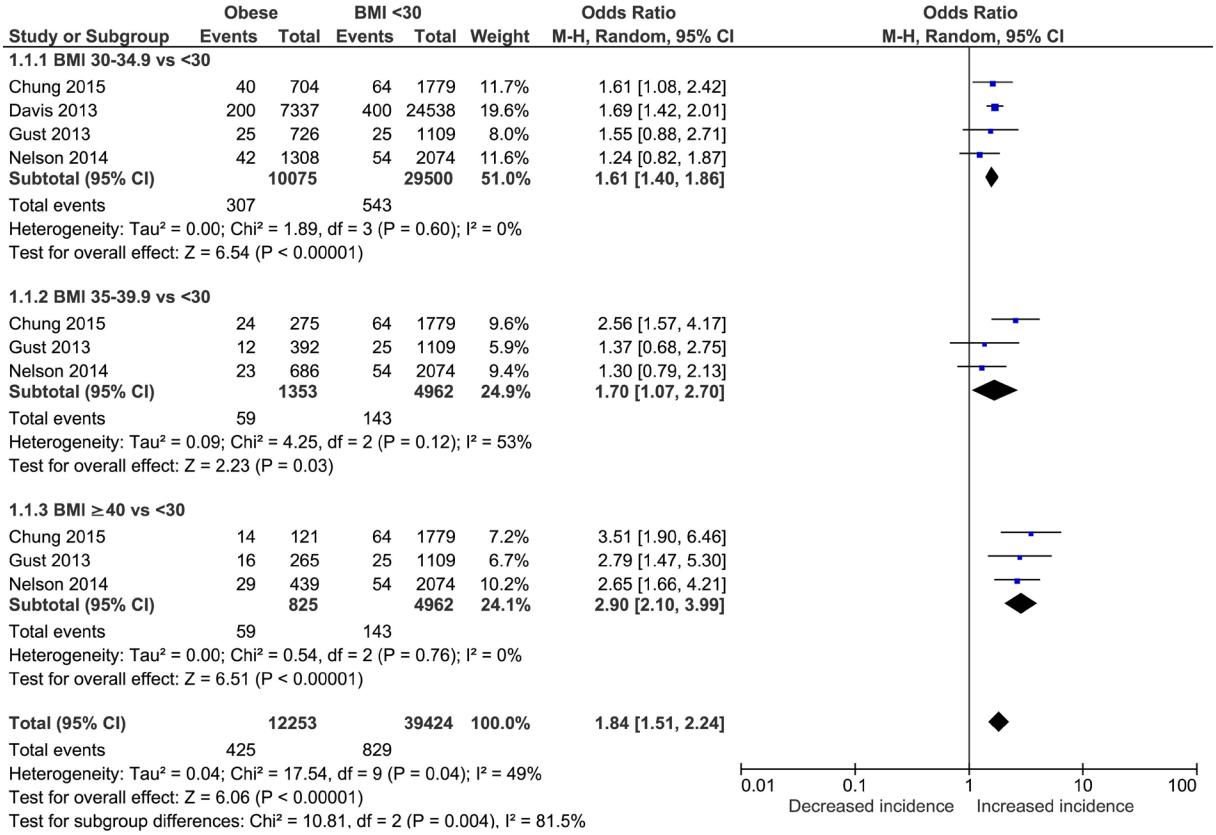


Figure 1. Prisma flow diagram.

3.1. Pre-Operative Phase

Significant pre-operative risk factors (**Figure 2** and **Figure 3**) for developing SSI in breast wounds are class 3 obesity versus non-obese (OR = 2.90, CI = 2.10 - 3.99, $p < 0.001$), diabetes mellitus (OR = 2.52, CI = 1.78 - 3.59, $p < 0.001$), smoking (OR = 2.39, CI = 1.57 - 3.63, $p < 0.001$), American Society of Anesthesiologists (ASA) Physical Status classification ≥III (OR = 2.37, CI = 1.51 - 3.74, $p < 0.001$), class 2 obesity versus non-obese (OR = 1.70, CI = 1.07 - 2.70, $p = 0.03$), class 1 obesity when compared to non-obese and normal BMI respectively (OR = 1.61, CI = 1.40 - 1.86, $p < 0.001$; OR = 1.93, CI = 1.59 - 2.35, $p < 0.001$), overweight versus normal BMI (OR = 1.66, CI = 1.15 - 2.40, $p = 0.007$), and hypertension (OR = 1.63, CI = 1.39 - 1.90, $p < 0.001$). Overall, being overweight or obese versus normal BMI and being obese versus non-obese was significant for increasing the incidence of SSI (OR = 1.70, CI = 1.36 - 2.13, $p < 0.001$; OR = 1.84, CI = 1.52 - 2.24, $p < 0.001$ respectively). Interventions shown to be statistically significant in reducing surgical site infections in breast surgery (**Figure 6**) is antibiotics prophylaxis (RR = 0.58, CI = 0.36 - 0.95, $p = 0.03$).

Insignificant pre-operative risk factors are neoadjuvant radiotherapy (OR = 1.26, CI = 0.55 - 2.89, $p = 0.58$), neoadjuvant chemotherapy (OR = 0.96, CI =



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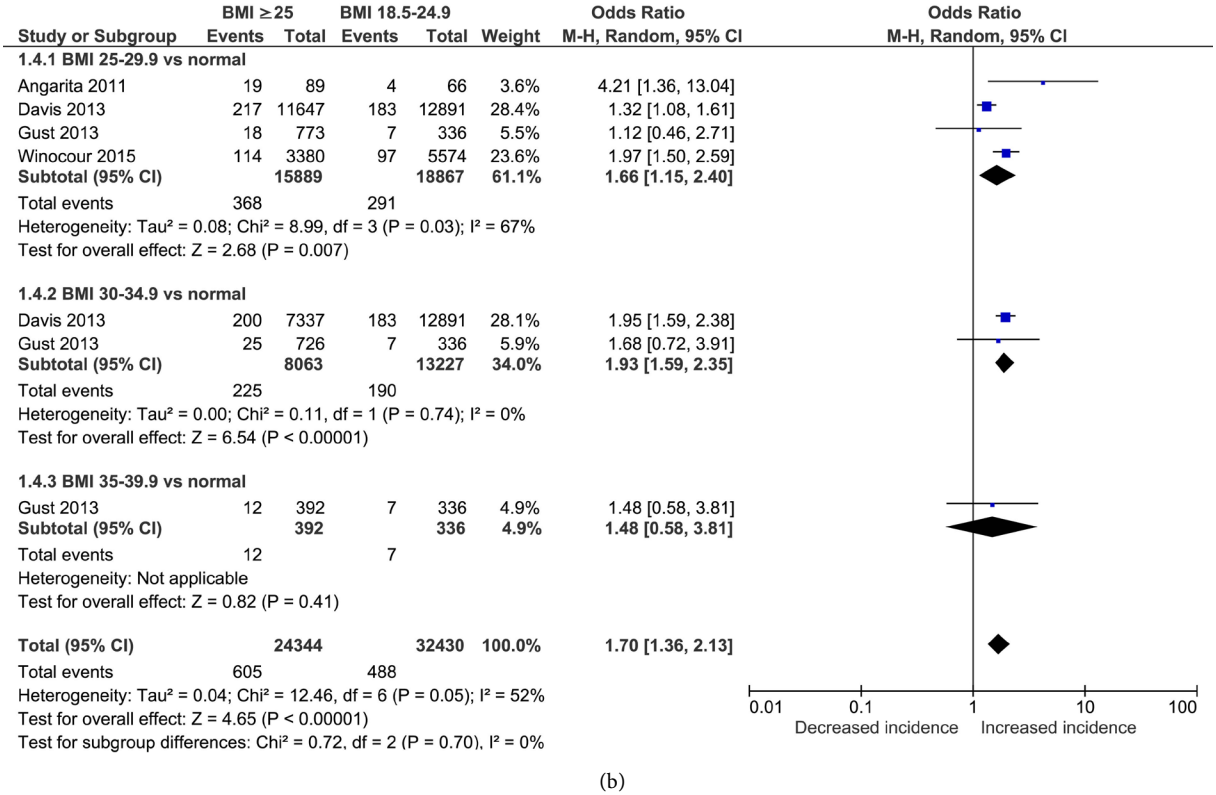
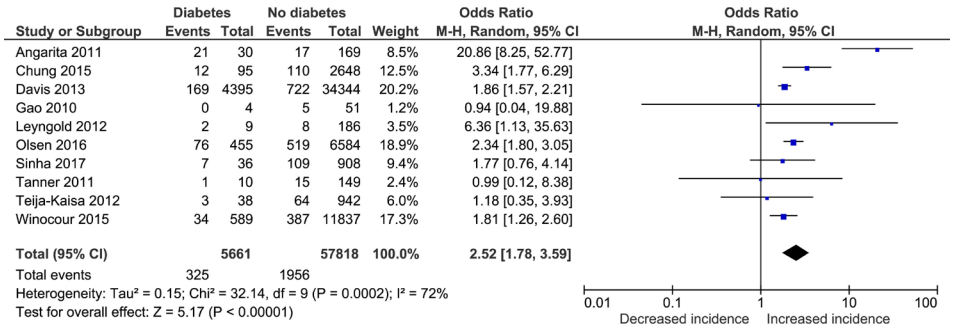


(b)

Figure 2. (a) Obese vs non obese; (b) Overweight/obese vs normal.



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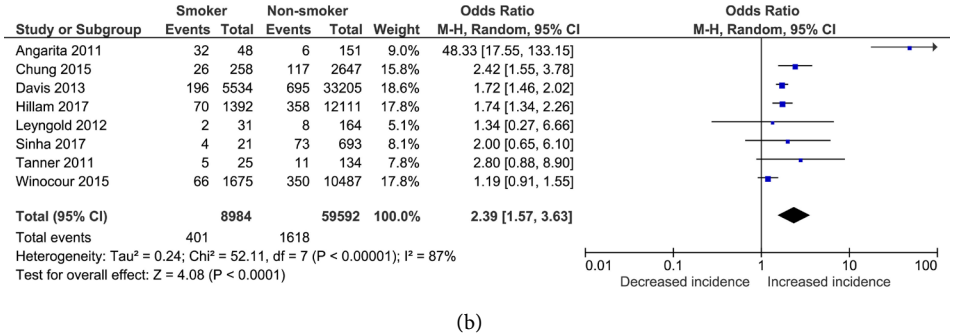

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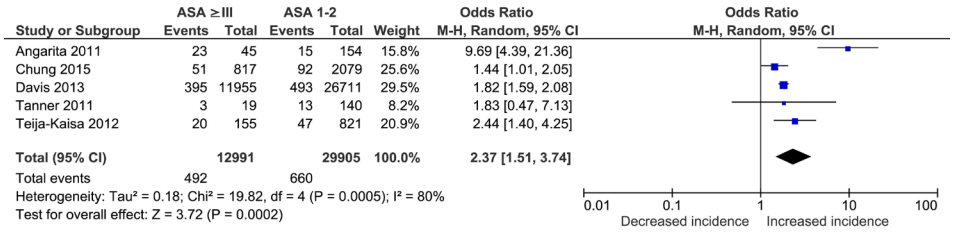

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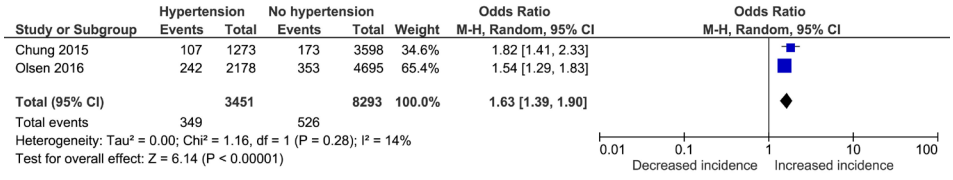


(d)

Figure 3. (a) Diabetes; (b) Smoking; (c) ASA; (d) Hypertension.

0.84 - 1.10, p = 0.55), age ≥ 50 years old (OR = 1.26, CI = 0.97 - 1.64, p = 0.09) and steroids use (OR = 1.04, CI = 0.81 - 1.32, p = 0.78). Hair removal (RR = 1.26, CI = 0.46 - 3.44, p = 0.66) was not shown to be statistically significant in reducing breast SSI.

3.2. Intra-Operative Phase

Significant intra-operative risk factors (**Figure 4**) are surgical wound classifications 3 or 4 (OR = 6.16, CI = 2.52 - 15.02, p < 0.001), the use of surgical drains (OR = 2.80, CI = 1.06 - 7.38, p = 0.04), and axillary lymph node dissection (ALND) (OR = 1.46, CI = 1.18 - 1.80, p < 0.001).

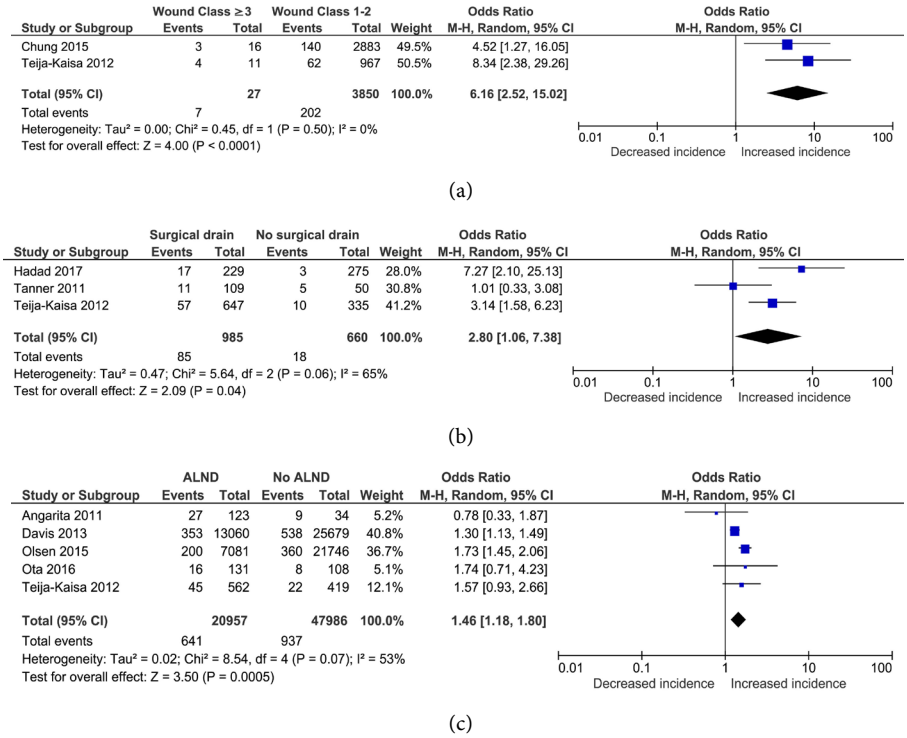


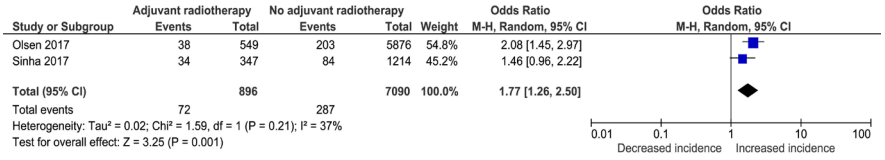
Figure 4. (a) Surgical wound class; (b) Surgical drains; (c) ALND.

Insignificant intra-operative risk factors are inpatient admission (OR = 3.59, CI = 0.18 - 72.11, p = 0.40), operative time > 2 hours (OR = 2.87, CI = 0.32 - 25.47, p = 0.34), immediate breast reconstruction (IBR) versus mastectomy only (OR = 2.66, CI = 0.72 - 9.83, p = 0.14), IBR versus delayed reconstruction (OR = 1.39, CI = 0.73 - 2.64, p = 0.32), a cellular dermal matrix (ADM) use (OR = 1.32, CI = 0.22 - 8.06, p = 0.06), breast cancer stage II - IV versus breast cancer stage 0 - I (OR = 1.24, CI = 0.54 - 2.88, p = 0.61), breast cancer versus prophylactic stage (OR = 1.10, CI = 0.82 - 1.47, p = 0.53), and sentinel lymph node biopsy (SLNB) (OR = 0.46, CI = 0.06 - 3.57, p = 0.46).

3.3. Post-Operative Phase

Adjuvant radiotherapy (OR = 1.77, CI = 1.26 - 2.50, p = 0.001) and re-operated patients (OR = 1.65, CI = 1.01 - 2.70, p = 0.05) are significant post-operative risk factors (**Figure 5**). Interventions shown to be statistically significant in reducing surgical site infections in breast surgery (**Figure 6**) are post-operative antibiotics (RR = 0.57, CI = 0.33 - 0.98, p = 0.04), and drain antisepsis care (RR = 0.15, CI = 0.03 - 0.82, p = 0.03).

Adjuvant chemotherapy (OR = 1.98, CI = 0.97 - 4.06, p = 0.06) was found to be an insignificant postoperative risk factor for breast SSI. Duration of post-operative antibiotics ≥24 hours versus <24 hours (RR = 0.75, CI = 0.51 - 1.10, p = 0.14) and the administration of antibiotics until drain removal versus antibiotics for 24 hours (RR = 1.00, CI = 0.56 - 1.80, p = 0.99) were not shown to be statistically significant in reducing SSI in breast surgery.



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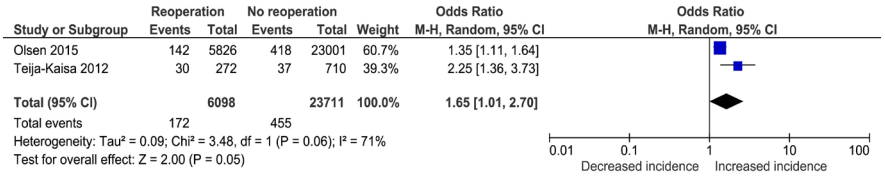

(b)

Figure 5. (a) Adjuvant radiotherapy; (b) Reoperation.

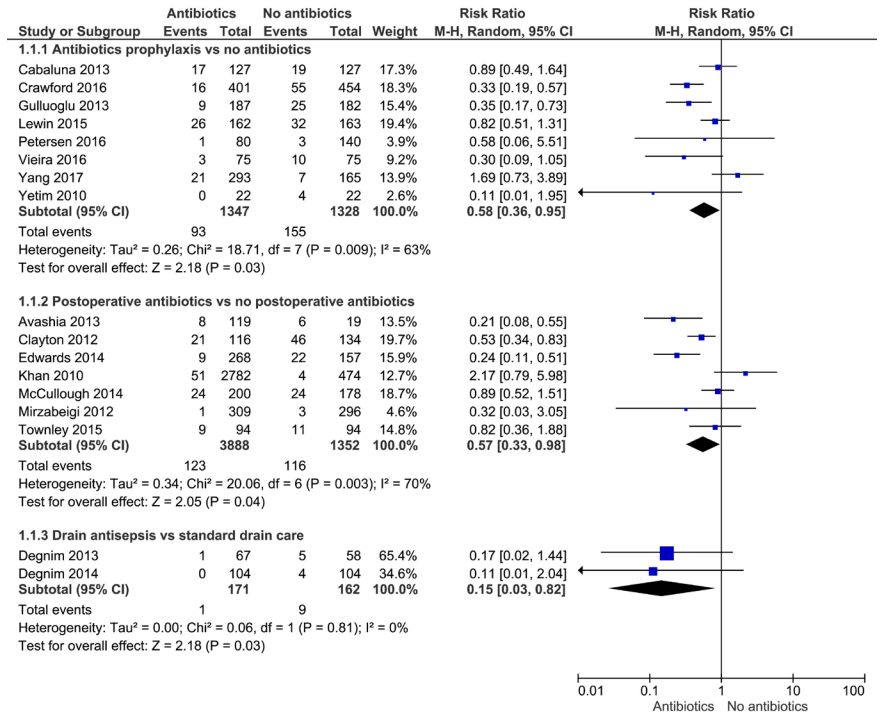

Figure 6. Antibiotics vs none.

4. Discussion

This meta-analysis identifies a number of peri-operative factors associated with adverse wound outcomes. Given the volume of breast surgery, both benign and malignant, reduction of adverse wound outcomes is vital; particularly SSO. The importance of preventing SSO is critical in patients having breast surgery (mastectomy) with reconstruction using alloplastic (implant) material and anticipated to have adjuvant chemotherapy and/or radiation treatment. In patients having SSO, their outcome can be compromised as the timing to proceed with necessary chemotherapy or radiation could be delayed, with potential reduction on survival.

Defining and collecting surgical site infection data is somewhat problematic. There have been many reviews of the nomenclature of wound complications. Terms such as surgical site occurrence (SSO) were introduced in 2010 [90]. Current definitions of SSO are subject to debate in many areas of surgery. The standardized definition of an SSI, developed by the Centres for Disease Control and Prevention (CDC), is an infection occurring in part of the body where surgery took place, including superficial, deep, and organ space infection [5]. It has been suggested that some SSIs are not relevant and in an effort to add more transparency, the term "surgical site occurrences requiring procedural interventions" (SSOPI) has been introduced recently [91]. Another term that has been used is "surgical site event" [92].

Post-operative breast surgery infections even when delayed, or initially thought to be indolent, can be devastating with implant loss or delays in adjuvant treatment. Recently it has been suggested that SSIs following breast cancer surgery decrease oncological survival [3] [93], while others do not support this [94] [95].

Disregarding considerations regarding the reliability of definitions and surveillance, it is clear that understanding risk factors for infection is crucial to preventing SSO and optimising care. The cost of SSI after breast surgery was reported at $4091 by one study [96]. The care bundle is not a novel concept, but it is integral for the provision of a team-based approach to patient care. The risk factors identified by this study were grouped into pre-operative, operative and post-operative, which may aid in a tailored approach to intervention.

Patient factors such as obesity and the degree of obesity, smoking, diabetes, recent surgery, and anaesthetic risk will significantly increase the SSI risk. The Breast Care team needs to consider these factors while initially tailoring an optimal surgical strategy and even consider modifying the use of implant based reconstruction in these high-risk patients.

Neo-adjuvant chemotherapy is increasingly used and is not associated with an increased SSI risk.

5. Conclusion

This meta-analysis has identified significant risk factors for developing breast related adverse surgical site infections. Planned strategy to mitigate against these should be incorporated into Breast Surgery Care Bundles. Current SSO levels in breast surgery are unacceptably high and need to be addressed. Incorporating wound bundles as key reportable performance indicators or as a mandatory field in oncologist registries may encourage their wider adoption. This may help address concerns expressed about the incidence of wound infection mastectomy [15].

Author Contributions

M. S., S. V., and A. J. contributed to the idea conception. S. V., M. G., and A. J.

did the literature search and analysis. S. V., M. S., R. D. and M. V. did the co-writing and editing of the article. S. V., M. G., and A. J. did the statistical analyses and interpretations. M. S., R. D., M.V., S. V., and A. J. did the approval of final article submission.

Ethical Approval

This study was ethically approved by the Galway University Hospitals Research Ethics Committee.

Fund

This study was supported by funding from the School of Medicine, National University of Ireland, Galway; Breast Development Fund Letterkenny; and Donegal Clinical Research Academy (DCRA).

Conflicts of Interest

The authors have no conflicting interests.

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Supplemental Files

Table S1. MINORS grading of studies included in the meta-analysis.

Study ID	*Non-comparative*								*Comparative*				Total Score	Study design
MINORS criteria	*Clearly stated aim*	*Inclusion of consecutive patients*	*Prospective Data Collection*	*Endpoints appropriate to study aim*	*Unbiased assessment of study endpoint*	*Follow-up period appropriate to study aim*	*<5% lost to follow-up*	*Prospective calculation of study size*	*Adequate control group*	*Contemporary groups*	*Baseline equivalence of groups*	*Adequate statistical analyses*		
Quantitative Analysis														
Angarita 2011 [26]	2	2	2	2	0	2	2	1					13/16	Retrospective cohort
Avashia 2013 [27]	2	2	1	2	0	2	2	1					12/16	Retrospective cohort
Bowen 2017 [28]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Cabaluna 2013 [29]	2	2	2	2	2	2	2	2	2	2	2	2	24/24	RCT
Chung 2015 [30]	2	2	1	2	0	2	2	2					13/16	Retrospective cohort
Clayton 2012 [31]	2	2	1	2	0	1	2	2					12/16	Retrospective cohort
Crawford 2016 [32]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Davis 2013 [33]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Decker 2012 [34]	2	2	2	2	0	2	2	2					14/16	Prospective cohort
Degnim 2013 [35]	2	2	2	2	2	2	2	2	2	2	2	2	24/24	RCT
Degnim 2014 [36]	2	2	2	2	2	2	2	2	2	2	2	2	24/24	RCT
Dikmans 2017 [37]	2	2	2	1	2	2	2	2	2	2	2	2	23/24	RCT
Drury 2016 [38]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Edwards 2014 [39]	2	2	2	2	0	1	2	2					13/16	Retrospective cohort
Franchelli 2012 [40]	2	2	1	1	0	2	2	1	2	2	2	0	17/24	RCT
Fraser 2016 [41]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Gao 2010 [42]	2	2	2	2	0	1	2	1					12/16	Retrospective cohort
Gulluoglu 2013 [43]	2	2	2	2	2	2	2	2	2	2	1	2	23/24	RCT
Gust 2013 [44]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort

Continued

Hadad 2017 [45]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Hillam 2017 [46]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Khan 2010 [47]	2	2	2	2	0	0	2	1					11/16	Retrospective cohort
Lewin 2015 [48]	2	2	2	2	1	2	2	2	2	2	2	2	23/24	RCT
Leyngold 2012 [49]	2	2	2	1	0	0	2	2					11/16	Retrospective cohort
Liu 2011 [50]	2	2	2	1	0	2	2	2					13/16	Retrospective cohort
Liu 2012 [51]	2	2	2	2	0	0	2	2					12/16	Retrospective cohort
McCullough 2014 [52]	2	2	2	2	0	1	2	1					12/16	Retrospective cohort
Mirzabeigi 2012 [53]	2	2	2	1	0	2	2	1					12/16	Retrospective cohort
Nelson 2014 [54]	2	2	2	2	0	2	2	1					13/16	Retrospective cohort
Nguyen 2012 [55]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Olsen 2015 [56]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Olsen 2016 [57]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Olsen 2017 [58]	2	2	1	2	0	2	2	1					12/16	Retrospective cohort
Ota 2014 [59]	2	2	2	2	0	2	2	1					13/16	Retrospective cohort
Ota 2016 [60]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Peled 2010 [61]	2	2	2	2	0	2	2	1					13/16	Retrospective cohort
Petersen 2016 [62]	2	2	2	1	0	2	2	1					12/16	Retrospective cohort
Phillips 2013 [63]	2	2	2	2	0	2	2	1	2	2	2	1	20/24	RCT
Phillips 2016 [64]	2	2	2	2	0	2	2	1	2	2	2	1	20/24	RCT
Sinha 2017 [65]	2	2	2	2	0	2	2	2					14/16	Prospective cohort
Sorkin 2017 [66]	2	2	2	2	0	2	1	2					13/16	Prospective cohort
Tanner 2011 [67]	2	2	2	2	0	2	2	2					14/16	Prospective cohort

Continued

Teija-Kaisa 2012 [68]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Townley 2015 [69]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Vardanian 2011 [70]	2	2	2	1	0	2	2	2					13/16	Retrospective cohort
Vieira 2016 [71]	2	2	2	2	2	2	2	1	2	2	2	1	22/24	RCT
Winocour 2015 [72]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Yang 2017 [73]	2	2	2	2	0	0	2	2					12/16	Retrospective cohort
Yetim 2010 [74]	2	2	2	1	0	2	2	1	2	2	2	1	19/24	RCT
Qualitative Analysis														
Chattha 2017 [75]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Cooney 2016 [76]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Cordeiro 2016 [77]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
de Oliveira 2014 [78]	2	2	2	2	2	2	2	2	2	2	2	1	23/24	Non-randomised controlled trial
Dieterich 2013 [79]	2	2	2	2	0	2	2	2					14/16	Prospective cohort
Gil-Londoño 2017 [80]	2	2	2	2	0	2	2	2					14/16	Prospective cohort
Giordano 2013 [81]	2	2	2	1	0	2	2	1					12/16	Retrospective cohort
Golfam 2011 [82]	2	2	2	2	2	2	2	1	2	2	0	1	20/24	RCT
Gülçelık 2017 [83]	2	2	2	2	0	0	2	1					11/16	Retrospective cohort
Mittal 2017 [84]	2	2	2	1	0	2	2	1	2	2	2	1	19/24	RCT
Parikh 2016 [85]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Pellino 2014 [86]	2	2	2	2	0	2	2	1	2	2	2	1	20/24	RCT
Pettke 2016 [87]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Santosa 2016 [88]	2	2	2	2	0	2	2	2					14/16	Retrospective cohort
Williams 2011 [89]	2	2	2	2	2	2	2	2	2	2	2	2	24/24	RCT

Table S2. Characteristics of studies included in the meta-analysis.

https://data.mendeley.com/datasets/g46xn6x9n5/draft?a=b6b121da-b2a7-4b7d-80c7-50dd0f137ffb

Abbreviations

ADM: Acellular Dermal Matrix,
ALND: Axillary Lymph Node Dissection,
AMP: Antimicrobial Prophylaxis,
ASA: American Society of Anesthesiologists Physical Classification System,
BCS: Breast Conserving Surgery,
BMI: Body Mass Index,
BR: Breast Reconstruction,
CDC: Centers for Disease Control and Prevention Guideline for Prevention of Surgical Site Infections,
CI: Confidence Interval,
DCIS: Ductal Carcinoma *in Situ*,
DR: Delayed Reconstruction,
ECOG: Eastern Cooperative Oncology Group performance status,
IBBR: Implant-Based Breast Reconstruction,
IBR: Immediate Breast Reconstruction,
IORT: Intraoperative Radiotherapy,
IR: Immediate Reconstruction,
ITEBR: Immediate Tissue Expander-Based Breast Reconstruction,
MINORS: Methodological Index for Nonrandomised Studies,
MLD: Manual Lymphatic Drainage,
MRM: Modified Radical Mastectomy,
NNIS: National Nosocomial Infection Surveillance,
NPWT: Negative Pressure Wound Therapy,
OR: Odds Ratio,
RCT: Randomised Controlled Trial,
PI: Permanent Implant,
RR: Risk Ratio,
SLNB: Sentinel Lymph Node Biopsy,
SR: Subsequent Reconstruction,
SSI: Surgical Site Infection,
SSO: Surgical Site Occurrence,
TE: Tissue Expander,
TEBR: Tissue Expander-Based Reconstruction,
TM: Total Mastectomy,
TNM: Tumour Node Metastasis classification,
WLE: Wide Local Excision.