Effect of taxane-based adjuvant chemotherapy on breast cancer-related lymphedema: A propensity score matching study

KANG Dan[1,2], YAN Huang[1,3], LU Qing[4], CHEN Haibing[5], WANG Ling[6]

(1. Nursing Department, Third Xiangya Hospital, Central South University, Changsha 410013; 2. Outpatient Nursing Unit, Third Xiangya Hospital, Central South University, Changsha 410013; 3. Emergency Department, Third Xiangya Hospital, Central South University, Changsha 410013; 4. Xiangya School of Nursing, Central South University, Changsha 410013; 5. School of Nursing, Jilin Medical University, Jilin 132013; 6. Department of Anesthesiology, Third Xiangya Hospital, Central South University, Changsha 410013, China)

ABSTRACT

Objective: Breast cancer-related lymphedema (BCRL) is a common complication of breast cancer treatment. Previous studies have suggested an association between BCRL and adjuvant chemotherapy; however, whether taxane-based regimens independently influence the risk of BCRL remains controversial due to potential confounding factors. Propensity score matching (PSM) can effectively reduce confounding bias. This study aims to investigate the association between taxane-based adjuvant chemotherapy and BCRL using PSM.

Methods: This retrospective study was conducted using data from the electronic medical record system of Xiangya Third Hospital, Central South University. BCRL was diagnosed based on objective measurements of limb circumference. Taxane-based adjuvant chemotherapy was defined as chemotherapy regimens including docetaxel, paclitaxel, or albumin-bound paclitaxel. PSM was applied to control for potential confounders, followed by Logistic regression analysis in the matched cohort to evaluate the association between taxane-based chemotherapy and BCRL.

Results: A total of 1 494 patients were included in this study. Before PSM, taxane-based adjuvant chemotherapy was not significantly associated with BCRL (*OR*=0.979, 95% *CI* 0.587 to 1.580; *P*=0.932). After PSM, 363 matched patients were obtained, and the association remained non-significant (*OR*=0.959, 95% *CI* 0.540 to 1.672; *P*=0.885).

Conclusion: Taxane-based adjuvant chemotherapy is not an independent risk factor for BCRL, regardless of adjustment for known confounding factors. Further multicenter, prospective studies are warranted to further validate these findings.

Date of reception: 2025-08-19

First author: KANG Dan, Email: 3556884878@qq.com, ORCID: 0009-0001-7540-4179

Corresponding author: YAN Huang, Senior nurse, Email: Huangnn2021@163. com, ORCID: 0000-0003-4646-0814; WANG Ling, Professor, Email: 1322788113@qq.com, ORCID: 0009-0009-5954-9341

Foundation item: This work was supported by the Hunan Provincial Administration of Traditional Chinese Medicine Foundation, China (D2022072).

Open access: This is an open access article under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) (https://creativecommons.org/licenses/by-nc-nd/4.0/).

©Journal of Central South University (Medical Science). All rights reserved.

KEY WORDS brreast cancer-related lymphedema; edema; breast cancer; taxane-based adjuvant chemotherapy; propensity score-matching

紫杉醇类辅助化疗对乳腺癌相关淋巴水肿的影响：一项倾向性评分匹配研究

康丹[1,2]，严煌[1,3]，卢庆[4]，陈海兵[5]，王玲[6]

(1. 中南大学湘雅三医院护理部，长沙 410013；2. 中南大学湘雅三医院门诊综合护理单元，长沙 410013；
3. 中南大学湘雅三医院急诊科，长沙 410013；4. 中南大学湘雅护理学院，长沙 410013；
5. 吉林医药学院护理学院， 吉林 132013；6. 中南大学湘雅三医院麻醉科，长沙 410013)

[摘 要] 目的：乳腺癌相关淋巴水肿(breast cancer-related lymphedema，BCRL)是乳腺癌治疗的常见并发症，既往研究认为其与辅助化疗有关。但由于混杂因素干扰，辅助化疗中常用的紫杉醇类药物是否独立影响BCRL尚存争议。倾向性评分匹配(propensity score matching，PSM)可有效控制混杂偏倚，本研究旨在采用该法探讨紫杉醇类辅助化疗与BCRL之间的关联。**方法：**本研究为回顾性设计，数据来自中南大学湘雅三医院的电子病历系统。BCRL的诊断依据为患肢周长的客观测量结果。紫杉醇类辅助化疗定义为含多西他赛、紫杉醇或白蛋白结合型紫杉醇的化疗方案。通过PSM控制混杂因素，并对匹配后样本进行Logistic回归分析，评估紫杉醇类化疗与BCRL的关系。**结果：**本研究共纳入1 494例患者。PSM前，紫杉醇类辅助化疗与BCRL未表现出显著相关性(*OR*=0.979，95% *CI* 0.587~1.580；*P*=0.932)。PSM后共匹配363例，结果仍无统计学意义(*OR*=0.959，95% *CI* 0.540~1.672；*P*=0.885)。**结论：**无论是否控制其他已知危险因素，紫杉醇类辅助化疗均非BCRL的独立危险因素。未来需开展多中心、前瞻性研究进一步验证。

[关键词] 乳腺癌相关淋巴水肿；水肿；乳腺癌；紫杉醇类辅助化疗；倾向性评分匹配

Breast cancer is one of the most diagnosed types of cancer and the leading cause of cancer-related mortality among women worldwide[1]. Recent advances in breast cancer diagnosis and treatment have significantly improved long-term survival[2], but postoperative complications are still a major concern[3]. Up to 20% of breast cancer survivors are affected by breast cancer-related lymphedema (BCRL) [4], one of the most common and troublesome complications of breast cancer treatment[5]. BCRL is marked by an abnormal buildup of lymphatic fluid in the parts of the body that are affected[6-7]. This can cause long-term physical and mental symptoms that can make a patient’ s quality of life much worse[8-10]. In addition, breast cancer survivors face a lifetime risk of lymphedema, and there is currently no cure for BCRL. Thus, strategies to prevent the onset of BCRL and improve the quality of life for breast cancer survivors are urgently required.

Existing risk factors for development of lymphedema include axillary lymph node dissection (ALND) [11], regional lymph node radiation (RLNR) [12], the number of positive lymph nodes[13], a higher body mass index (BMI) [14], cellulitis[3], and low-level limb volume changes[15]. All of these factors contribute to an increased risk for the development of lymphedema and have been studied extensively. However, there are still many unanswered questions regarding lymphedema risk factors. Multiple studies have examined the relationship between BCRL and chemotherapy[16-18]. The results of these studies have been inconclusive, indicating that much more research is required in this area.

One of standard treatments for breast cancer is taxane-based adjuvant chemotherapy, which has been shown to considerably increase patients’ overall survival and progression-free survival[19-20]. Taxane-based adjuvant therapy, particularly docetaxel, promotes fluid retention in the extremities because of an increase in extracellular fluid[21]. To prevent or postpone the onset

©Journal of Central South University (Medical Science). All rights reserved.

of fluid retention caused by taxanes, patients frequently receive corticosteroids during treatment[22]. The long-term effects of arm edema from taxane-based adjuvant chemotherapy are not yet known, though. There is conflicting evidence regarding the relationship between taxane-based adjuvant chemotherapy and the emergence of lymphedema in breast cancer survivors[16-17, 23]. These contradictory findings imply that further study is required to better comprehend the link between taxane-based adjuvant chemotherapy and arm edema. These previous results likely varied based on demographic factors, tumor characteristics, surgical procedures, and treatment protocols. Moreover, these current studies had clear faults, such as the fact that none of them addressed the combined impact of many hazards while examining a single risk. In addition, these studies were conducted on Western populations, and there is a dearth of information on Chinese breast cancer patients. Further research is needed that accounts for a variety of characteristics and patient populations to correctly draw conclusions about the association between taxane-based chemotherapy and BCRL.

Prior studies[16, 23] mainly relied on conventional regression models. A traditional regression model may be biased due to unmeasured or residual confounding given the abundance of potential confounding variables, whereas adding more variables may lead to model overfitting and potentially prevent the identification of the association between the relevant exposure and the outcome[24-25]. The propensity score matching (PSM) method is widely used for controlling confounding in observational research. It is especially beneficial in studies where there are numerous covariates that may confound a rare outcome, where there may be potential confounding by indication, and where there are resource limitations that preclude the conduct of randomized clinical trials[26-27]. By balancing the distribution of covariates between exposed and unexposed cases, the PSM approach can help reduce possible bias from confounding, and when implemented correctly, it can produce reliable results even in observational studies. This study aims to investigate the association between taxane-based adjuvant chemotherapy and BCRL in Chinese using PSM.

1 Materials and Methods

1.1 Ethics statements

The study design and use of clinical data were approved by the institutional review board of the Third Xiangya Hospital of Central South University (Approval number: 2023-S527). Due to the retrospective nature of the study, the requirement for informed consent was waived, and all patient data were anonymized.

1.2 Subjects

A retrospective study was conducted. We examined the medical records of individuals who underwent breast cancer surgery in the Third Xiangya Hospital, Central South University from January 2013 to September 2023. Inclusion criteria were: Female patients aged 18 years or older, with a confirmed diagnosis of breast cancer, and undergoing surgical treatment for breast cancer. Individuals who met any of the following criteria were excluded: 1) Had metastasis, bilateral or recurrent breast cancer; 2) had upper limbs or the neck with a history of major surgery; 3) lacked clinical data and follow-up information; 4) had chemotherapy prior to breast cancer surgery; 5) had less than 2 courses of adjuvant chemotherapy or had neoadjuvant chemotherapy. BCRL group included patients who suffered postoperative BCRL, while control group included patients who did not experience postoperative BCRL during the follow-up period. Figure 1 depicts the patient selection process flowchart.

1.3 Data extraction

Medical and nursing records uploaded to the electronic medical record system were mined for information. We received patient information, tumor information, and therapy information from the database. Patient information included age, gender, height, weight, educational level, marital status, arm lymphedema swelling severity, and comorbidities. Tumor information included the stage of cancer, tumor stage, lymph node (N) stage, and lymph node metastasis status. Treatment information, namely the type of therapy, included the number of lymph nodes removed, ALND, chemotherapy with paclitaxel, docetaxel, or other regimens, radiotherapy, and endocrine therapy.

©Journal of Central South University (Medical Science). All rights reserved.

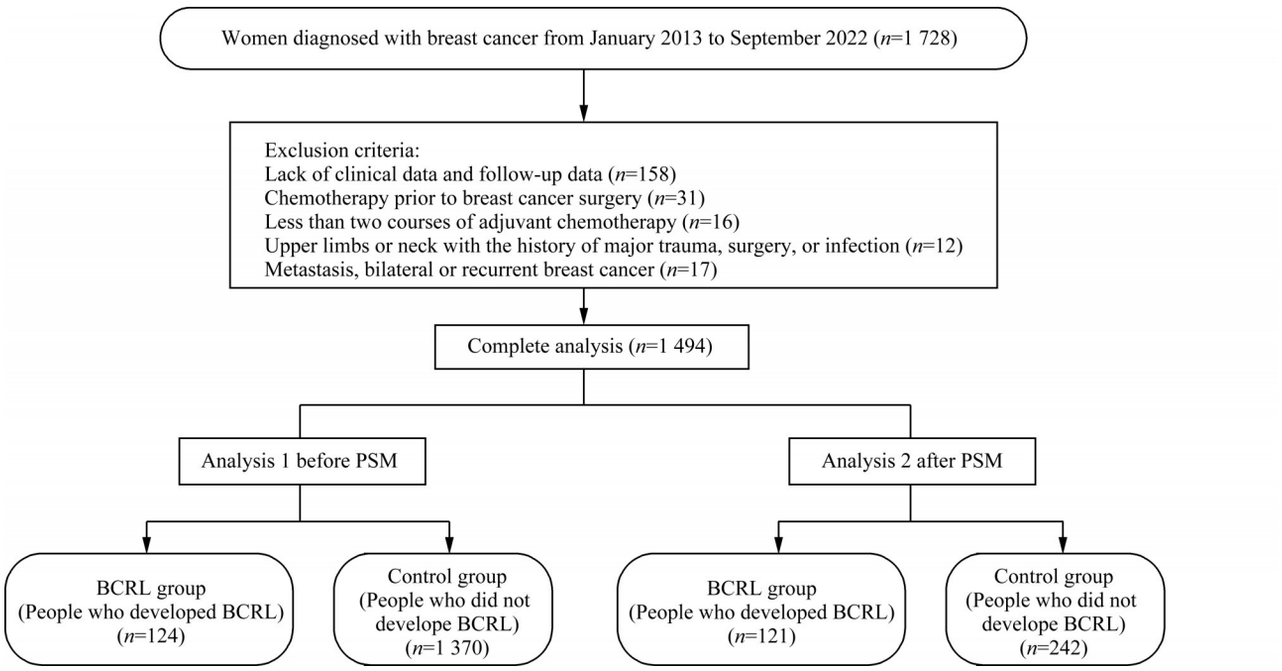


Figure 1 Flow chart of participant enrollment

BCRL: Breast cancer-related lymphedema; PSM: Propensity score matching.

1.4 Identification of chemotherapy

Paclitaxel, albumin paclitaxel, and docetaxel are all components of taxane-based chemotherapy. Dexamethasone premedication was given before chemotherapy as per each institution's practice[28]. Neoadjuvant chemotherapy recipients were not included in this analysis. If a patient changed chemotherapy regimens during adjuvant therapy, the final regimen prevailed.

1.5 Diagnosis and measurements of BCRL

The diagnosis of BCRL was made with an objective measurement of limb circumference. The physiatrist measured the circumference of both arms at the metacarpophalangeal joint, the wrist, 10 cm distal to the antecubital fossa of the elbow, the elbow, and 10 and 20 cm proximal to the elbow[29], after feeling the skin and subcutaneous tissue texture of the entire arm. Patients were diagnosed with lymphedema if they had a circumferential difference (CD) of less than 1 cm between their arms, or if they had a CD of less than 1 centimeter in conjunction with pitting edema or hardening of the subcutaneous tissue. If the CDs of any measured site were less than 2 cm, more than 2 cm but less than 3 cm, or greater than 3 cm, the lymphedema was classed as mild, moderate, or severe, respectively[30]. Patients diagnosed with BCRL were given care and monitored in special clinics.

1.6 PSM

PSM is an efficient statistical technique that can reduce the influence of confounding variables[31], such as a high BMI, more invasive surgery, advanced-stage cancer, radiation, and so on, that may contribute to outcome bias. The propensity score was assigned using a multivariable Logistic regression model and estimated based on the probability that a patient would develop arm lymphedema. A one-to-two nearest neighbor matching technique with a caliper width of 0.02 was implemented. Age, BMI, TNM stage, ALND, lymph node metastases, number of lymph nodes resected, sentinel lymph node biopsy, surgical type, and radiotherapy were used to create the propensity score.

1.7 Reduction of bias

We intended to address potential sources of bias by doing the following. All cases and matched controls were drawn from the same cohort. We also matched the propensity scores of cases and controls to reduce bias arising from confounding and other factors. Lastly, the

©Journal of Central South University (Medical Science). All rights reserved.

variables were obtained from trained postgraduate students who did not participate in clinical management.

1.8 Statistical analysis

SPSS 25 (IBM) and R 4.0 statistical analyses (R Project for Statistical Computing) were used to analyze the data. Quantitative data were represented using mean± standard deviation and the independent samples *t* test for normally distributed data. *M* (P_{25}, P_{75}) and the Mann-Whitney *U* test were used for skewed data. The ratio, or composition ratio and frequency, were used for count data, and the chi-square test or Fisher's exact test was employed. The association between taxane-based chemotherapy and BCRL was assessed using logistic regression and expressed as an odds ratio (*OR*) and 95% confidence interval (*CI*). Model 1 was not modified. Adjustments were made to Model 2 to account for BMI, ALND, sentinel lymph node biopsy, radiation, and TNM stage. Model 3 was modified for variables in Model 2 plus additional factors, including age, lymph node metastases, lymph nodes that were removed, and breast surgery. To limit the influence of confounding variables, we applied matching strategies based on propensity scores. Standardized mean difference (*SMD*) was calculated to evaluate the efficacy of PSM between the 2 groups. $P<0.05$ (2-sided) was considered statistically significant.

2 Results

2.1 Characteristics of patients before PSM

A total of 1 494 participants were enrolled in this study (Figure 1). According to the diagnostic criteria for BCRL, 124 (8.3%) of the participants had lymphedema, while 1 370 (91.7% of the subjects) did not. The median age of the total study population was 56 (50.0, 62.0) years. The features of the baseline are reported in Table 1. There were no statistically significant variations in age between the BCRL and control groups ($P=0.445$). Patients in the BCRL group had a substantially higher BMI than those in the control group [24.0 (21.9, 25.9) vs 23.0 (21.2, 25.2), $P=0.021$]. Patients in the BCRL group had a higher TNM stage ($P=0.010$), more lymph node metastasis (54.8% vs 38.6%, $P=0.001$), more ALND (30.6% vs 19.1%, $P=0.003$), more radiotherapy (28.2% vs 13.9%, $P<0.001$), and more chemotherapy (90.3% vs 80.6%, $P=0.011$), but fewer sentinel lymph node biopsy (12.9% vs 25.1%, $P=0.003$).

A multivariable Logistic regression analysis was done to determine the potential causes of BCRL occurrences (Table 2). The included parameters were as follows: BMI, TNM stage, sentinel lymph node biopsy, ALND, radiotherapy, chemotherapy, and lymph node metastasis. Variables that showed a significant influence on this event were BMI (*OR*=0.938, 95% *CI* 0.882 to 0.998; $P=0.042$) and radiotherapy (*OR*=0.581, 95% *CI* 0.362 to 0.946; $P=0.026$).

Table 1 Characteristics of patients in BCRL and control groups before and after PSM

Characteristics	Before PSM/[No.(%)]				After PSM/[No.(%)]			
	BCRL group (*n*=124)	Control group (*n*=1 370)	*P*	*SMD*	BCRL group (*n*=121)	Control group (*n*=242)	*P*	*SMD*
Age/years	55.0(51.0, 60.0)	56.0(50.0, 63.0)	0.445*	0.110	55.0(51.0, 60.0)	55.0(50.0, 61.0)	0.813*	0.028
BMI/(kg·m^{-2})	24.0(21.9, 25.9)	23.0(21.2, 25.2)	0.021*	0.217	24.0(21.9, 25.9)	24.2(21.9, 26.7)	0.399*	0.077
TNM stage			0.010†	0.288			0.801†	0.108
I	27(21.8)	377(27.5)			25(20.7)	43(17.8)		
II	53(42.7)	676(49.4)			52(43.0)	109(45.0)		
III	42(33.9)	310(22.6)			42(34.7)	88(36.4)		
IV	2(1.6)	6(0.4)			2(1.7)	2(0.8)		
Sentinel lymph node biopsy			0.003‡	0.315			1.000‡	<0.001
Yes	16(12.9)	344(25.1)			16(13.2)	32(13.2)		
No	108(87.1)	1 026(74.9)			105(86.8)	210(86.8)		

©Journal of Central South University (Medical Science). All rights reserved.

Table 1 (to be continued)

Characteristics	Before PSM/[No.(%)]				After PSM/[No.(%)]			
	BCRL group (*n*=124)	Control group (*n*=1 370)	*P*	*SMD*	BCRL group (*n*=121)	Control group (*n*=242)	*P*	*SMD*
ALND			0.003‡	0.271			0.968‡	0.018
Yes	38(30.6)	261(19.1)			37(30.6)	72(29.8)		
No	86(69.4)	1 109(80.9)			84(69.4)	170(70.2)		
Removed lymph nodes			0.061‡	0.191			0.767‡	0.047
<15	34(27.4)	497(36.3)			33(27.3)	61(25.2)		
≥15	90(72.6)	873(63.7)			88(72.7)	181(74.8)		
Radiotherapy			<0.001‡	0.356			0.769‡	0.047
Yes	35(28.2)	191(13.9)			34(28.1)	63(26.0)		
No	89(71.8)	1 179(86.1)			87(71.9)	179(74.0)		
Chemotherapy			0.011‡	0.279			0.011‡	0.275 -
Yes	112(90.3)	1 104(80.6)			111(91.74)	198(81.82)		
No	12(9.7)	266(19.4)			10(8.26)	44(18.18)		
Lymph node metastasis			0.001‡	0.330			0.738‡	0.050
Yes	68(54.8)	529(38.6)			67(55.4)	128(52.9)		
No	56(45.2)	841(61.4)			54(44.6)	114(47.1)		
Types of breast cancer surgery			0.355†	0.110			1.000†	<0.001
Breast-conserving surgery	7(5.6)	116(8.5)			6(5.0)	14(5.8)		
Mastectomy	117(94.4)	1 254(91.5)			115(95.0)	228(94.2)		

Quantitative data are represented using mean±standard deviation. The ratio (or composition ratio) and frequency were used for count data. *M* (P_{25}, P_{75}) were used for skewed data. *Mann-Whitney *U* test; †Fisher's exact test; ‡Chi-square test. BCRL: Breast cancer-related lymphedema; PSM: Propensity score matching; BMI: Body mass index; *SMD*: Standardized mean difference; ALND: Axillary lymph node dissection.

Table 2 Multivariate Logistic regression analysis of the variables associated with the risk of BCRL

Variables	*OR*	95% *CI*	*P*
BMI	0.938	0.882 to 0.998	0.042
Sentinel lymph node biopsy	1.712	0.971 to 3.184	0.074
ALND	0.702	0.458 to 1.093	0.110
Lymph node metastasis	0.723	0.436 to 1.199	0.209
Radiotherapy	0.581	0.362 to 0.946	0.026
Chemotherapy	0.624	0.316 to 1.133	0.144
TNM stage	0.917	0.654 to 1.289	0.616

OR: Odds ratio; *CI*: Confidence interval.

2.2 Characteristics of patients after PSM

By using a 1∶2 PSM, 121 BCRL group subjects were finally matched with 242 control group subjects. We compared the characteristics between the 2 groups and found that these differences were well controlled after PSM (Table 1).

2.3 Relationship between taxane-based chemotherapy and the risk of BCRL

Table 3 presents the frequency distribution of adjuvant taxane chemotherapy in the BCRL and control groups before and after PSM. The unadjusted, marginally adjusted, and completely adjusted models are showed in Table 4. The link between taxane-based chemotherapy and the risk of BCRL was not significant in the primary population (*OR*=0.676, 95% *CI* 0.418 to 1.055; *P*=0.097). The result was not statistically significant after further adjustment (*OR*=0.979, 95% *CI* 0.587 to 1.580; *P*=0.932). A multivariable Logistic

©Journal of Central South University (Medical Science). All rights reserved.

regression analysis of the PSM population showed that there was no statistically significant difference between the BCRL and control groups (*OR*=0.959, 95% *CI* 0.540 to 1.672; *P*=0.885).

Table 3 Frequency distribution of adjuvant taxane chemotherapy before and after PSM

Adjuvant taxanes	Before PSM/[(No. (%)]		After PSM/[(No. (%)]	
	BCRL group (*n*=124)	Control group (*n*=1 370)	BCRL group (*n*=121)	Control group (*n*=242)
Yes	106(85.5)	988(72.12)	98(81)	173(71.49)
No	18(14.5)	382(27.88)	23(19)	69(28.51)

The ratio (or composition ratio) and frequency were used for count data.

Table 4 Relationship between taxane-based chemotherapy and the risk of BCRL in different models before and after PSM

Models	Before PSM		After PSM	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
Crude model	0.676(0.418 to 1.055)	0.097	0.975(0.558 to 1.668)	0.926
Model 1	0.864(0.527 to 1.367)	0.546	0.958(0.545 to 1.652)	0.880
Model 2	0.979(0.587 to 1.580)	0.932	0.959(0.540 to 1.672)	0.885

All models used the non-taxane chemotherapy group as the reference. Crude model was not adjusted for other covariates. Model 1 was adjusted for BMI, ALND, sentinel lymph node biopsy, radiotherapy, and TNM stage. Model 2 was adjusted for BMI, ALND, sentinel lymph node biopsy, radiotherapy, TNM stage, age, lymph node metastasis, removed lymph nodes, and breast surgery.

3 Discussion

Taxane-based chemotherapy is now used to treat patients with node-positive and high-risk node-negative breast cancer because it has been shown to lower mortality[32]. Taxanes are being given to more patients in the early stages of breast cancer as the use of anthracycline-alone therapies declines[33]. Therefore, a comprehensive assessment of the quality of life and long-term effects of taxanes is required. Given the increase in extracellular fluid volume, adjuvant taxane-based therapy enhances fluid retention in the extremities. Due to the similarities between the mechanism of fluid retention and the onset of lymphedema in breast cancer patients[34-35], the association between taxane-based chemotherapy and lymphedema requires more investigation. The link between BCRL and taxane-based therapy has been described but not exhaustively studied.

This retrospective analysis observed no significant association between taxane-based adjuvant chemotherapy and an elevated incidence of lymphedema compared with no adjuvant chemotherapy or non-taxane chemotherapy. Our findings appear to contradict the findings of prior research[36-37], which suggested that taxane-based adjuvant treatment has a considerable association with BCRL. This disparity may be partially explained by design and approach differences. In a larger retrospective cohort research by Cariati, et al[16], the diagnosis of BCRL was based on changes in the arm's appearance and/or volumetric measures between the ulna styloid process and the anterior axillary fold of both arms, which may be less reliable than the quantitative test. In a similar study by Jung, et al[23], which looked at patients who had ALND, taxane-based chemotherapy was found to be an independent risk factor for lymphedema. Localized forearm or hand edema might have gone unnoticed because they were only measured through the circumference of the upper arm. What's more, because the studies were not randomized, it was challenging to balance variables between the 2 groups. Since the PSM methods offered a control group that was very similar to what could be found in a randomized controlled trial, our work was not

©Journal of Central South University (Medical Science). All rights reserved.

limited in this way. In this study, the PSM method diminished the disparities between the BCRL and control groups. Consequently, the relationships between taxane-based adjuvant chemotherapy and BCRL were independent of the confounding factors evaluated in this investigation, including patient demographics, treatment, and clinicopathologic characteristics.

Our results are consistent with a major prospective cohort research[17] undertaken at the Massachusetts General Hospital in the United States. They studied the link between taxane-based chemotherapy and the incidence of lymphedema in 1 221 breast cancer patients who were followed for 2 years. In a multivariate analysis, patients who received taxane-based chemotherapy were not significantly different from those who did not. These may be due to the low cumulative incidence of lymphedema across the cohort and instability of multivariate analysis in lymphedema risk factors (e.g. ALND) identification. In this study, the use of PSM removed the effect of other risk variables on BCRL, which may explain our findings. A study[38] from the 2022 San Antonio Breast Cancer Symposium also showed that adjuvant chemotherapy, including taxane-based chemotherapy, was not associated with a significant increase in the risk of BCRL. To determine adjusted hazard ratios, a Cox regression model was employed in the study. The results were adjusted for BMI at baseline, ALND, RLNR, age at diagnosis, and smoking history. The findings demonstrated that adjuvant chemotherapy is not an independent risk factor for BCRL. Our results were similar in that we conducted a multifactorial analysis of the primary population before PSM, and after adjusting for other factors, the results also indicated that chemotherapy was not a risk factor for BCRL.

Previous study[35] has shown that exposure to taxanes can induce endothelial inflammation, leading to abnormal capillary permeability. Other researchers[36] have concluded that taxanes cause progressive protein accumulation in the interstitial space due to abnormal capillary permeability, thereby enlarging the interstitial extracellular fluid compartment and often leading to fluid retention in edema. Although the mechanism of this fluid retention shares certain similarities with the pathogenesis of lymphedema in breast cancer patients, the findings of this study suggest that drug-induced edema and lymphedema may represent two distinct pathophysiological processes. Edema caused by taxane drugs is typically reversible and cyclical, whereas lymphedema is a chronic, progressive condition resulting from damage to the lymphatic system. The findings of this study suggest that clinicians should be vigilant against misinterpreting transient edema during chemotherapy as an early manifestation of lymphedema. Given the well-established survival benefit of taxane-based therapies, these results further support their value in adjuvant breast cancer treatment. For patients, this discovery may also alleviate concerns that chemotherapy could exacerbate lymphedema, thereby improving treatment adherence and quality of life.

This is the first study to our knowledge that employs PSM to analyze and evaluate the relationship between taxane-based treatment and the risk of BCRL. Since the propensity score was applied to all the selected patients and the final matching was based on the propensity score, overfitting in this study was substantially mitigated compared to normal multivariate regression. Our results fill a gap in the research on the relationship between lymphedema and taxane-based chemotherapy among Chinese breast cancer patients. Moreover, our findings will improve patient education about the potential association between BCRL and adjuvant chemotherapy, particularly taxane-based chemotherapy.

Several limitations should be carefully noted in this investigation. The first systematic error source is recall bias, a well-known cause of erroneous associations between exposures and the outcome of interest. Second, the retrospective study design made it impossible to make causal inferences on the association between taxane-based treatment and BCRL. Therefore, additional prospective trials are required to assess whether taxane-based chemotherapy increases the incidence of BCRL. In addition, our findings cannot be extended to the broader Chinese population because all subjects were selected from the same province.

This study used a PSM analysis to indicate that taxane-based chemotherapy does not increase the incidence of BCRL beyond that of other known risk factors. However, more study is needed to assess the association of taxane-based treatment with BCRL risk. It is suggested that prospective study designs, large

©Journal of Central South University (Medical Science). All rights reserved.

samples, and various centers be used in future research.

Contributions： KANG Dan Research design, paper writing and revision; YAN Huang and WANG Ling Research design, paper supervision and revision; LU Qing and CHEN Haibing Data collecting, analysis, and correction. The final version of the manuscript has been approved and read by all authors.

Conflict of interest: The authors declare that they have no conflicts of interest to disclose.

References

[1] Martínez-Jaimez P, Armora Verdú M, Forero CG, et al. Breast cancer-related lymphoedema: Risk factors and prediction model [J]. J Adv Nurs, 2022, 78(3): 765-775. https://doi.org/10.1111/jan.15005.

[2] DeSantis CE, Ma JM, Gaudet MM, et al. Breast cancer statistics, 2019[J]. CA Cancer J Clin, 2019, 69(6): 438-451. https://doi.org/10.3322/caac.21583.

[3] Asdourian MS, Skolny MN, Brunelle C, et al. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis[J/OL]. Lancet Oncol, 2016, 17(9): e392-e405[2025-08-01]. https://doi.org/10.1016/S1470-2045(16)30204-2.

[4] DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis[J]. Lancet Oncol, 2013, 14(6): 500-515. https://doi.org/10.1016/S1470-2045(13)70076-7.

[5] He L, Qu H, Wu Q, et al. Lymphedema in survivors of breast cancer (Review)[J]. Oncol Lett, 2020: 2085-2096. https://doi.org/10.3892/ol.2020.11307.

[6] McEvoy MP, Ravetch E, Patel G, et al. Prevention of breast cancer-related lymphedema[J]. Clin Breast Cancer, 2021, 21(2): 128-142. https://doi.org/10.1016/j.clbc.2021.02.009.

[7] Dayan JH, Ly CL, Kataru RP, et al. Lymphedema: pathogenesis and novel therapies[J]. Annu Rev Med, 2018, 69: 263-276. https://doi.org/10.1146/annurev-med-060116-022900.

[8] Boyages J, Xu Y, Kalfa S, et al. Financial cost of lymphedema borne by women with breast cancer: Financial cost of lymphedema[J]. Psycho Oncol, 2017, 26(6): 849-855. https://doi.org/10.1002/pon.4239.

[9] Dominick SA, Natarajan L, Pierce JP, et al. The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL Study[J]. Psycho Oncol, 2014, 23(9): 1049-1056. https://doi.org/10.1002/pon.3510.

[10] De Vrieze T, Gebruers N, Nevelsteen I, et al. Breast cancer-related lymphedema and its treatment: how big is the financial impact? [J]. Support Care Cancer, 2021, 29(7): 3801-3813. https://doi.org/10.1007/s00520-020-05890-3.

[11] McDuff SGR, Mina AI, Brunelle CL, et al. Timing of lymphedema after treatment for breast cancer: when are patients most At risk?[J]. Int J Radiat Oncol, 2019, 103(1): 62-70. https://doi.org/10.1016/j.ijrobp.2018.08.036.

[12] Ferguson CM, Swaroop MN, Horick N, et al. Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer[J]. J Clin Oncol, 2016, 34(7): 691-698. https://doi.org/10.1200/JCO.2015.61.5948.

[13] Fu M, Axelrod D, Guth A, et al. Patterns of obesity and lymph fluid level during the first year of breast cancer treatment: a prospective study[J]. J Pers Med, 2015, 5(3): 326-340. https://doi.org/10.3390/jpm5030326.

[14] Schmitz KH, Troxel AB, Dean LT, et al. Effect of home-based exercise and weight loss programs on breast cancer-related lymphedema outcomes among overweight breast cancer survivors: the WISER survivor randomized clinical trial[J]. JAMA Oncol, 2019, 5(11): 1605-1613. https://doi.org/10.1001/jamaoncol.2019.2109.

[15] McLaughlin SA, Brunelle CL, Taghian A. Breast cancer-related lymphedema: risk factors, screening, management, and the impact of locoregional treatment[J]. J Clin Oncol, 2020, 38(20): 2341-2350. https://doi.org/10.1200/jco.19.02896.

[16] Cariati M, Bains SK, Grootendorst MR, et al. Adjuvant taxanes and the development of breast cancer-related arm lymphoedema [J]. Br J Surg, 2015, 102(9): 1071-1078. https://doi.org/10.1002/bjs.9846.

[17] Swaroop MN, Ferguson CM, Horick NK, et al. Impact of adjuvant taxane-based chemotherapy on development of breast cancer-related lymphedema: results from a large prospective cohort[J]. Breast Cancer Res Treat, 2015, 151(2): 393-403. https://doi.org/10.1007/s10549-015-3408-1.

[18] Zhu W, Li D, Li X, et al. Association between adjuvant docetaxel-based chemotherapy and breast cancer-related lymphedema[J]. Anti Cancer Drugs, 2017, 28(3): 350-355. https://doi.org/10.1097/cad.0000000000000468.

[19] Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer[J]. J Clin Oncol, 2003, 21(6): 976-983. https://doi.org/10.1200/JCO.2003.02.063.

[20] Martín M, Seguí MA, Antón A, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer[J]. N Engl J Med, 2010, 363(23): 2200-2210. https://doi.org/10.1056/nejmoa0910320.

[21] Brønstad A, Berg A, Reed RK. Effects of the taxanes paclitaxel and docetaxel on edema formation and interstitial fluid pressure [J/OL]. Am J Physiol Heart Circ Physiol, 2004, 287(2): H963-H968[2025-08-01]. https://doi.org/10.1152/ajpheart.01052.2003.

[22] Goble S, Bear HD. Emerging role of taxanes in adjuvant and neoadjuvant therapy for breast cancer The potential and the questions[J]. Surg Clin N Am, 2003, 83(4): 943-971. https://doi.

©Journal of Central South University (Medical Science). All rights reserved.

org/10.1016/S0039-6109(03)00071-9.

[23] Jung SY, Shin KH, Kim M, et al. Treatment factors affecting breast cancer-related lymphedema after systemic chemotherapy and radiotherapy in stage II/III breast cancer patients[J]. Breast Cancer Res Treat, 2014, 148(1): 91-98. https://doi.org/10.1007/s10549-014-3137-x.

[24] Thiese MS. Observational and interventional study design types; an overview[J]. Biochem Med, 2014, 24(2): 199-210. https://doi.org/10.11613/BM.2014.022.

[25] Grosu S, Rospleszcz S, Hartmann F, et al. Associated factors of white matter hyperintensity volume: a machine-learning approach [J]. Sci Rep, 2021, 11: 2325. https://doi.org/10.1038/s41598-021-81883-4.

[26] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies[J]. Multivar Behav Res, 2011, 46(3): 399-424. https://doi.org/10.1080/00273171.2011.568786.

[27] Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect[J]. Am J Epidemiol, 2006, 163(3): 262-270. https://doi.org/10.1093/aje/kwj047.

[28] Morris MJ, Loriot Y, Sweeney CJ, et al. *Radium*-223 in combination with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase 1 dose escalation/randomised phase 2a trial[J]. Eur J Cancer, 2019, 114: 107-116. https://doi.org/10.1016/j.ejca.2019.04.007.

[29] Yoo JN, Cheong YS, Min YS, et al. Validity of quantitative lymphoscintigraphy as a lymphedema assessment tool for patients with breast cancer[J]. Ann Rehabil Med, 2015, 39(6): 931. https://doi.org/10.5535/arm.2015.39.6.931.

[30] Bar Ad V, Cheville A, Solin LJ, et al. Time course of mild arm lymphedema after breast conservation treatment for early-stage breast cancer[J]. Int J Radiat Oncol, 2010, 76(1): 85-90. https://doi.org/10.1016/j.ijrobp.2009.01.024.

[31] Morgan CJ. Reducing bias using propensity score matching [J]. J Nucl Cardiol, 2018, 25(2): 404-406. https://doi.org/10.1007/s12350-017-1012-y.

[32] MacKey JR, Martin M, Pienkowski T, et al. Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial[J]. Lancet Oncol, 2013, 14(1): 72-80. https://doi.org/10.1016/S1470-2045(12)70525-9.

[33] Giordano SH, Lin YL, Kuo YF, et al. Decline in the use of anthracyclines for breast cancer[J]. J Clin Oncol, 2012, 30(18): 2232-2239. https://doi.org/10.1200/jco.2011.40.1273.

[34] Semb KA, Aamdal S, Oian P. Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment[J]. J Clin Oncol, 1998, 16(10): 3426-3432. https://doi.org/10.1200/JCO.1998.16.10.3426.

[35] Béhar A, Pujade-Lauraine E, Maurel A, et al. The pathophysiological mechanism of fluid retention in advanced cancer patients treated with docetaxel, but not receiving corticosteroid comedication[J]. Brit J Clinical Pharma, 1997, 43 (6): 653-658. https://doi.org/10.1046/j.1365-2125.1997.00613.x.

[36] Tokumoto H, Akita S, Nakamura R, et al. Investigation of the association between breast cancer-related lymphedema and the side effects of taxane-based chemotherapy using indocyanine green lymphography[J]. Lymphatic Res Biol, 2022, 20(6): 612-617. https://doi.org/10.1089/lrb.2021.0065.

[37] Jeong SH, Chun SM, Lee H, et al. Association between chemotherapy and the risk of developing breast cancer-related lymphedema: a nationwide retrospective cohort study [J]. Support Care Cancer, 2025, 33(2): 143. https://doi.org/10.1007/s00520-025-09169-3.

[38] Jung AW, Juhel B, Smith LH, et al. Abstract P1-12-05: The impact of adjuvant chemotherapy, taxanesincluding, on breast cancer-related lymphedema risk[J/OL]. Cancer Res, 2023, 83(5_Supplement): P1-12-05[2025-08-01]. https://doi.org/10.1158/1538-7445.SABCS22-P1-12-05.

(Edited by YOU Yi)

©Journal of Central South University (Medical Science). All rights reserved.