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Complications and Thromboembolic Events Associated with Tamoxifen Therapy in Patients with Breast Cancer Undergoing Microvascular Breast Reconstruction: A Systematic Review and Meta-Analysis

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Abstract

Purpose—Tamoxifen therapy is integral in the treatment of patients with hormone receptor-positive breast cancer. However, there is an association between tamoxifen and thromboembolic events. Flap and systemic thromboembolic events have devastating consequences in microvascular breast reconstruction. Currently, there is conflicting data on the association between tamoxifen therapy and thromboembolic complications for patients undergoing microvascular breast reconstruction. The objective of this study is to determine if perioperative tamoxifen therapy modifies the risk of complications and thromboembolic events for patients with breast cancer undergoing microvascular breast reconstruction.

Methods—A comprehensive literature search was performed across 6 databases from January 2003 to February 2016. Pooled estimates and relative risk (RR) were calculated using a random-effects model, confounding was examined with meta-regression, and risk of bias was evaluated. Primary outcomes were thrombotic flap complications and total flap loss. Study quality was assessed using Downs and Black criteria.

Results—Of 95 studies reviewed, 4 studies comprising 1700 patients and 2245 procedures were included for analysis. Compared to non-recipients, patients on tamoxifen were at increased risk of developing thrombotic flap complications (pooled RR: 1.5; 95% CI: 1.14–1.98) and total flap loss

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(pooled RR: 3.35; 95% CI: 0.95–11.91). There was no significant heterogeneity present in either outcome and no evidence of publication bias.

Conclusions—Perioperative tamoxifen therapy may increase the risk of thrombotic flap complications and flap loss for patients with breast cancer undergoing microvascular reconstruction. These findings further the ability of providers to make evidence-based recommendations in the perioperative management of patients with breast cancer.

Keywords

Breast reconstruction; breast cancer; tamoxifen; selective estrogen receptor modulator; thromboembolism

INTRODUCTION

Breast cancer is the most common non-cutaneous malignancy among women in the United States.[1] For women diagnosed with breast cancer, distinct histological and molecular tumor subtypes contribute to different clinical presentations, treatment responses, and prognoses. A significant proportion of women with breast cancer have hormone receptor-positive tumors, subtypes that express estrogen receptors (ER-positive) or progesterone receptors (PR-positive).[2] Systemic hormone therapy reduces recurrence rates, prolongs survival, and lowers mortality for women with hormone receptor-positive breast tumors.[3,4] The most widely used therapy is tamoxifen, a selective estrogen receptor modulator (SERM). Treatment with tamoxifen for 5 years reduces recurrence rates in ER-positive breast cancer by half during treatment and by a third in the subsequent 5 years.[5] Furthermore, tamoxifen treatment reduces breast cancer mortality by nearly a third throughout the first 15 years and has efficacy in reducing the risk of contralateral breast cancer.[5,6]

Despite the efficacy of hormone therapy, there are significant potential adverse effects. Of particular concern, tamoxifen is an independent risk factor for thromboembolic events, a significant contributor to patient morbidity and mortality.[7,8] Breast cancer patients treated with tamoxifen have an estimated 1.5- to 7.1-fold increased risk of thromboembolic events compared to patients not treated with tamoxifen.[7,9,8] In patients undergoing surgical treatment for breast cancer, specifically mastectomy with microvascular breast reconstruction, this increased risk of thromboembolic events may be particularly problematic. There is increasing evidence that microvascular breast reconstruction is associated with improved quality of life and cosmetic outcomes for some patients, when compared to prosthetic reconstruction or mastectomy alone.[10–14] However, patients undergoing microvascular reconstruction have an increased susceptibility for systemic thromboembolic events given the prolonged duration of surgery, hospital length of stay, and period of non-ambulatory time following surgery.[13,15,16,14,17] In addition to systemic events, the hypercoagulable circulatory environment potentiated by tamoxifen may impact the microvascular anastomosis and contribute to thrombotic flap complications, including total flap loss. Therefore, there are concerns that patients on tamoxifen are at an increased risk for thromboembolic and flap complications following microvascular breast reconstruction.

Currently, there is a lack of convincing evidence on the association of tamoxifen therapy and thromboembolic complications for patients undergoing microvascular breast reconstruction as prior reports have produced conflicting results and conclusions.[18–21] Therefore, it is unclear whether tamoxifen cessation prior to reconstruction is warranted, representing a significant limitation in perioperative management. Thus, we undertook this study to determine if perioperative tamoxifen has an effect on complications and thromboembolic events for patients with breast cancer undergoing microvascular reconstruction. Our intention is to provide a qualitative and quantitative summation of current evidence that can lend clarity to this important area of research and guide evidence-based management decisions.

METHODS

The authors followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines throughout this investigation, as recommended by the EQUATOR Network.[22,23] The study research question, search strategy, inclusion and exclusion criteria, outcome measures, protocol for data extraction, and protocol for analyses were determined a priori by the authors.

Study Identification

The published literature was searched using strategies designed by a medical librarian for the concepts of breast cancer, flap or microvascular reconstruction, and hormone therapy including tamoxifen, selective estrogen receptor modulators, and aromatase inhibitors. These strategies were established using a combination of standardized terms and key words, and implemented in Ovid Medline, EMBASE, Scopus, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases. All searches were completed in February 2016. All results were exported to EndNote and the automatic duplicate finder was used to remove duplicate citations. References were then hand-searched and relevant articles retrieved.

Study Selection

All published observational studies and randomized-controlled trials comparing patients undergoing microvascular breast reconstruction on perioperative hormone therapy to patients not on perioperative hormone therapy were eligible for inclusion. Titles and abstracts were screened independently by two reviewers, with discrepancies resolved by discussion. A study was eligible if it included 1) patients with breast cancer undergoing microvascular reconstruction, 2) compared patients on perioperative tamoxifen therapy to those who were not, and 3) listed systemic and/or flap complications including, but not limited to, deep vein thrombosis, pulmonary embolism, partial flap loss, total flap loss, and arterial and/or venous thrombosis. We defined microvascular reconstruction as any procedure involving free flap tissue transfer to the breast that required an anastomosis. Articles in all languages were considered. A study was excluded if 1) subjects were not human, 2) there was no control group or comparison made, or 3) full article text could not be obtained.

Data Extraction and Quality Assessment

Articles that met inclusion criteria underwent independent data extraction by two reviewers using a standardized form. Data extracted included first author, publication year, publication country, journal, demographics, number of patients and flaps, tamoxifen timing and use, flap timing and type, flap and systemic complications, and potential confounders including medical comorbidities, radiation therapy, body-mass index (BMI), age, systemic or intraoperative anticoagulant use, and length of surgery. Primary outcomes were thrombotic flap complications and total flap loss. Secondary outcomes were systemic thromboembolic events, overall flap complications, partial flap loss, and arterial or venous anastomotic complications. Analyses were performed at the flap level as this data was available in each of the included studies. All patients receiving tamoxifen within 28 days of the procedure were considered to be on perioperative therapy. The Downs and Black tool was used by two reviewers to independently assess study quality, and modified to exclude four questions regarding randomized controlled trials.[24] Cutoffs were determined by dividing the possible 23 points into quartiles. A score of 19 or above was designated as high quality, 11–18 indicated moderate quality, 3–10 indicated fair quality, and 2 or below indicated low quality.

Statistical Analysis

Comparisons of the risk of thrombotic flap complication and total flap loss between patients who had perioperative tamoxifen therapy versus those who did not were treated as the primary endpoints of interest, while overall flap complications, partial flap loss, and arterial or venous anastomotic complications were treated as secondary endpoints of interest. As such, relative risks (RR) and 95% confidence intervals were selected as the primary summary measure of association and calculated for each study and endpoint, and weighted averages of the RRs were computed to obtain the pooled estimate as visualized on forest plots.

Statistical heterogeneity across studies was assessed using the chi-square (Cochran Q statistic) test and quantified using the I-square statistic, with $P < 0.1$ indicating significant between-study heterogeneity as opposed to the conventional 0.05 given our small number of studies.[25] Given inevitable heterogeneity between studies, particularly for secondary outcomes, we utilized the more conservative DerSimonian and Laird random-effects model. [26]

For secondary endpoints, there was a need to control for certain confounding variables such as age, BMI, smoking, exposure to radiation therapy, and cardiovascular comorbidities to minimize heterogeneity. These were performed using univariate meta-regressions, and the residual I-square were observed. Publication bias was assessed by visual appraisal of funnel plots. If any asymmetry was observed, the Begg and Harbord tests were performed to determine if “small study effect” was present using two-tailed $P < 0.05$ for significance. [27,28] Statistical Analyses were conducted in STATA 14.1 (StataCorp LP, College Station, TX).

RESULTS

Study selection

The results of the search strategy and selection process are outlined in the PRISMA flow diagram (Fig. 1). Initially, 154 citations were identified. After removal of duplicates, there were 95 unique studies. Abstracts and titles were screened, and 32 were preliminarily determined to meet criteria. Following full review, 4 studies met criteria for data extraction and analysis.[18–21]

Study Characteristics and Quality Assessment

Articles reported data collection for patients undergoing operations between 1993 and 2012, with all articles published after 2012. Characteristics of studies included are listed in Table 1. In total, studies evaluated 1,700 patients and 2,245 microvascular flaps. Of these, 320 patients undergoing 369 flaps were on tamoxifen and 1,380 patients undergoing 1876 flaps were not on tamoxifen. All studies reported the number of flaps experiencing a thrombotic complication, the number of flaps experiencing total flap loss, and the number of flaps with any complication; three of four studies reported the outcomes of partial flap loss, any arterial anastomotic complication, and any venous anastomotic complication. Additionally, all studies included data on relevant covariates of exposure to radiation therapy, BMI, age, tobacco use, and cardiovascular disease. However, data was not always complete: only two studies reported the incidence of systemic thromboembolic complications. Furthermore, three studies did not report data on systemic prophylactic anticoagulation or intraoperative anticoagulation and two studies did not include data on adjuvant chemotherapy. All studies were of moderate quality, with a median score of 14 and a range of 13–18, on modified Downs and Black Quality Assessment Scale. Inter-rater reliability was excellent and indicated substantial agreement (Cohen's Kappa = 0.80).[29]

Clinical Outcomes

Patients undergoing microvascular breast reconstruction on perioperative tamoxifen, when compared to patients not on perioperative tamoxifen, were at an increased risk of developing thrombotic flap complications [pooled RR = 1.5 (95% CI: 1.14, 1.98)] and total flap loss [pooled RR = 3.35 (95% CI = 0.95–11.91)]. No significant heterogeneity was present in the data for the outcome thrombotic flap complications ($\chi^2 = 0.98$, $I^2 = 0.0\%$, $P = 0.807$) (Fig. 2). No evidence of publication bias was present for the outcome thrombotic flap complications on funnel plot visual appraisal and this was confirmed by Begg's and Harbord tests (Fig. 3). For the outcome total flap loss, minor heterogeneity was present; however this did not achieve statistical significance ($I^2 = 33.9\%$, $P = 0.209$) (Fig. 4). No evidence of publication bias was present for the outcome total flap loss as assessed by visual appraisal of funnel plot and confirmed by Begg's and Harbord tests. Sensitivity analyses were separately performed for the outcomes thrombotic flap complications and overall flap loss. Analyses of these outcomes demonstrated no significant change to the overall estimate with serial removal of studies.

The risk of overall flap complications was slightly higher for patients on perioperative tamoxifen [RR = 1.11 (95% CI=0.72, 1.71)], however the data contained significant

heterogeneity ($I^2 = 65.9\%$, $P = 0.032$) (Fig. 5). To explore sources of heterogeneity, a series of univariate regression analyses were performed including relevant clinical covariates of age, BMI, exposure to radiation therapy, current tobacco use, and presence of a cardiovascular comorbidity. After controlling for age, only 28% ($P=0.27$) residual heterogeneity remained (Fig. 6).

DISCUSSION

In this meta-analysis we demonstrated patients with breast cancer on perioperative tamoxifen hormone therapy, compared to patients not on tamoxifen, are at an increased risk for developing thrombotic flap complications and total flap loss when undergoing microvascular breast reconstruction. These findings add clarity to an important question that has previously lacked consensus: should tamoxifen therapy be held perioperatively for patients undergoing postmastectomy microvascular reconstruction? Pooled data from all available reports on the topic suggest temporarily discontinuing tamoxifen may be necessary to minimize the risk of complications.

This study has several implications for clinical practice. Tamoxifen is an integral part of adjuvant systemic treatment for a large proportion of women with breast cancer; therefore, it can be expected that a subset of women presenting for surgical evaluation will be on tamoxifen.[30,14] There is overwhelming evidence tamoxifen reduces mortality, the risk of contralateral cancer, and the risk of recurrence in patients with hormone positive breast cancer.[6,3,2] However, there is also substantial evidence supporting an association between tamoxifen and thromboembolic events.[31,7,9,8] In 1991, the Eastern Cooperative Oncology Group (ECOG) demonstrated patients with breast cancer receiving adjuvant tamoxifen were at an increased risk of venous and arterial thrombosis compared to patients not receiving adjuvant therapy.[32] These results have been corroborated in several landmark studies.[33–36] The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1) and the first International Breast Cancer Intervention Study (IBIS-I) separately confirmed a significantly increased rate of thromboembolic events for patients on tamoxifen compared to placebo.[33,34] Furthermore, the risk is notably higher in the 3 months after initiation of tamoxifen, compared to the 3 months prior to therapy, and this risk may continue to be higher during the first 2 years after exposure.[9,37] This is important because women with tumors amenable to resection will likely undergo operative treatment within this timeframe. Patients undergoing surgical treatment for breast cancer are already considered high-risk for thromboembolic events, with an estimated 10-fold increased event rate; tamoxifen may compound this risk.[8]

In microvascular breast reconstruction, a concerning complication is thrombotic flap events, specifically small-vessel anastomotic thrombosis with clot propagation and embolization. This threatens flap survival by limiting the restoration of circulation, and maintenance of perfusion, in transferred tissue and directly contributes to flap loss. Despite advances in technique, thrombosis rates have not substantially improved and continue to compromise outcomes.[38–40] Flap loss resulting from thrombosis can contribute to additional operations and poor outcomes; therefore, efforts to minimize these complications are essential.[41] Based on overwhelming evidence tamoxifen increases the risk of systemic

thromboembolic events in patients with breast cancer, there have been concerns a potentially prothrombotic environment would similarly increase the risk of flap thrombotic events. In 2012, Kelley, et al. lent this credibility by demonstrating an increased risk of flap loss and a lower rate of flap salvage for patients on tamoxifen undergoing microvascular reconstruction.[19] However, subsequent clinical reports presented conflicting data, leaving a lack of clarity regarding recommendations for perioperative tamoxifen use.[20,21] The perioperative management of women undergoing breast reconstruction requires a coordinated approach to ensure optimal oncological and reconstructive outcomes. Patients interact with multiple providers and a consistent approach based on the best available evidence facilitates comprehensive care.

The results of this meta-analysis support temporary discontinuation of tamoxifen at least 4 weeks, or 28 days, prior to surgical treatment. We considered patients who received tamoxifen within 28 days of surgery to be on tamoxifen to standardize the time to discontinuation of therapy as the existing literature used inconsistent definitions and time frames. The timing of discontinuing therapy is based on the studies included and supported by our understanding of pharmacokinetics and bioavailability of tamoxifen and its metabolites. Tamoxifen is biotransformed by cytochrome P450 enzymes into active metabolites, specifically 4-hydroxy tamoxifen and 4-hydroxy *N*-desmethyl tamoxifen (endoxifen), which have an approximately 30- to 100-fold greater antiestrogenic effect compared to tamoxifen.[42–45] The half-life of these metabolites is estimated at 14 days, compared to approximately 7 days for tamoxifen.[42,46,44,47] Furthermore, studies have confirmed tamoxifen and its metabolites may be retained in tissue and circulation up to 28 days after cessation at concentrations high enough to interfere with estrogen receptor activity.[48,46,49] Additionally, plasma concentrations of tamoxifen metabolites exhibit large interindividual variation in breast cancer patients, providing further support for holding tamoxifen treatment two half-lives to ensure adequate elimination.[50] It is important to acknowledge we were unable to determine optimal timing for restarting tamoxifen postoperatively as studies included did not report this. Our practice is to be conservative and restart tamoxifen at the initial 2-weeks postoperative visit. There are myriad studies supporting that a majority of flap thrombotic events occur within the first three days postoperatively; however, there are some reports of late venous thrombosis in microvascular reconstruction up to 12 days postoperatively.[38,51–54]

The mechanisms of tamoxifen increasing susceptibility to thrombosis are complex and represent a dynamic interplay of events yet to be fully elucidated. Thrombosis is a coordinated response to vascular injury consisting of a platelet plug, a fibrin-based clot, and activation of the inflammatory and repair processes.[55] In microvascular surgery, vessels are deliberately divided and subsequently reanastomosed, creating vessel wall injury, and exposing tissue factor on the subendothelial surface, resulting in the initiation of platelet activation, aggregation, and the coagulation cascade. Tissue factor is a principal initiator of the extrinsic pathway of coagulation, resulting in fibrin production which polymerizes to form a clot and strengthens the initial platelet plug.[41,56] This combination of fibrin production and platelet activation/aggregation are central events in arterial and venous thrombosis by contributing to intimal hyperplasia, smooth muscle cell degeneration, and formation of intraluminal thrombi at the anastomotic site.[41,57–59,40,60] The role of

tamoxifen in increasing platelet activation and aggregation is considered the primary mechanism by which it induces a prothrombotic environment in patients with breast cancer. Recently, investigators demonstrated tamoxifen promotes calcium entry into platelets, which is critical to platelet activation and aggregation, and may lead to prothrombotic platelet phenotypes in breast cancer patients on hormone therapy.[61–65] Furthermore, tamoxifen increases the number of activated-platelet derived, tissue factor-bearing microparticles, which play a role in a variety of thromboembolic pathologies, including atherosclerosis, thrombocytopenia, and thrombosis.[66–69] These mechanisms, combined with the existing thrombogenic environment present in patients with breast cancer, may explain the higher rate of systemic thromboembolic events observed in prior studies and thrombotic microvascular events observed in this meta-analysis.

There are certain limitations to this study that have implications for future research. This meta-analysis included a small sample size of studies. While there is a significant amount of literature on thrombotic complications following microvascular breast reconstruction, few studies report perioperative exposure to hormone therapy. Similar to other meta-analyses, we were limited by data available in the reports included for evaluation. By identifying these gaps in the reported literature, this meta-analysis can serve to improve the quality of future studies on the topic. We were unable to make conclusions regarding the risk of systemic thromboembolic events for patients on tamoxifen as these data were not consistently included in studies. Future studies reporting on systemic thromboembolic events are necessary to further delineate potential risks. Furthermore, there was substantial heterogeneity in regards to the reporting of relevant covariates, making it difficult to determine the impact of these potentially confounding variables. All future studies should report relevant covariates, including adjuvant chemotherapy, exposure to radiation therapy, and systemic prophylactic anticoagulation treatment, so these factors can be controlled for analytically.[70]

CONCLUSIONS

Perioperative tamoxifen therapy modifies the risk of thrombotic flap complications and total flap loss for patients undergoing microvascular breast reconstruction. Based on the results of this meta-analysis, temporarily discontinuing tamoxifen therapy at least 4 weeks prior to operative treatment may minimize the risk of complications. Further high quality studies that report and control for relevant covariates and report both systemic and flap thrombotic events are necessary to expand our understanding of the potential risks of tamoxifen therapy in microvascular breast reconstruction. Ultimately, the findings of this study further the ability of providers to make evidence-based recommendations in the perioperative management of patients with breast cancer.

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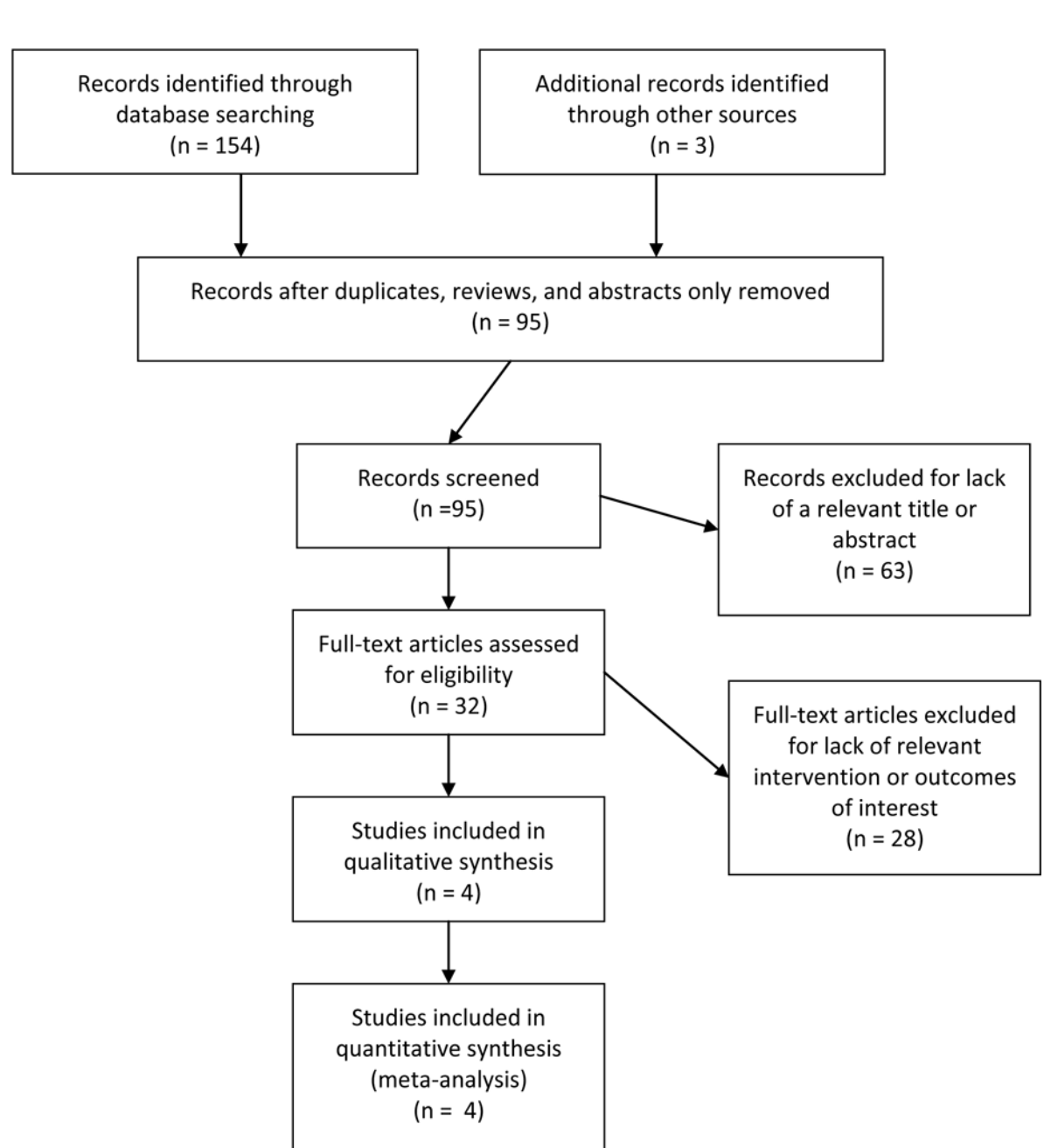


Fig. 1. PRISMA flow diagram of articles screened and selected for meta-analysis.

Identification

Screening

Eligibility

Included

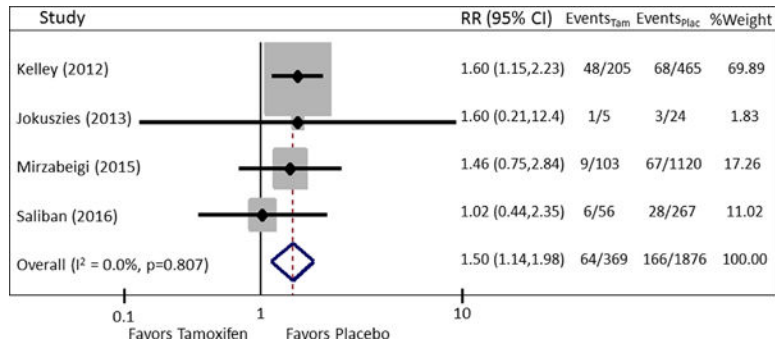


Fig. 2. Forest Plot of pooled RR for the outcome thrombotic flap complications. Pooled RR is 1.50, 95% CI: 1.14 –1.98. No significant heterogeneity is present ($\chi^2 = 0.98$, $I^2 = 0.0\%$, $P = 0.807$).

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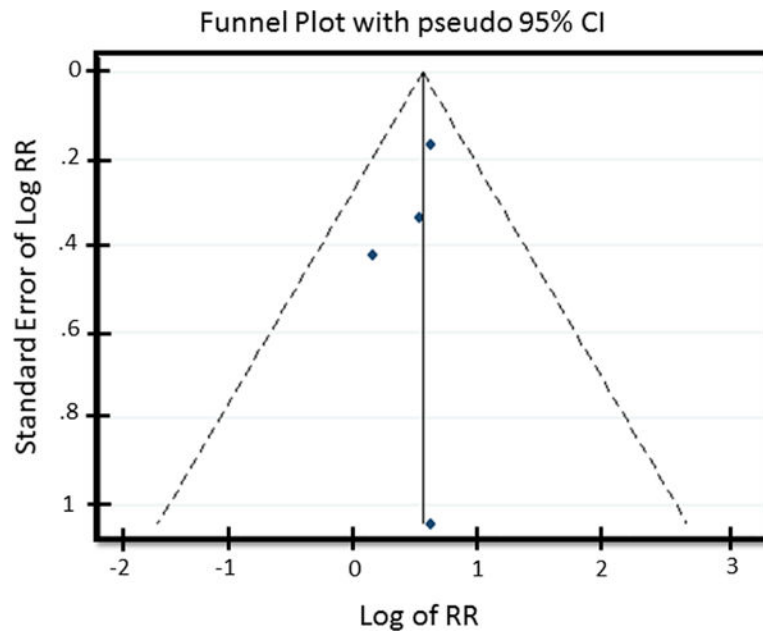


Fig. 3. Funnel Plot assessing publication bias for outcome thrombotic flap complications.

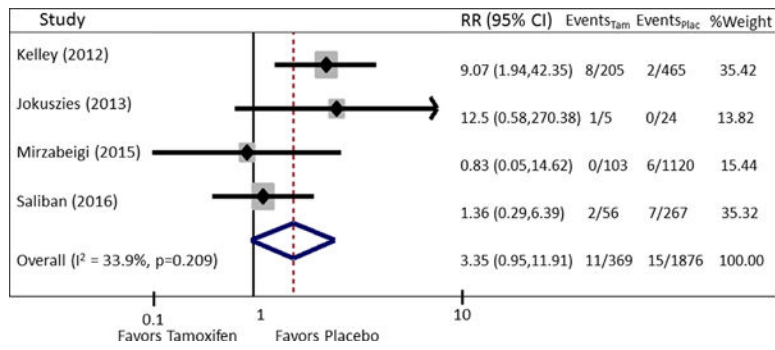


Fig. 4. Forest plot of pooled RR for outcome of total flap loss. Pooled RR is 3.35, 95% CI: 0.95–11.91. Minor heterogeneity is present; however this did not achieve statistical significance (I² = 33.9%, P = 0.209).

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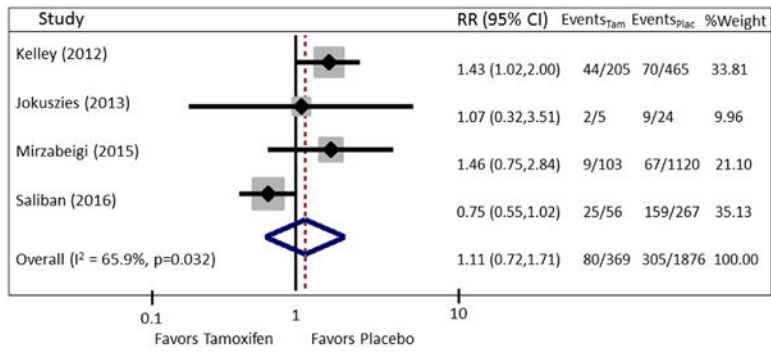


Fig. 5. Forest plot of pooled RR for outcome of overall flap complications. Pooled RR is 1.11, 95% CI: 0.72–1.71. There is significant heterogeneity ($I^2 = 65.9\%$, $P = 0.032$) present.

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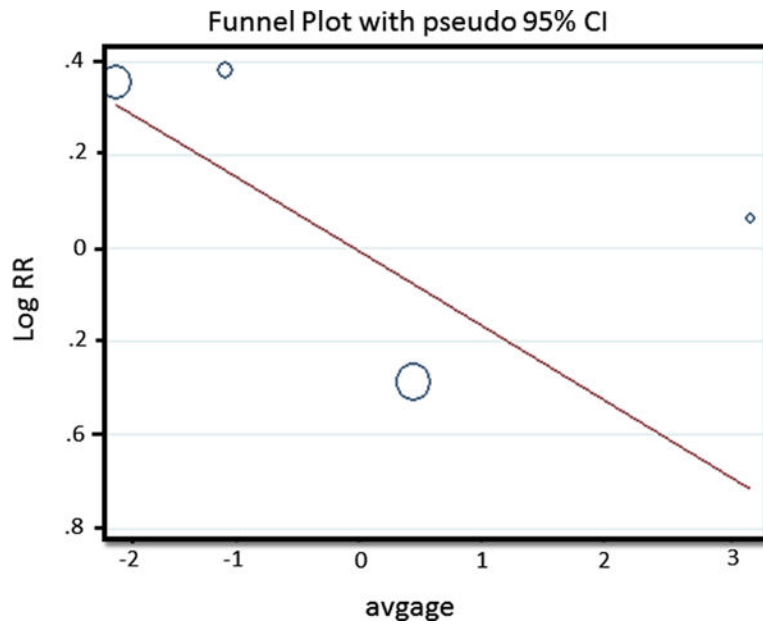


Fig. 6. Regression analysis of the impact of age on overall flap complications. Residual I^2 after adjusting for age = 28.1%

Characteristics of Studies Comparing Breast Reconstruction Outcomes for Patients on Tamoxifen versus Patients not on Tamoxifen

Table 1

Author	Location	Year	Study Design	N: Patients on Tamoxifen	N: Flaps performed in patients on tamoxifen	N: Patients not on tamoxifen	N: Flaps performed in patients not on tamoxifen	Quality Rating*
Kelley[19]	USA	2012	Cohort	205	205	465	465	Moderate
Jokuszies[18]	Germany	2013	Cohort	5	5	24	24	Moderate
Mirzabegi[20]	USA	2015	Cohort	67	103	706	1120	Moderate
Saitban[21]	USA	2016	Cohort	43	56	185	267	Moderate

* See Methods section, Data Extraction and Quality Assessment subsection, for details on determination of Quality Rating.