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Review Article

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Risk Factors Associated with Breast Cancer-Related Lymphedema: A Systematic Review and Meta-Analysis

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Abstract

Background: *Lymphedema is a chronic, progressive condition that commonly occurs after treatment for breast cancer. Therefore, this study aimed to assess the incidence and risk factors of breast cancer-related lymphedema (BCRL).*

Methods: *PubMed, Web of Science, Embase, MEDLINE, CNKl, Wang Fang DATA, Vip Database, and SinoMed were searched from January 2000 to January 2022. Risk of bias was assessed using the Newcastle-Ottawa Scale. Estimates of pooled incidence and risk factors estimates were calculated with 95% confidence intervals (CI), with sub-group analyses according to country, study design, population characteristics, the definition of lymphedema, and risk of bias. Heterogeneity was measured using I2 and publication bias was analyzed by funnel plot.*

Results: *34 studies comprising 23,988 participants were included in this study, with a follow-up period ranging from 1 to 10.2 years. The estimated pooled cumulative incidence at 1,2,3,5 years post-operative for patients respectively was 20%, 17%, 18% and 23%. Factors like: stage III cancer (RR: 1.34; 95% Cl: 1.17-1.52), age≥50 (RR: 1.47; 95% Cl: 1.23-1.76), BMI ≥25 (RR: 2.09; 95% Cl: 1.85-2.36), ALND (RR: 2.72; 95% Cl: 1.89-3.92), axillary radiotherapy (RR: 2.19; 95% Cl: 1.64-2.92), Neo-adjuvant chemotherapy (RR: 1.61; 95% Cl: 1.08-2.39), adjuvant taxane-based chemotherapy (RR: 1.65; 95% Cl: 1.25-2.19) and postoperative wound complications (RR: 1.66; 95% Cl: 1.13- 2.43) were significantly associated with BCRL.*

Conclusions: *Our analyses suggest that BCRL risk is significantly associated with cancer stage, age, BMI, ALND, radiotherapy, chemotherapy, and postoperative wound complications.*

Keywords: Breast Cancer, Lymphedema, Risk Factors, Predictors, Incidence, Systematic Review

Introduction

Female breast cancer had surpassed lung cancer as the most commonly diagnosed in the world [1, 2]. Breast cancer-related lymphedema is a chronic complication that occurs after treatment for breast cancer, which is sustainable and vicious circle. The incidence of BCRL varies with study designs or timing, method of assessment, ranged from 41.1% to 49% within 10 years after operation, and 57.8 % – 65.3 % of BCRL occurred within 3 years after operation [3-5]. The upper limb lymphedema can not only affect patients' psychology with morphological changes but also accompanied by a series of symptoms, bringing life and work problems to patients [6, 7]. At present, the treatment of chronic lymphedema is mainly to relieve symptoms, and the effect is not durable. Several studies have found that early detection and treatment of BCRL can prevent its progression and decrease the need for costly treatments [8, 9]. Therefore, it is increasingly urgency to recognize and prevent BCRL early.

BCRL has different risk factors, including demographic, physiological and biochemical, and treatment-related factors. Most studies, axillary radiotherapy and axillary lymph node dissection are considered to be the most important risk factors for lymphedema resulting from disruption of the lymphatic system [10, 11]. The impact of BMI on BCRL has been confirmed in various studies, such as risk factors, model studies, and meta-analysis. Related studies have found that the occurrence of BCRL is closely related to serum phospholipid fatty acid composition and phenotype [12, 13]. The effect of chemotherapy on BCRL is controversial. Nor-

man et al. found the lowest incidence occurs after SLNB and no chemotherapy [14]. But the discussion in the study of Tsai et al. that chemotherapy was not the direct cause of BCRL, and breast cancer patients receiving chemotherapy were more likely to receive invasive surgery and postoperative radiotherapy. Other risk factors such as edema within 3 months, lymphatic obstruction, inflammation, immune response, complement activation, wound healing and fibrosis will affect the occurrence and development of lymphedema [15-17].

Previous studies mainly included all observational studies for systematic reviews of the estimated risk factors of BCRL. Lin et al. assessed the association between loco-regional therapy and BCRL, Torgbenu et al. estimated the risk factors in low and middle-income countries for secondary lymphedema related to cancer [10, 18]. And several studies have focused on the association between individual factors and lymphedema. In addition, there are many controversial risk factors and different research results. Moreover, the study design is crucial to the exploration of causality. Therefore, we aimed to systematically review and calculate RRs for the identification of the most important risk factors and incidence of BCRL in cohort studies. The results of this study are expected to provide health-related education and care to health professionals.

Methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and registered on the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO/; protocol CRD42021266474) [19, 20]. The screening, data extraction, and methodological quality appraisal of eligible studies were independently performed by the first author (QL, YMD). And any conflicts are resolved by an independent reviewer (TY).

Literature Search Strategy

The PubMed, Web of Science, Embase, MEDLINE, CNKl, Wang Fang DATA, Vip Database, and SinoMed were searched for studies published on 1 January 2000 and updated on 15 January 2022. The retrieval is carried out by the combination of keywords and free words (Supplemental file1). Keywords were adjusted across databases. More details of the search strategy are given in supplemental file1. And it will be re-run before the final analysis.

Selection Criteria

The first author (QL) assessed titles and abstracts, then 10% of articles were independently screened by a second author (YMD), with screening continued by TY alone after finding 100% agreement. Full-text articles assessed by two authors (QL, YMD) independently selected studies based on the following inclusion criteria:

1. The subjects of the study were breast cancer patients over 18 years old,
2. The study design type was a cohort study, including prospective cohort study and retrospective cohort study,
3. The outcome indicators were dichotomous variables,
4. The study provided OR/RR/HR value of predictive factor analysis and the 95% confidence interval may be able to obtain the above data through data calculation.

Criterion (2) is due to the strong ability of cohort studies to confirm causality; Criteria (3) and (4) are formulated according to the needs of research synthesis and analysis methods.

The Exclusion Criteria Were as Follows:

1. No clear diagnostic criteria for BCRL,
2. Studies with duplicate published data, incomplete reporting, or serious missing.

Criteria (1) and (2) are both to reduce bias, and lack of clear diagnostic criteria for BCRL will cause information bias, etc.; there may be publication bias in data duplication, incomplete reporting, or serious deletion.

Data Extraction and Quality Assessment

According to inclusion and exclusion criteria, the literature was screened in the order of reading the title, abstract, and full text of the literature, and the exclusions were recorded. The included literature was extracted after the literature quality evaluation. Reference STROBE and related systematic reviews to develop the information extraction table for included literature, the extracted content includes first author, publication year, country or region, study population, study type, study time, sample size, BCRL incidence, follow-up time, involved risk factors, adjusted OR/RR/HR and 95% CI and outcome measures [21, 22]. Data extraction and quality assessment were independently completed by two researchers (QL, YMD) trained in evidence-based courses, and inconsistencies were resolved by discussion or a third author (TY).

We assessed the methodological quality of included cohort studies using the Newcastle-Ottawa Scale (NOS), which includes 3 aspects of selection, comparability, and outcome [23]. It is divided into 8 items and 9 items that can be marked with stars. All items of the tool were filled in for each included study with the response of yes or no, the total score is 9 points. For this scale, there is no clear threshold for distinguishing the evaluation quality, and the high quality is defined as more than 4-8 points [24]. In this paper, the high quality is defined as more than 6 points.

Statistical Analysis

The literature information collecting, extraction, and management were done using Excel 2019 and Endnote X9, and RevMan 5.3.3 was used for data analysis. The OR/RR/HR values and 95 % CI of each risk factor were extracted for combined analysis [25]. To unify the expression, the following values were expressed as RR values, and the OR/HR value was transformed. The pooled RR was considered significant if the 95% CI did not include 1.0, with a p-value < 0.05 (two-sided). Heterogeneity between studies was investigated using I^2, if $I2 \geq 50$ %, the heterogeneity source of

subgroup analysis is considered [26]. If there is still unacceptable heterogeneity among studies after subgroup analysis, the random effect model is adopted. Moreover, sensitivity analysis was conducted by removing each study individually to evaluate the quality and consistency of the results. The sensitivity analysis was not examined in only two studies. This study analyzed the publication bias of funnel plots for 5 or more included studies.

Results

Study Identification

We initially identified 6260 records, and 3728 studies remained after duplicates were removed. After screening the titles and abstracts, 216 studies were selected for full-text review. The remaining 34 studies were included in the current meta-analysis. The literature search process is summarized in Figure 1.

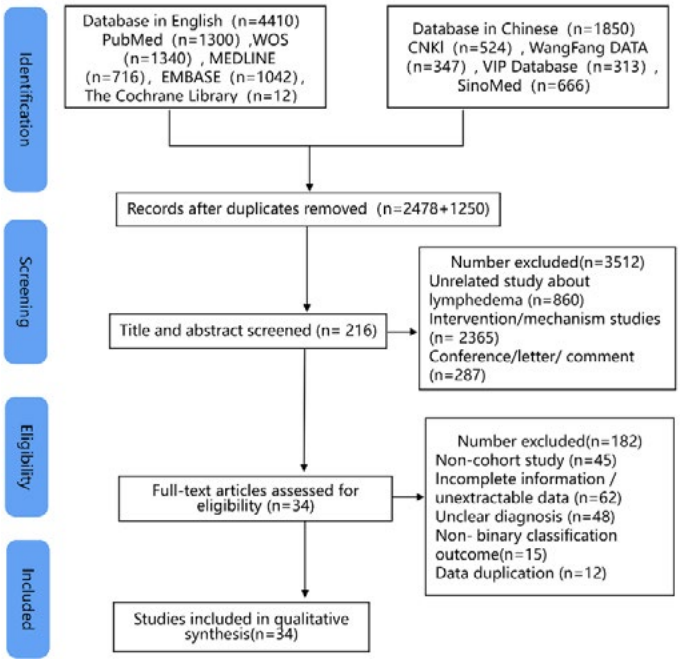


Figure 1: Flow chart of literature search and article selection process

Study Characteristics

The study included 23988 breast cancer patients from 9 countries (Table 1). 22 studies were reported in English and 11 were reported in Chinese. Of the 34 studies, most were prospective cohorts (n=20, 58.82%), 12 were retrospective cohort studies, and 2 studies were unclear in study design. Methods used for measuring and defining lymphedema included: circumference measurement (n = 22, 64.71%), volume measurement (n =7, 20.59%), patient self-report by Norman score (n=1), combine Norman and circumference (n = 3), and BIS (n = 1) [27-60]. All studies reported incidence. 13 studies reported the risk of developing BCRL who underwent breast cancer surgery and ALND, and 3 studies involve all patients who received radiotherapy. Variations in the timing or the onset of BCRL ranged from 12 months to over 10 years postoperative and treatment.

Table 1: Studies Characteristics

Study	Country	study design	Sample size	population characteristics	Measurement method	Lymphedema definition
Byun,2021	Korea	retrospective	5549	underwent primary breast surgery	circumference	≥2 cm difference
Chen,2012	China	prospective	247	underwent ALND	circumference	> 0 cm difference
Cihangir,2004	Turkey	NA	240	all patients underwent MRM and ALND	circumference	≥2 cm difference
Feng,2018	China	retrospective	464	underwent ALND	circumference	≥2 cm difference
Gross,2018	USA	prospective	492	underwent RNI	circumference	≥2.5cm or ≥2cm difference on at least 2 visits
Herd-Smith,2001	Italy	NA	1278	unilateral invasive carcinomas and underwent ALND	circumference	> 5% differences
Hu,2016	China	retrospective	281	underwent unilateral breast cancer surgery	Norman; circumference	Norman;
≥2 cm difference						
Huang,2011	China	retrospective	408	underwent unilateral breast cancer surgery	circumference	≥2 cm difference
Huang,2012	China	prospective	126	received radical mastectomy and ALND	circumference	≥ 2 cm difference
Jammall,2013	USA	prospective	787	underwent treatment for primary breast cancer	volume	RVC≥10 %
Jung,2014	Korea	retrospective	867	underwent curative breast surgery including unilateral ALND	circumference	> 5% differences
Kilbreath,2016	Australia	prospective	450	diagnosed with breast cancer	BIS	exceeded the normative-based, dominance-controlled thresholds, or increased by at least 0.1
Kim,2015	Korea	prospective	313	After NCT	circumference	> 5% differences
Kim,2016	Korea	retrospective	1073	underwent curative breast surgery with ALND	circumference	> 5% differences
Li,2017	China	prospective	409	underwent breast cancer surgery and ALND	volume	> 200 mL differences
Lin,2020	China	retrospective	305	underwent ALND	circumference	≥2 cm difference
Liu,2016	China	prospective	141	underwent unilateral breast cancer surgery	Norman; circumference	Norman ； > 2 cm difference
McDuff, 2019	USA	prospective	2266	received surgery for unilateral or bilateral breast cancer	volume	10% relative arm volume increase arising >3 months postoperatively

Monleon,2015	Spain	retrospective	371	diagnosed for primary breast cancer	circumference	≥2 cm difference
Norman,2010	USA	prospective	631	diagnosed for primary breast cancer	Norman	degree score was >0
Rastogi,2018	India	prospective	100	underwent MRM along with ALND followed by adjuvant radiotherapy.	circumference	≥2 cm difference
Ribeiro,2017	Brazil	prospective	964	undergoing ALND	volume	> 200 mL differences
Roberts2021	USA	prospective	1161	underwent unilateral breast cancer surgery	volume	RVC ≥ 10% occurring ≥ 3 months
Swaroop,2015	USA	prospective	1121	unilateral breast cancer	volume	RVC ≥ 10 % measured at least 3 months after surgery
Wang,2016	China	prospective	358	diagnosed with breast cancer and underwent ALND	circumference	≥2 cm difference
Wang,2018	China	prospective	61	underwent ALND and ARM	circumference	> 0 cm difference
Warren,2014	USA	prospective	1476	underwent unilateral and bilateral breast surgery	volume	10% arm volume
Yang,2019	China	retrospective	383	underwent MRM	circumference	≥2 cm difference
Yuan,2021	China	prospective	312	underwent ALND and ICG injection	circumference	> 0 cm difference
Zhang,2017	China	retrospective	103	underwent NCT	circumference	≥2 cm difference
Zhang,2018	China	prospective	197	underwent MRM and radiotherapy	circumference	≥2 cm difference
Zheng,2015	China	retrospective	348	underwent MRM	circumference	≥2 cm difference
Zhu,2017	China	retrospective	319	primary breast cancer	circumference	increase was at least 5%
Zou,2018	China	prospective	387	primary breast cancer	Norman; circumference	Norman; ≥2 cm difference

ALND axillary lymph node dissection, MRM modified radical mastectomy, RVC relative volume change, NCT neoadjuvant chemotherapy, ARM axillary reverse mapping, ICG Indocyanine Green, NA not applicable.

Of 34 studies, the reported incidence of BCRL ranged from 5% to 42.9% between 12 months and 10 years (Table 2). The cumulative incidence in the most of studies was at 1 year, 2 years, 3 years, or 5 years. The independent risk factors in the studies included: age, BMI, ALND, radiotherapy, neo-adjuvant chemotherapy, etc.

Table 2: Studies reporting lymphedema incidence and risk factors

Study	Mean/Median Follow-up	incidence	Risk factors
Byun,2021	60.1(12.0–140.2) months	2years:9.0%;3 years:10.5%;5 years:11.9%	BMI, number of dissected nodes, taxane-based chemotherapy, extent of surgery, RT
Chen,2012	8~30months	19.9%	age, BMI, ALND, radiotherapy, postoperative complications
Cihangir,2004	30(18~43) months	28%	BMI, Axillary radiotherapy
Feng,2018	24months	23.28%	BMI, radiotherapy

Gross,2018	5.5(3.6-7.6) years	2 years:23.5%;5 years:31.8%	age, BMI, Number of lymph nodes removed, Radiation
Herd-Smith,2001	56 months	15.9%	radiotherapy, the number of lymph nodes removed
Hu,2016	41(36~48) months	Norman :31.7%; circumference :27.0%	radiotherapy, BMI, hypertension, ALND
Huang,2011	3year	24.0%	BMI, ALND, radiotherapy,
Huang,2012	18(13~24) months	42.9%	BMI, radiotherapy
Jammall,o2013	27(6–68) months	5 %	BMI, RLNR, ALND
Jung,2014	5.1(3.0–9.1) years	LE event:42.2 %;persistent LE:28.7 %	advanced stage, N-ALNs, NAC, breast RT with SCRT, taxane
Kilbreath,2016	18 months	10.2%	arm swelling at 6-months: arm swelling within 4 weeks of surgery, taxane-based chemotherapy, BMI; arm swelling at 12-months: arm swelling at POST, high body weight, taxane-based chemotherapy, high MET-min/ week
Kim,2015	5.6(3.0~9.1) years	59%	age, N-ALNs
Kim,2016	5.1(3.0~8.7) years.	25.3%	Stage (III), chemotherapy with taxane, breast RT with SCRT
Li,2017	68(60~83) months	22.3%	BMI, Neoadjuvant chemotherapy, ALND, Radiation therapy
Lin,2020	27(1~36) months	5.9%	ALND III, Axillary radiotherapy, BMI, diabetes
Liu,2016	24months	Norman :1year:24.8%;1.5year: 28.4%;2year:30.5%;circumference :1year:20.6%;1.5year: 27.0%;2year:27.7%	ALND, radiotherapy, MRM, number of removed axillary lymph nodes
McDuff, 2019	4 years	2years: 7.1%; 5years:13.7%	BMI, ALND, RLNR
Monleon,2015	24.4(0.7–75.6) months	124 (33.4%)	ALND
Norman,2010	5 years	27.7%	ALND, chemotherapy
Rastogi,2018	24(16–30) months	13%	BMI, N-LNs dissected, nodal ratio, RLNR
Ribeiro,2017	10 years	2 years:13.5%, 5 years:30.2%,10 years:41.1%	radiotherapy, obese, seroma, chemotherapy infusion in the affected limb, advanced disease staging
Roberts2021	49.1 months	7.90%	BMI, ALND, RLNR
Swaroop,2015	39.7(7.7–103.3) months	16.37 %	Age, ALND, Docetaxel
Wang,2016	12mouths	31.84%	hypertension, dominant arm, ALND, Radiotherapy, Surgical infection /seroma /early edema
Wang,2018	12 months	42.9%	age, BMI
Warren,2014	25.4(3.4-82.6) months	24 months:6.8%,60 months:13.7%	RLNR, ALND, No. of LNs removed, BMI,10% swelling ≤3 months postoperatively
Yang,2019	3years	1year:7.57%;2year:15.67%; 3year:18.53%	radiotherapy, postoperative weight gain, number of lymph node dissection, and knowledge of lymphedema

Yuan,2021	15(12~19) months	14.4%	BMI, taxane, radiotherapy, and proportion of arm lymph flow above the level of the axillary vein
Zhang,2017	4.5(2.0~7.5) years	39.8%	N-ALNs, neo-adjuvant chemotherapy
Zhang,2018	12 months	19.3%	total number of dissected lymph node
Zheng,2015	27(1~96) months	1years:8.4%; 3years:20.9%; 5years:25.3%	BMI, ALND, Axillary radiotherapy
Zhu,2017	2.81 years	27.59%	N-ALNs of ≥10, MRM, RLNR, Docetaxel therapy
Zou,2018	2 years	Norman :32.5%; circumference :29.4%	ALND, radiotherapy, MRM, number of positive lymph nodes, BMI
BMI body mass index, ALND axillary lymph node dissection, RLNR regional lymph node radiation, N-ALNs the number of axillary lymph nodes, NAC neoadjuvant chemotherapy, breast RT with SCRT, MRM modified radical mastectomy, LN lymph node.			

Quality Assessment

The methodological quality of the 34 studies included in this review was judged to be of high quality, t with the scores for all study quality of more than 6 (Figure 2). the median NOS score for study quality was 7, ranging from 6 to 8. The high risk of bias from item4(n=16,47.06%), item6 (n=23, 67.65%), item7(n=10, 29.41%) item8(n=17,50%), respectively the exclusion of patients who had developed lymphedema at the start of the study was not stated, the assessment of the results was not described in detail, the follow-up period was not long enough, i.e., less than 3 years, and the adequacy of the cohort follow-up was not described.

Figure 2: Risk of bias assessment with NOS. NOS questions item1: Representativeness of the exposed cohort. Item2: Selection of the non-exposed cohort. item3: Ascertainment of exposure. Item4: Demonstration that outcome of interest was not present at start of study. item5: Comparability of cohorts on the basis of the design or analysis. item6: Assessment of outcome. item7: Was follow-up long enough for outcomes to occur. item8: Adequacy of follow up of cohorts.

Incidence of Lymphedema Following Breast Cancer Treatment

In this systematic review and meta-analysis, the estimated pooled cumulative incidence at 1-year post-operative for patients was ranging from 8% to 29%; the estimated pooled cumulative incidence at 18 months was ranging from 14% to 43%; the estimated pooled cumulative incidence at 2 years was ranging from 9% to 24%; 3 years was 21% (95% CI 19-23, I^2 = 44%, n =3 studies) on Chinese and 5 years was ranging from 14% to 27% (Table 3).

Table 3: The estimated pooled cumulative BCRL incidence

Analysis		Number of study	Meta-analysis		
			RR	95 % CI	I^2
cumulative incidence at 1 years					
Main analysis (all in Chinese)		7	0.20	[0.12, 0.27]	95%
study design	prospective	5	0.25	[0.16, 0.33]	91%
	retrospective	2	0.08	[0.06, 0.10]	0%
population characteristics	All patients undergoing ALND	3	0.29	[0.14, 0.44]	95%
	primary breast cancer	3	0.11	[0.06, 0.16]	84%
	underwent MRM and radiotherapy	1	0.19	[0.14, 0.25]	-
LE definition	≥2 cm difference	5	0.17	[0.09, 0.26]	96%
methodological quality	6	2	0.31	[0.09, 0.53]	90%
	7	2	0.23	[0.06, 0.40]	97%
	8	3	0.11	[0.06, 0.17]	86%
cumulative incidence at 18 months					
Main analysis (all in prospective)		4	0.21	[0.11, 0.30]	96%
population characteristics	undergoing MRM and ALND	1	0.43	[0.34, 0.52]	-
	primary breast cancer	3	0.14	[0.07, 0.20]	92%
LE definition	≥2 cm difference	2	0.35	[0.19, 0.50]	87%
cumulative incidence at 2 years					
Main analysis		13	0.17	[0.13, 0.20]	97%
Country	China	4	0.24	[0.17, 0.30]	88%
	USA	5	0.11	[0.07, 0.16]	97%
study design	prospective	9	0.15	[0.11, 0.19]	97%
	retrospective	4	0.20	[0.10, 0.31]	98%
population characteristics	All patients undergoing ALND	2	0.18	[0.09, 0.28]	95%
	diagnosed for primary breast cancer	9	0.16	[0.12, 0.19]	97%
	Underwent adjuvant radiotherapy.	2	0.19	[0.08, 0.29]	86%
LE definition	≥2 cm difference	7	0.23	[0.15, 0.31]	98%
	RVC ≥ 10%	4	0.09	[0.05, 0.12]	96%
methodological quality	6	5	0.26	[0.19, 0.32]	86%
	7	4	0.09	[0.05, 0.12]	96%
	8	4	0.15	[0.10, 0.21]	97%
cumulative incidence at 3 years					
Main analysis		4	0.18	[0.11, 0.26]	96%
Country	China	3	0.21	[0.19, 0.23]	44%
	Korea	1	0.10	[0.10, 0.11]	-
methodological quality	8	3	0.18	[0.09, 0.26]	96%
cumulative incidence at 5 years					

Main analysis		10	0.23	[0.18, 0.28]	98%
Country	Korea	3	0.22	[0.10, 0.34]	99%
	China	2	0.24	[0.21, 0.27]	0%
	USA	4	0.21	[0.14, 0.29]	97%
study design	prospective	6	0.23	[0.17, 0.30]	98%
	retrospective	4	0.23	[0.13, 0.33]	99%
population characteristics	All patients undergoing ALND	4	0.27	[0.24, 0.30]	76%
	diagnosed for primary breast cancer	5	0.18	[0.14, 0.22]	96%
LE definition	≥2 cm difference	2	0.18	[0.05, 0.32]	97%
	> 5% differences	2	0.27	[0.24, 0.30]	64%
	volume > 200mL differences	2	0.26	[0.19, 0.34]	90%
	10% arm volume	2	0.14	[0.13, 0.15]	0%
methodological quality	7	3	0.21	[0.14, 0.28]	98%
	8	5	0.24	[0.14, 0.34]	98%

Adjusted Risk Factors of lymphedema following breast cancer treatment

10 potential risk factors for BCRL amongst breast cancer patients were evaluated in the present meta-analysis. Meta-analysis after converting OR/HR values to RR values, Cancer stage, surgery method, age, BMI, Lymph node related, radiotherapy, chemotherapy, chemotherapy, postoperative wound complications, and diabetes were associated with an increased risk of BCRL.

sTable 1: Sensitivity analysis: Risk Ratio for Breast cancer-related lymphedema of modified radical mastectomy versus breast-conserving surgery.

Study excluded	Pooled effect		I-squared (%)	I-sq. P-value
	RR	95% CI		
Kim2015	1.40	[0.94, 2.09]	71	0.009
McDuff 2019	1.51	[1.09, 2.10]	64	0.03
Norman2010	1.49	[1.02, 2.16]	66	0.02
Rastogi2018	1.29	[0.94, 1.78]	60	0.04
Roberts2021	1.49	[1.05, 2.11]	67	0.02
Zhu2017	1.27	[1.05, 1.53]	46	0.11
* if I2 ≥ 50 %, the heterogeneity source of subgroup analysis is considered and estimated by random effect model.				

The stage at diagnosis and type of surgery

Advanced stage at diagnosis (III) (RR: 1.34; 95% Cl: 1.17-1.52; I^2=0%) were more susceptible to BCRL than patients with stage I or II cancer (Figure 3), modified radical mastectomy (RR: 1.26; 95% Cl: 1.02-1.56; I^2 = 64%, Random) were more susceptible to BCRL than patients with breast-conserving surgery (Figure 4). The sensitivity analysis did influence the results excessively by omitting some studies, which validated the rationality and reliability of the result probably (sTable 1). The funnel plot for modified radical mastectomy showed no sign of publication bias as the observed outcome was evenly distributed around the average (Figure 5).

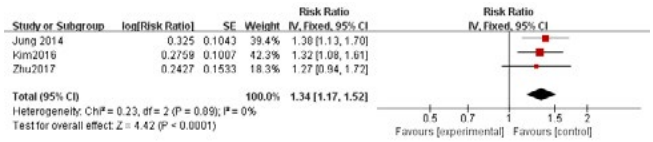


Figure 3: Forest plot of stage III cancer versus stage I or II cancer

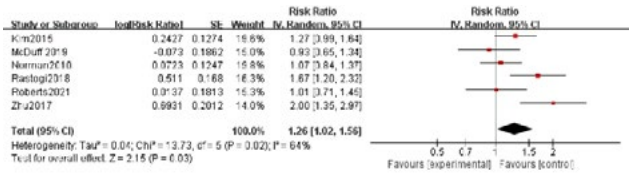


Figure 4: Forest plot of modified radical mastectomy versus breast-conserving surgery

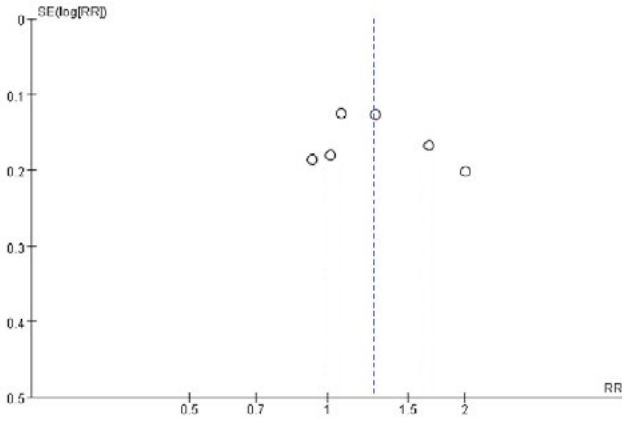
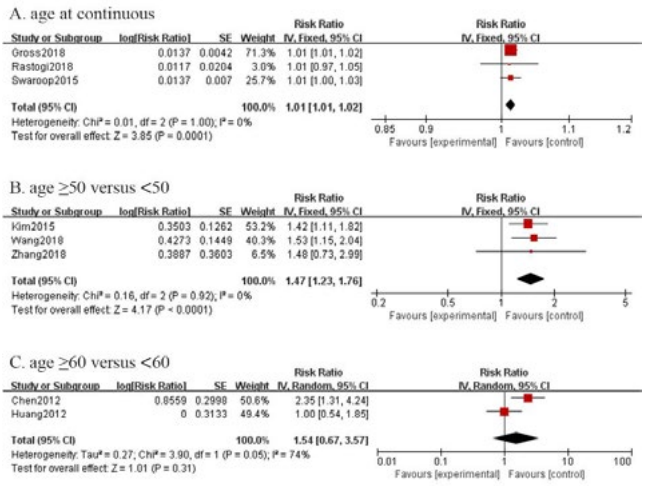


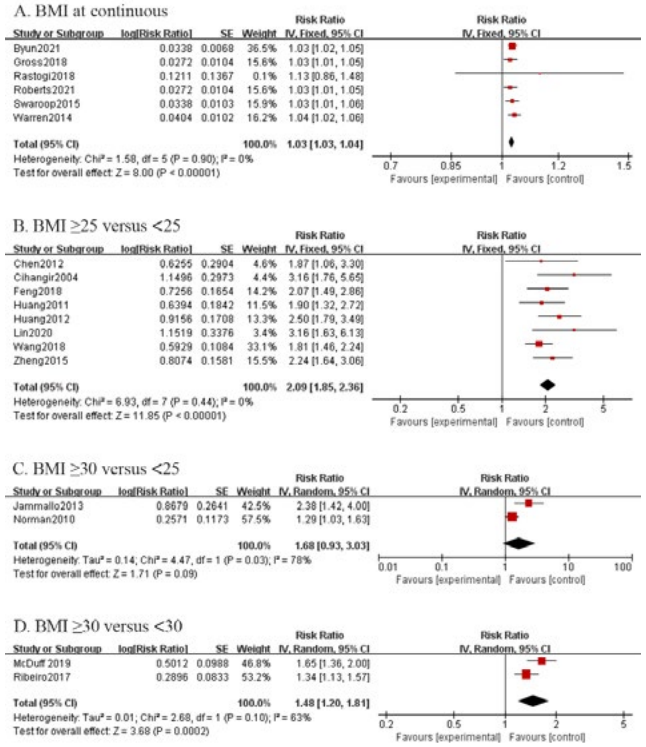
Figure 5: Funnel plot for modified radical mastectomy



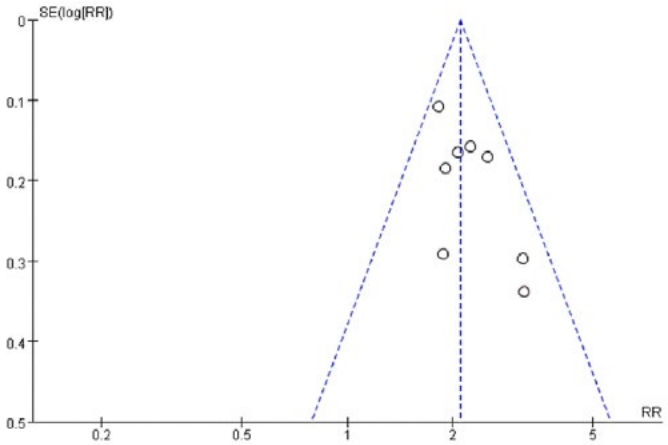
sFigure 1: Risk Ratio for breast cancer related lymphedema risk of age.

Age

Age at continuous (RR: 1.01; 95% Cl: 1.01-1.02; $I^2 = 0\%$; sFig.1-A), age≥50 (RR: 1.47; 95% Cl: 1.23-1.76; $I^2 = 0\%$; sFig.1-B) were associated with an increase in the BCRL rate, and age≥60 wasn't associated with a risk of developing arm lymphedema (RR: 1.54; 95% Cl: 0.67- 3.57; $I^2 = 74\%$, Random; sFigure S1-C) among breast cancer woman compared with age < 60. We evaluated the effect of each study on the pooled results by excluding a single study sequentially, the sensitivity analysis did not influence the results excessively.



sFigure 2: Risk Ratio for breast cancer related lymphedema risk of BMI.

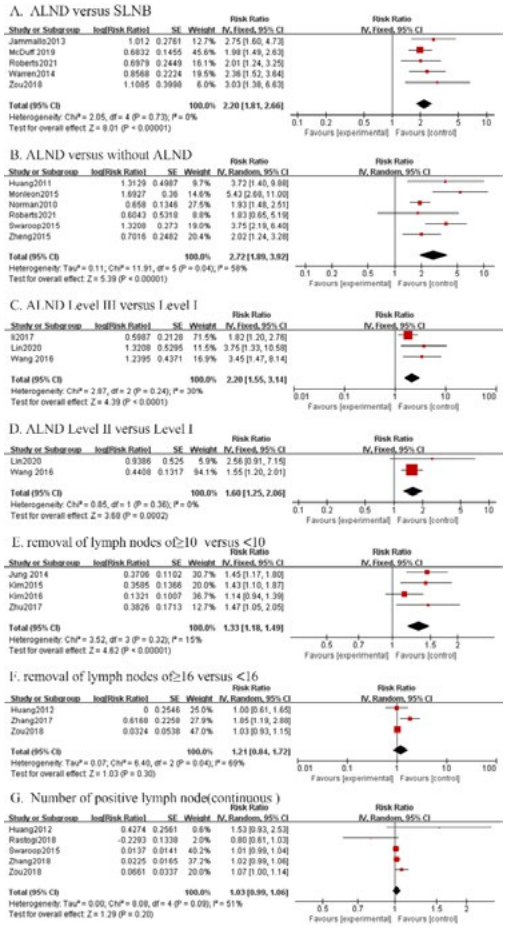


sFigure 3: funnel plot for BMI ≥25 versus BMI < 25

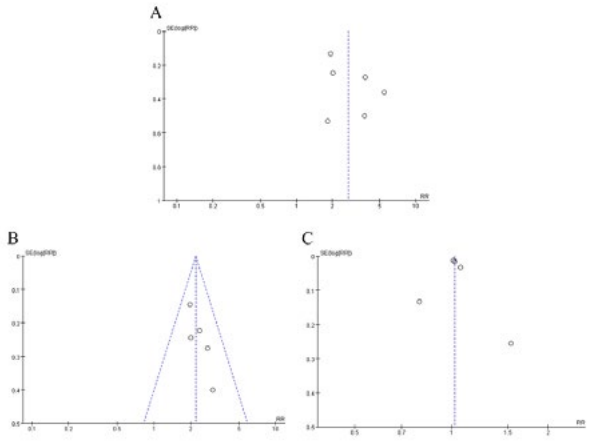
BMI

BMI at continuous (RR: 1.03; 95% Cl: 1.03-1.04; $I^2 = 0\%$; s) (sFigure 2) were associated with an increase in the BCRL rate, Breast cancer patients with BMI ≥25 had higher risk of BCRL compared to participants with BMI < 25 (RR: 2.09; 95% Cl: 1.85-2.36; $I^2 = 0\%$) (sFigure 2B), BMI ≥30 was associated with a risk of developing arm lymphedema compared with BMI < 30, but compared to participants with BMI < 25(RR: 1.48; 95% Cl: 1.20- 1.81; $I^2 = 63\%$, Random) (sFigure 2C), breast patients with BMI ≥30 were

not increase in the BCRL rate (RR: 1.68; 95% Cl: 0.93- 3.03; I^2 = 78%, Random) (sFigure 2D). The sensitivity analysis results showed that the stability of the results had no significant changes. And the funnel plot for BMI ≥25 showed no sign of publication bias as the observed outcome was roughly symmetrical, the funnel plot for BMI at continuous indicates that the publication bias is mild (sFigure 3).



sFigure 4: Risk Ratio for breast cancer related lymphedema risk of the surgery of lymph nodes.



sFigure 5: funnel plot for the surgery of lymph nodes. A ALND vs without ALND, B ALND vs SLNB, C Number of positive lymph node at continuous.

sTable 2: Sensitivity analysis: Risk Ratio for Breast cancer-related lymphedema of ALND versus without ALND.

Study excluded	Pooled effect		I-squared (%)	I-sq. P-value
	RR	95% CI		
Huang2011	2.64	[1.78, 3.93]	64	0.03
Monleon2015	2.20	[1.79, 2.70]	34	0.19
Norman2010	3.02	[2.25, 4.04]	43	0.14
Roberts2021	2.86	[1.91, 4.28]	66	0.02
Swaroop2015	2.52	[1.70, 3.72]	53	0.07
Zheng2015	2.99	[1.87, 4.78]	65	0.02
* if $I^2 \geq 50$ %, the heterogeneity source of subgroup analysis is considered and estimated by random effect model.				

sTable 3: Sensitivity analysis: Risk Ratio for Breast cancer-related lymphedema of the number of positive lymph node.

Study excluded	Pooled effect		I-squared (%)	I-sq. P-value
	RR	95% CI		
Huang2012	1.02	[1.00, 1.04]	46	0.13
Zou2018	1.01	[0.97, 1.06]	51	0.11
Zhang2018	1.03	[0.95, 1.11]	63	0.04
Swaroop2015	1.03	[0.95, 1.11]	60	0.06
Rastogi2018	1.02	[1.00, 1.04]	34	0.21
Zheng2015	2.99	[1.87, 4.78]	65	0.02
* if $I^2 \geq 50$ %, the heterogeneity source of subgroup analysis is considered and estimated by random effect model.				

sTable 5: Sensitivity analysis: Risk Ratio for Breast cancer-related lymphedema of Adjuvant taxane-based chemotherapy versus without Adjuvant taxane-based chemotherapy.

Study excluded	Pooled effect		I-squared (%)	I-sq. P-value
	RR	95% CI		
Byun2021	1.63	[0.99, 2.69]	79	0.009
Jung 2014	1.65	[1.15, 2.36]	79	0.008
Kim2016	1.48	[1.11, 1.97]	63	0.07
Swaroop2015	1.76	[1.56, 1.99]	38	0.20
* if $I^2 \geq 50$ %, the heterogeneity source of subgroup analysis is considered and estimated by random effect model.				

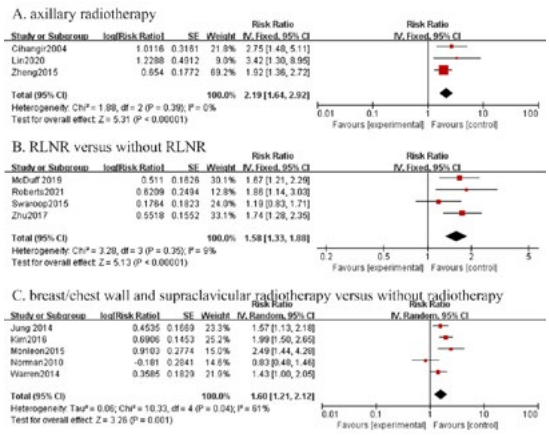
Lymph node related

For type of axillary surgery, Breast cancer patients with ALND were associated with an increase in the BCRL rate compared with SLNB (RR: 2.20; 95% Cl: 1.81, 2.66; I^2 = 0%; (sFigure 4A) and without ALND (RR: 2.72; 95% Cl: 1.89-3.92; I^2 =58%, Random, (sFigure 4B). The sensitivity analysis results showed that the studies by Menleon et al. and Norman et al. were the source of heterogeneity, and omitting both studies separately showed statistically significant results that the studies were the source of heterogeneity (sTable 2). Levels for ALND, larger extend of axillary surgery (Level III vs. Level I: RR: 2.20; 95% Cl: 1.55-3.14, I^2 =30%, sFigure 4C Level II vs. Level I: RR: 1.60,95% Cl: 1.25-2.06, I^2 =0%) (sFigure 4D) were associated with BCRL. For the number of lymph nodes removed, the removal of lymph nodes of≥10 was associated with a risk of developing arm lymphedema (RR: 1.33; 95% Cl: 1.18-1.49; I^2 =15%) (sFigure 4E) compared with when a smaller number of lymph nodes were removed, but the number removed≥16 was not associated with risk (RR: 1.21; 95% Cl: 0.84-1.72; I^2 =69%, Random) (sFigure 4F). And Number of positive lymph node were not more susceptible to BCRL (RR: 1.03; 95% Cl: 0.99- 1.06; I^2 = 51%, Random) (sFigure 4G). The sensitivity analysis results showed that the studies by Huang and Rastogi were the source of heterogeneity, and omitting the studies separately showed statistically significant results (sTable 3). The funnel plot was roughly symmetrical, hinting at a low risk of publication bias (sFigure 5).

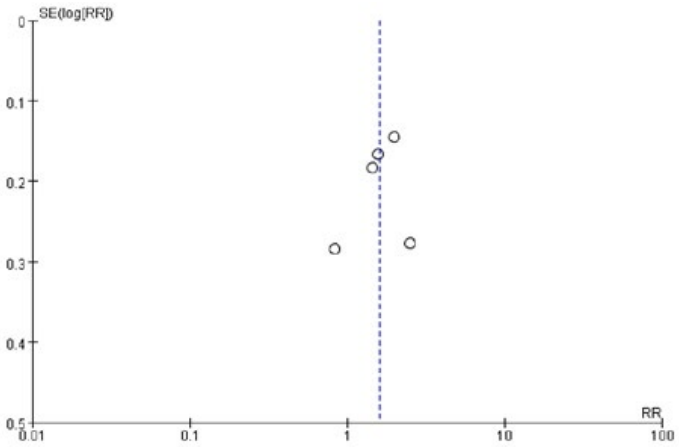
Radiotherapy

sTable 4 shows the sub group analyses for population characteristics and evaluation method. A positive association between radiotherapy and BCRL was observed in all subgroup analyses. For the location of radiotherapy, axillary radiotherapy was associated with a higher risk of developing arm lymphedema (RR: 2.19; 95% Cl: 1.64- 2.92; I^2 = 0%, Random) (sFigure 6A) compared without axillary, received regional lymph node irradiation (RLNR) compared without RLNR was associated with a higher risk of developing arm lymphedema (RR: 1.58; 95% Cl: 1.33-1.88; I^2=9%) (sFigure 6B) the location of radiotherapy was breast/chest wall and the supraclavicular field (SCRT) was more susceptible to BCRL than patients without radiotherapy (RR: 1.60; 95% Cl: 1.21-2.12; I^2 = 61%, Random) (sFigure 6C). The sensitivity analysis results showed that the stability of the results had no significant changes (Table 5).

The funnel plot for the breast with SCRT was distributed around the average, hinting at low risk of publication bias (Figure 7).



sFigure 6: Risk Ratio for breast cancer related lymphedema risk of the location of radiotherapy



sFigure 7: funnel plot for the surgery of lymph nodes

sTable 4: Sensitivity analysis: Risk Ratio for Breast cancer-related lymphedema of radiotherapy.

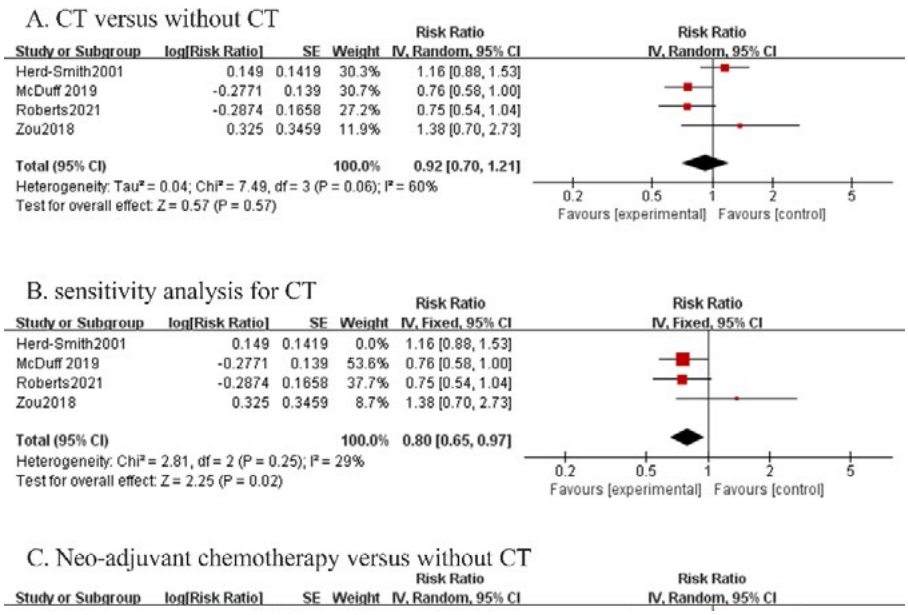
Study excluded	Pooled effect		I-squared (%)	I-sq. P-value
	RR	95% CI		
Chen2012	1.78	[1.51, 2.11]	60	0.01
Feng2018	1.84	[1.53, 2.21]	65	0.004
Herd-Smith2001	1.86	[1.68, 2.06]	27	0.20
Huang2011	1.85	[1.54, 2.23]	65	0.003
Huang2012	1.88	[1.53, 2.33]	65	0.003
li2017	1.79	[1.51, 2.12]	61	0.009
Ribeiro2017	1.88	[1.53, 2.31]	65	0.003
Wang 2016	1.78	[1.50, 2.12]	60	0.01
Wang2018	1.89	[1.58, 2.25]	63	0.005
Zou2018	1.78	[1.50, 2.12]	60	0.010
* if $I^2 \geq 50$ %, the heterogeneity source of subgroup analysis is considered and estimated by random effect model.				

sTable 5: Sensitivity analysis: Risk Ratio for Breast cancer-related lymphedema of Adjuvant taxane-based chemotherapy versus without Adjuvant taxane-based chemotherapy.

Study excluded	Pooled effect		I-squared (%)	I-sq. P-value
	RR	95% CI		
Byun2021	1.63	[0.99, 2.69]	79	0.009
Jung 2014	1.65	[1.15, 2.36]	79	0.008
Kim2016	1.48	[1.11, 1.97]	63	0.07
Swaroop2015	1.76	[1.56, 1.99]	38	0.20
* if $I^2 \geq 50$ %, the heterogeneity source of subgroup analysis is considered and estimated by random effect model.				

Chemotherapy

Breast cancer patients who received chemotherapy was not associated with an increased BCRL rate in 4 studies included (RR: 0.92; 95% Cl: 0.70-1.21; I^2 = 60%, Random) (sFigure 8A), The sensitivity analysis results showed that chemotherapy was associated with a decrease BCRL rate (RR: 0.80; 95% Cl: 0.65-0.97; I2 = 29%) (sFigure 8B) when omitting the study by Herd-Smith. Neo-adjuvant chemotherapy (RR: 1.61; 95% Cl: 1.08-2.39; I^2 = 77%, Random) (sFigure 8C) and adjuvant taxane-based chemotherapy (RR: 1.65; 95% Cl: 1.25-2.19; I^2 = 69%, Random) (sFigure 8D) were associated with an increase in the BCRL rate. The sensitivity analysis results have shown that omitting the study by Swaroop et al showed statistically significant results that were the source of heterogeneity (sTable 6), and the study by li et al was the source of heterogeneity in the analysis of adjuvant neo-adjuvant chemotherapy (sTable 7).



sFigure 8: Risk Ratio for breast cancer related lymphedema risk of Chemotherapy

sTable 6: Sensitivity analysis: Risk Ratio for Breast cancer-related lymphedema of adjuvant neo-adjuvant chemotherapy versus without adjuvant neo-adjuvant chemotherapy

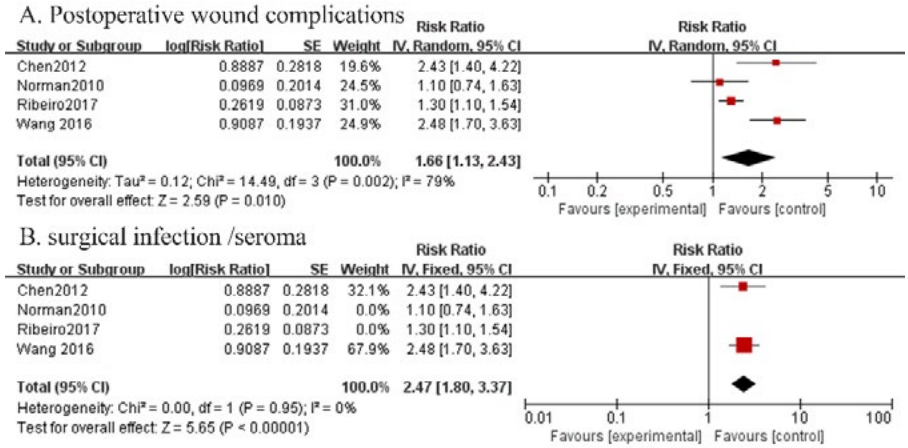
Study excluded	Pooled effect		I-squared (%)	I-sq. P-value
	RR	95% CI		
Huang2012	1.72	[1.11, 2.67]	84	0.002
Jung 2014	1.87	[1.24, 2.81]	52	0.12
li2017	1.31	[1.10, 1.56]	3	0.36
Zhang2017	1.47	[1.25, 1.74]	84	0.002
* if $I^2 \geq 50$ %, the heterogeneity source of subgroup analysis is considered and estimated by random effect model.				

sTable 7: Subgroup analysis based on risk score

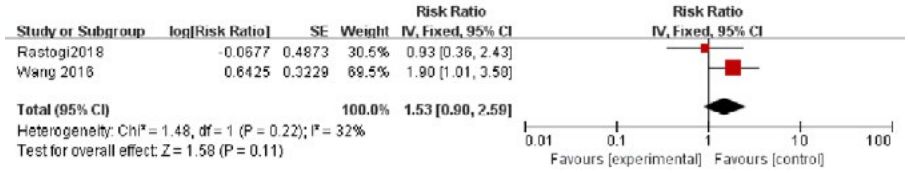
Analysis		Number of study	Meta-analysis		
			RR	95 % CI	I^2
BMI at continuous	Main analysis	6	1.03	[1.03, 1.04]	0%
	6	2	1.03	[1.01, 1.05]	97%
	7	2	1.04	[1.02, 1.05]	86%
	8	2	1.03	[1.02, 1.04]	90%
BMI ≥25 vs BMI 25	Main analysis	8	2.09	[1.85, 2.36]	0%
	6	5	1.95	[1.68, 2.26]	0%
	7	1	2.50	[1.79, 3.49]	-
	8	2	2.39	[1.80, 3.16]	0%
No. LNR at continuous	Main analysis	5	1.04	[1.02, 1.06]	83%
	6	1	1.29	[1.08, 1.55]	
	7	1	1.03	[1.01, 1.05]	
	8	3	1.04	[1.02, 1.07]	89%

ALND vs none	Main analysis	6	2.72	[1.89, 3.92]	58%
	6	3	3.82	[2.31, 6.31]	30%
	7	2	2.58	[1.35, 4.91]	79%
	8	1	2.02	[1.24, 3.28]	
ALND vs SLNB	Main analysis	5	2.20	[1.81, 2.66]	0%
	6	1	2.01	[1.24, 3.25]	-
	7	3	2.18	[1.75, 2.71]	0%
	8	1	3.03	[1.38, 6.63]	-
Number of positive lymph node	Main analysis	5	1.03	[0.99, 1.06]	51%
	6	2	0.95	[0.71, 1.26]	78%
	7	2	1.15	[0.79, 1.68]	62%
	8	1	1.02	[0.99, 1.06]	-
CT	Main analysis	10	1.84	[1.55, 2.18]	61%
	6	6	1.77	[1.32, 2.38]	68%
	7	2	1.95	[1.43, 2.65]	59%
	8	1	2.92	[1.56, 5.47]	-
breast with SCRT vs without RT	Main analysis	5	1.60	[1.21, 2.12]	61%
	6	2	2.09	[1.63, 2.69]	0%
	7	3	1.37	[1.10, 1.71]	47%

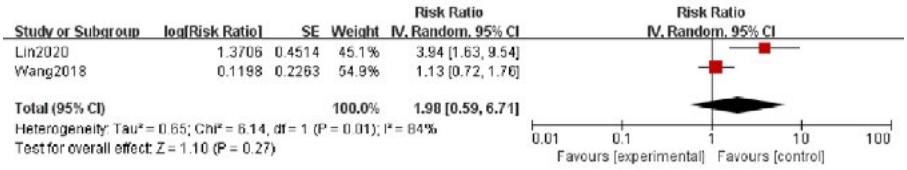
Postoperative wound complications were associated with a risk of developing arm lymphedema (RR: 1.66; 95% Cl: 1.13- 2.43; I^2 = 79%, Random) (sFigure 9A), the subgroup analyses for surgical infection /seroma were associated with a higher risk (RR: 2.47; 95% Cl: 1.80-3.37; I2 = 0) (sFigure 9B). Surgery on dominance limb (RR: 1.53; 95% Cl: 0.90- 2.59; I^2 = 32%) (sFigure 10) and diabetes (RR: 1.98; 95% Cl: 0.59-6.71; I^2 = 84%, Random) (sFigure 11) were not associated with an increase BCRL rate.



sFigure 9: Risk Ratio for breast cancer related lymphedema risk of postoperative wound complications



sFigure 10: Risk Ratio for breast cancer related lymphedema risk of surgery on dominance limb



sFigure 11: Risk Ratio for breast cancer related lymphedema risk of diabetes

Discussion

This systematic review and meta-analysis of 34 cohort studies with 23988 breast cancer evaluated risk factors and incidence of lymphedema. The cumulative incidence rates varied widely among studies according to Country, study design, and population characteristics. etc.

In our study, advanced stage at diagnosis and larger surgical range were risk factors of BCRL. Elderly patients are more likely to have lymphedema, probably aging reduces lymph venous anastomoses and decreased pump activity, which causes substantial changes in the lymphatic system, larger BMI was more susceptible to BCRL, it may be associated with an impaired contractile function of muscle pumps, increased lymphatic fluid and elevated levels of inflammatory factors in adipose tissue [61-64]. Our study showed that the larger range of lymph node dissection and the number of lymph node dissections were, the higher incidence of lymphedema. It directly caused great trauma to the lymphatic system and blood vessels, resulting in lymph reflux disorder at the surgical site. For the number of positive lymph nodes, sensitivity analysis showed that the results were not stable in this study, which may require more studies to prove.

This study showed that adjuvant therapy increases the incidence of lymphedema. For radiotherapy, axillary radiotherapy has the greatest impact on BCRL, which is consistent with the results from previous studies [18]. After radiotherapy, lymphatic vessels expand and connective tissue proliferates, making lymphatic fibrosis [65]. At the same time, radiotherapy may lead to lymphangitis and affect the occurrence of lymphedema. In this study, neoadjuvant chemotherapy and adjuvant taxane-based chemotherapy are risk factors for lymphedema. The relationship between chemotherapy and BCRL occurrence is still unclear. Related studies suggest that chemotherapy-related neutropenia may lead to infection in patients and reduce body immunity, or taxanes impose a burden on the lymphatic system of the surgical side limb [66, 67]. Related studies had shown that postoperative complications such as surgical infection and seroma may occur in patients with breast cancer, which can reduce the local lymphatic drainage function through lymphadenitis, resulting in lymphatic obstruction and fibrosis, leading to lymphatic reflux disorder, which is the same as the results of this study. Totally, Lymphedema following cancer treatment might be influenced by any measures or events that disorder the circulation of the lymphatic system.

Subgroup analysis was performed according to country of origin, study design, population characteristics, and the definition of lymphedema. In the subgroup analysis of radiotherapy, retrospective studies may overestimate the risk, and country, research design, and definition were the sources of heterogeneity. There was great heterogeneity in the pooled lymphedema incidence, and no heterogeneity source was found in the subgroup analysis. The quality of all included studies was high quality, through subgroup analysis based on risk score, the bias risk included in the study has little effect on Meta-analysis (Table 8). Only in the breast with SCRT, the risk of bias was the source of heterogeneity of pooled results. The analysis showed that the risk score of 6 points was greater than that of 7 points, but the sample size of the subgroup was small and the results needed careful consideration. At the same time, although the funnel plot was roughly symmetrical, hinting at low risk of publication bias, there may be a risk of bias. Some studies reported only significant risk factors for results.

Some limitations in our meta-analysis should be mentioned. First, considering the time of lymphedema and the argument intensity of causality, this study included only cohort studies. Second, our results were not based on raw data and based on adjusted estimates, thus, potential publication bias is likely to exist. Third, only in quality evaluation, the limitation of follow-up time to more than three years may also affect the pooled results.

Conclusion

Our meta-analysis reported that BCRL risk is significantly associated with stage at diagnosis, type of surgery, age, BMI, ALND, radiotherapy, chemotherapy, and postoperative wound complications. Our study suggests that clinicians should strictly follow the treatment indications in the clinical treatment process to reduce the risk of lymphedema caused by unnecessary lymph node resection and excessive radiotherapy. After surgery, medical staff should make a timely preventive intervention and health guidance for high-risk factors of breast cancer patients to reduce the occurrence of BCRL. Future studies need to strengthen the standardization of research implementation and reporting, and the number of individual risk factors included in the literature is small. In the future, multi-center, large sample prospective cohort studies are needed to further clarify the correlation.

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List of abbreviations

BCRL: breast cancer-related lymphedema
RR: risk ratio
OR: odd ratio
HR: hazard ratio
CI: confidence intervals
BMI: body mass index
ALND: axillary lymph node dissection
SLNB: sentinel lymph node biopsy
RLNR: regional lymph node irradiation.

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SUPPORTING INFORMATION

Appendix A: Database Search Strategy in English

Table 1: Pubmed

#1	"Breast Neoplasms"[MeSH Terms] OR "breast cancer"[Title] OR "breast tumor"[Title] OR "mammary neoplasm"[Title] OR "mammary carcinoma"[Title] OR "breast neoplasm"[Title] OR "breast carcinoma"[Title] OR "breast malignan*"[Title] OR "breast metastas*"[Title] OR "mammary malignan*"[Title] OR "mammary metastas*"[Title]	346712
#2	"Lymphedema"[MeSH Terms] OR "lymphoedema"[Title] OR "Lymphedema"[Title] OR "lymphedemas"[Title] OR "lymphatic edema"[Title] OR "oedema"[Title] OR "edema"[Title] OR "swelling"[Title] OR "elephantias*"[Title] Sort by: Most Recent	56455
#3	"Risk"[MeSH Terms] OR "risk*"[Title/Abstract] OR "risk factor"[Title/Abstract] OR "risk factors"[Title/Abstract] OR "age"[Title/Abstract] OR "BMI"[Title/Abstract] OR "modified radical mastectomy"[Title/Abstract] OR "infection"[Title/Abstract] OR "chemotherapy"[Title/Abstract] OR "Radiotherapy"[Title/Abstract] OR "physical activity"[Title/Abstract] OR "exercise"[Title/Abstract] OR "early edema"[Title/Abstract] OR "seroma"[Title/Abstract] OR "hypertension"[Title/Abstract] OR "behavior"[Title/Abstract] OR "prevention"[Title/Abstract]	7333884
#4	#1 AND #2 AND #3 AND (2000:2021[pdat])	1300

Table 2: Web of Science

#1	TI=((breast cancer) OR (breast tumor) OR (mammary neoplasm) OR (mammary carcinoma) OR (breast neoplasm) OR (breast carcinoma) OR (breast malignan*) OR (breast metastas*) OR (mammary malignan*) OR (mammary metastas*))	74122
#2	TI=((Lymphedema) OR (lymphoedema) OR (Lymphedema) OR (lymphedemas) OR (lymphatic edema) OR (oedema) OR (edema) OR (swelling) OR (elephantias*))	356272
#3	TS=((Risk) OR (risk*) OR (risk factor) OR (risk factors) OR (age) OR (BMI) OR (modified radical mastectomy) OR (infection) OR (chemotherapy) OR (Radiotherapy) OR (physical activity) OR (exercise) OR (early edema) OR (seroma) OR (hypertension) OR (behavior) OR (prevention))	20207710
#4	#1 AND #2 AND #3 AND	1340

Table 3: Embase

#1	('breast cancer':ti OR 'breast tumor':ti OR 'mammary neoplasm':ti OR 'mammary carcinoma':ti OR 'breast neoplasm':ti OR 'breast carcinoma':ti OR 'breast malignan*':ti OR 'breast metastas*':ti OR 'mammary malignan*':ti OR 'mammary metastas*':ti)	291319
#2	(lymphoedema:ti OR lymphedema:ti OR lymphedemas:ti OR 'lymphatic edema':ti OR oedema:ti OR edema:ti OR swelling:ti OR elephantias*:ti)	61274
#3	(risk:ab,ti OR risk*:ab,ti OR 'risk factor':ab,ti OR 'risk factors':ab,ti OR age:ab,ti OR bmi:ab,ti OR 'modified radical mastectomy':ab,ti OR infection:ab,ti OR chemotherapy:ab,ti OR radiotherapy:ab,ti OR 'physical activity':ab,ti OR exercise:ab,ti OR 'early edema':ab,ti OR seroma:ab,ti OR hypertension:ab,ti OR behavior:ab,ti OR prevention:ab,ti)	9664943
#4	#1 AND #2 AND #3 AND	1042

Table 4: Medline

#1	TI ((breast cancer) OR (breast tumor) OR (mammary neoplasm) OR (mammary carcinoma) OR (breast neoplasm) OR (breast carcinoma) OR (breast malignan*) OR (breast metastas*) OR (mammary malignan*) OR (mammary metastas*)) AND TI ((Lymphedema) OR (lymphoedema) OR (Lymphedema) OR (lymphedemas) OR (lymphatic edema) OR (oedema) OR (edema) OR (swelling) OR (elephantias*)) AND AB ((Risk) OR (risk*) OR (risk factor) OR (risk factors) OR (age) OR (BMI) OR (modified radical mastectomy) OR (infection) OR (chemotherapy) OR (Radiotherapy) OR (physical activity) OR (exercise) OR (early edema) OR (seroma) OR (hypertension) OR (behavior) OR (prevention))	716