

Risk Factors for Breast Cancer-Related Upper Extremity Lymphedema: Is Immediate Autologous Breast Reconstruction one of them?

Research Article

Akif Serhat Gur*, Bulent Unal, Gretchen Ahrendt, Michael L. Gimbel, Oguz Kayiran, Ronald Johnson, Marguerite Bonaventura, Atilla Soran

*Magee-Womens Hospital of the University of Pittsburgh,
Medical Center Pittsburgh, 15213 PA, USA*

Received 25 November 2008; Accepted 2 January 2009

Abstract: Breast cancer related upper extremity lymphedema (BCRL) reduces the quality of life of those who have had surgery for breast cancer. The aim of this study is to evaluate the risk factors for BCRL and determine whether immediate autologous tissue breast reconstruction is one of them. A case control study was conducted comparing patients with BCRL (n=97) to surgically treated breast cancer patients without BCRL (control, n=126). The groups were matched for age, type of breast surgery and radiation therapy. Postoperative upper extremity infection, body mass index (BMI), occupation (level of hand-use), and immediate autologous tissue breast reconstruction were investigated as a risk factor of BCRL. Mastectomy was performed on 47.6 % (n=60) and 37.2% (n=36) of patients in the control and the BCRL groups, respectively. Eight patients (13.3%) had immediate autologous tissue breast reconstruction in the control mastectomy group. Six of 36 BCRL patients (16.7%) underwent mastectomy with immediate autologous tissue breast reconstruction. There was no significant difference between groups with respect to incidence or method of immediate reconstruction (p=0.65). Patient occupation (level of hand use) was found to be positively correlated to development of BCRL (p=0.0001). Upper extremity infection rate was 22.7% in the BCRL group and 4.0% in the controls (p=0.0001). The mean BMI in the control and BCRL groups 26.8 kg/m² and 29.1kg/m², respectively (p=0.003). In conclusion, in this study characteristics positively associated with development of BCRL included occupation, infection, and increased BMI. Immediate reconstruction of the breast was not found as a risk factor for BCRL. However larger studies are needed, to further evaluate the effect of breast reconstruction on BCRL.

Keywords: Breast Cancer • Arm lymphedema • Immediate reconstruction • Occupation • Body mass index • Infection

© Versita Warsaw and Springer-Verlag Berlin Heidelberg.

1. Introduction

Breast cancer-related upper extremity lymphedema (BCRL) is a chronic, progressive, and multifactorial process characterized by swelling in the arm and adjacent trunk and changes to the skin and underlying tissues [1]. BCRL is the most commonly reported complication after breast cancer (BC) related surgery and adversely affects the quality of life of BC patients. Although its incidence is decreasing due to early diagnosis, changing treatment strategies, and sentinel lymph node biopsy techniques, BCRL still remains a significant concern for patients and their health care providers [1,2]. Neither medical nor surgical treatment provides a cure for BCRL; therefore, risk stratification and prevention are the most important strategies in decreasing morbidity.

The etiology and risk factors of BCRL in patients with BC are multifactorial and not fully understood. Although BCRL-related studies are few, most group divide BCRL risk factors into three main categories: treatment related, disease related, and patient related [3,4]. Treatment related factors include surgery, radiotherapy (RT), chemotherapy, and combined treatments [5-7]. Disease related factors include tumor stage at time of diagnosis, pathologic nodal status, number of removed lymph nodes, and the location of the tumor in the breast [8,9]. Patient related factors include age at diagnosis, high body mass index (BMI), hypertension, history of infection or inflammation, hand dominance, and excessive use of the affected limb [1,10-12].

Breast reconstruction results in improved self-image, psychological well-being, and restoration of

* E-mail: akifserhatg@upmc.edu

physical form after mastectomy. To achieve optimal long-term results, the BC team consisting of medical, surgical, and radiation oncologists, must work closely together with the plastic surgeon in coordinating surgical excision, radiation, chemotherapy and reconstruction timing. Options for breast restoration include prosthetic-based reconstruction with an implant, autologous tissue reconstruction with a pedicled or free flap, and a combination of both methods. Any form of reconstruction may be performed at the time of mastectomy (immediate reconstruction) or at a date weeks to years later (delayed reconstruction) [13]. To our knowledge, the relationship between breast reconstruction and BCRL has not been specifically investigated. It is still unclear if performing breast reconstruction affects the risk of developing or worsening BCRL. Furthermore, it is not known whether the methods used vary in that potential risk.

The objective of this retrospective case-control study is to evaluate the risk factors for BCRL. The second objective is to investigate the effect of immediate breast reconstruction on BCRL after BC surgery.

2. Material and Methods

This study was designed as a 1:1 matched case-control study. The BCRL cases were matched by age (within 10 years), RT, and type of surgical extirpation (segmental mastectomy (SM) or modified radical mastectomy (MRM)). All patients underwent axillary dissection in both groups. Data was collected on 126 control patients without BCRL and 97 women with BCRL. The control patients were selected randomly from a similar patient population, adhering to the stratification criteria. Fifty-two of 97 patients in BCRL group represent patients reported in our previous study [12]. All patients had previously undergone their definitive surgical procedure and BCRL treatment at the Magee-Womens Hospital of the University of Pittsburgh Medical Center. The BCRL risk factors that were evaluated included: postoperative upper extremity infection (cellulitis) (y/n), occupation/hobby (self reported), BMI, and immediate reconstruction (y/n). The BMI risk factor was subdivided into a normal group ($BMI < 25 \text{ kg/m}^2$), an overweight group ($BMI 25-29.9 \text{ kg/m}^2$), and an obese group ($BMI \geq 30 \text{ kg/m}^2$).

Because delayed reconstructions might have been performed at outside institutions with inconsistent access to medical records, only immediate breast reconstruction procedures are included in this study. All immediate reconstructions included in this study involved autologous tissue in order to evaluate whether the flap tissue had an effect on lymphatic drainage. There was no patient in our lymphedema registry data that had

Table 1. Stillwell classification for lymphedema.

Insignificant	0-10% >normal arm
Slight	11-20% >normal arm
Moderate	21-40% >normal arm
Marked	41-80% >normal arm
Severe	more than 80% >normal arm

undergone implant/tissue expander reconstructions.

We used the Stillwell classification for the severity of BCRL [14] (Table 1). Based on the Stillwell classification, severity of BCRL was defined as none (controls), mild (<20% of initial volume) or moderate/severe ($\geq 20\%$ initial volume). Before starting on BCRL treatment, the Magee Womens Hospital physical therapy department calculated the volume of the normal and the affected arms in each BCRL patient. The measurement technique and BCRL evaluation method were performed as described previously [12].

The occupation/hobby factor was determined by the patient's present job and categorized as low, medium, or high activity, as described previously [12]. We created a much more simplified classification system in place of the Standard Occupational Classification System 2000 which is used by Federal statistical agencies to classify workers into occupational categories for the purpose of collecting, calculating, or disseminating data (<http://www.bls.gov/SOC/>) [15]. We narrowed the Standard Classification System to better adapt to our patient's occupations. According to this new system, Occupation Group I (retired, homemaker, clerk, attorney, or teller) included working continuously less than thirty minutes at a time and equal to or less than eight hours per day. Occupation Group II (secretary, bank teller, accountant, cook, or school teacher) included working continuously between thirty to sixty minutes at a time, and equal to or less than eight hours per day. Occupation Group III (physician, waitress, pianist, registered nurse, or laborer) included working continuously for more than one hour and at least eight hours per day.

2.1. Statistical analysis

The data was statistically analyzed with the SPSS version 14.0 software package (SPSS Inc, Chicago, IL). The BMI values were entered as continuous variables and analyzed with a one-way ANOVA test. The other parameters were analyzed as categorical variables with chi-square test. In addition, reconstruction data was compared with the other factors via Kruskal-Wallis test. The p value below 0.05 was accepted as statistically significant.

Table 2. Patients' characteristics.

	BCRL (-)	BCRL (+)	p value
	n=126	n=97	
AGE (years)	52.7 (range: 30-79)	55.6 (range: 32-83)	>0.05
OPERATION			0,145
sm	66 (52.4%)	58 (59.8%)	
mrm	60 (47.6%)	36 (37.2%)	
RADIOTHERAPY			0,091
no	37 (29.4%)	20 (20.6%)	
yes	89 (70.6%)	77 (79.4%)	

BCRL: breast cancer related upper extremity lymphedema

sm: segmental mastectomy,

mrm: modified radical mastectomy.

Table 3. Parameters associated with BCRL.

	BCRL (-)	BCRL (+)	p value
	n=126	n=97	
LYMPHEDEMA			
Stage I		53 (54.6%)	
Stage II		34 (35.1%)	
Stage III		9 (9.3%)	
INFECTION			
no	121 (96.0%)	75 (77.3%)	<0,0001
yes	5 (4.0%)	21 (22.7%)	
OCCUPATION			
1	92 (73.0%)	41 (45.3%)	
2	23 (18.3%)	19 (19.6%)	<0,0001
3	11 (8.7%)	34 (35.1%)	
BODY MASS INDEX (kg/m²)	26.8 kg/m ²	29.1 kg/m ²	0,003*
RECONSTRUCTION	8/60 (13.3%)	6/36 (16.7%)	0,594

BCRL: breast cancer related upper extremity lymphedema

*: p value was obtained via one-way ANOVA test.

3. Results

The mean age were 52.7 (range: 30-79 years) and 55.6 (range: 32-83 years) in control and BCRL group, respectively ($p>0.05$). Of the 97 patients with BCRL, 13.4% ($n=13$) were >70 years old while only 3.2% ($n=4$) of 126 control patients were >70 ($p=0.005$) (Table 2).

The infection rate was higher in the BCRL group (22.7%) compared to control patients (4.0%, $p<0.0001$). Of 126 patients in the control group 73% were in Occupation Group I, 18.3% were in Occupation Group II, and 8.7% were in Occupation Group III. The majority of BCRL patients were in Occupation Group II (19.6%) and III (35.1%), with only 45.3% in Occupation Group I ($p<0.0001$). The BMI of BCRL patients was higher than that of the controls. Thirty-six patients (37.2%) had BMIs greater than 30 kg/m² in BCRL group compared to 35 patients (27.7%) in the control group. The mean BMI in

control and BCRL patients were 26.8 kg/m² and 29.1 kg/m², respectively ($p=0.003$) (Table 3).

Of the 60 control patients with mastectomy, eight (13.3%) had undergone breast reconstruction, all of them were transverse rectus abdominis musculocutaneous (TRAM) (4 free, 4 pedicled). Six of 36 BCRL patients (16.7%) had undergone breast reconstruction: four TRAMs (1 free, 3 pedicled), one latissimus dorsi (pedicled) musculocutaneous flap, and one free superior gluteal artery perforator flap. The rate of reconstruction was not statistically different between the BCRL and control groups ($p>0.05$). Of the six BCRL patients who had undergone breast reconstruction, two (33%) had stage I BCRL and four (67%) had stage II BCRL. Of the unreconstructed BCRL patients, the majority (57%) had stage I BCRL.

4. Discussion

BCRL is the most commonly reported complication after BC related surgery and adversely affects the quality of life of BC patients. The BCRL literature is controversial and limited because studies tend to be retrospective, have small sample sizes, or are from a single institution. Additionally, the definitions of BCRL and measurement techniques vary widely. The risk factors for BCRL are described as treatment related, disease related, and patient related [3,4]. BMI is one of the patient related factors which could affect BCRL. The study from Memorial-Sloan Kettering Cancer Center showed the most statistically significant predictive factor was BMI and RT in patients treated with breast conserving surgery [9]. Johansson et al analyzed the risk factors of 71 BCRL patients and found that BMI adversely affects development of BCRL in the BC patients [16]. Our previous study confirms this finding [12]. In the present study, the mean BMI values were significantly different between the control and BCRL groups.

A correlation between postoperative upper extremity infections and upper extremity edema was reported in several studies [10,17,18]. Various studies have shown that cellulitis complicates lymphedema [19,20]. However, some studies did not demonstrate a significant effect of upper extremity infection on the BCRL [16,21]. We demonstrated previously that postoperative upper extremity infection significantly increases BCRL [12]. The present study confirms this finding.

Our group previously showed that level of hand use is a significant factor for BCRL [12]. In our prior study we classified the hand use as low, medium, and high according their occupation. In the present study we modified the classification of the level of hand use and more objective criteria are incorporated (total work time per day and time of continuous hand usage per hour). Based on our new classification we confirmed that occupation is a risk factor for BCRL. Hayes *et al.* [21] evaluated the effect of patient lifestyle on BCRL. They found that sedentary lifestyle is a risk factor for BCRL. But they also showed that the surgical treatment of dominant or nondominant side in breast cancer patients is not a risk factor for BCRL. Johanson *et al.* [16] evaluated the effect of occupation but they could not any correlation between occupation and BCRL. In the present study, use of a classification system which was based on objective criteria may account for the difference with the other studies. Further studies using of this type of classification system for occupation may be more valuable for studying the effect of occupation on BCRL.

It is not known why BCRL does not develop in all patients that undergo axillary surgery for BC. Previous anatomical studies have demonstrated that the performance of axillary dissection stimulates communication between the deep and superficial lymphatic systems, even in patients that show no evidence of BCRL [22]. Deutsch *et al.* [23] evaluated factors contributing to BCRL in patients enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B04 trial. NSABP B-04 showed that radical mastectomy is the most important factor for BCRL. Another study confirmed that extensive surgery (mastectomy), and age (>50 years) are risk factors for BCRL [21]. Because more extensive surgery may result in greater interruption of lymphatic drainage, it is plausible that breast reconstruction procedures may increase the risk of BCRL. The existing surgical literature has not addressed this possibility. A study from MD Anderson Cancer Center evaluated the effect of the transition from complete axillary lymph node dissection to sentinel lymph node biopsy on their practice of breast reconstruction after BC surgery [24]. They report that with increasing use of sentinel node biopsy for staging the clinically negative axilla, there is a significant increase in the rate of immediate free TRAM flap reconstructions. In this study, plastic surgeons preferentially utilized the internal mammary vessels instead of thoracodorsal vessels. They attributed the decrease in BCRL rates to increased utilization of sentinel lymph node biopsies. One may interpret this sub-group analysis that immediate TRAM reconstruction does not increase BCRL. In another study by Jhaveri *et al.* [25], autologous reconstruction was superior to implant surgery in reducing long term complications after BC surgery. Temple *et al.* [26] compared recipient vessel choice for delayed free TRAM flap reconstructions after completion of RT. The lymphedema rates were 4% for internal mammary recipient vessel group and 9% for the thoracodorsal recipient vessel group. Although the primary objective of this article was not the incidence of arm lymphedema, it does suggest that in patients undergoing delayed reconstruction, characteristics of the reconstructive method may impact the development of BCRL. In the present study, although the number of breast reconstruction patients was small in the groups, there was no significant effect of immediate reconstruction on BCRL in our patients.

In addition to the oncologic procedure, any reconstructive surgery in the axillary region can potentially further jeopardize lymphatic drainage. On the other hand, autologous tissue reconstruction may have a positive effect on lymph drainage. It is well known that communication between superficial and deep lymph

vessels may develop over time in patients who have had axillary dissection [22]. Studies investigating the hemodynamic changes that occur in free flaps for breast reconstruction showed that flap skin perfusion exceeded that of normal skin [27,28]. The effect of this increased blood flow may have a detrimental or beneficial effect on the lymph flow, and should be studied.

References

- [1] Nielsen I., Gordon S., Selby A., Breast cancer-related lymphoedema risk reduction advice: A challenge for health professionals, *Cancer Treat. Rev.*, 2008, 34, 621-8
- [2] Helms G., Kühn T., Moser L., Remmel E., Kreienberg R., Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection - data from a prospective randomised trial, *Eur. J. Surg. Oncol.*, 2008, in press, DOI:10.1016/j.ejso.2008.06.013
- [3] Petrek J.A., Pressman P.I., Smith R.A., Lymphedema: current issues in research and management, *CA Cancer J. Clin.*, 2000, 50, 292-307
- [4] Erickson V.S., Pearson M.L., Ganz P.A., Adams J., Kahn K.L., Arm edema in breast cancer patients, *J. Natl. Cancer Ins.*, 2001, 93, 96-111
- [5] Pressman P.I., Surgical treatment and lymphedema, *Cancer*, 1998, 83, 12(Suppl.), 2782-7
- [6] Meek A.G., Breast radiotherapy and lymphedema, *Cancer*, 1998, 83, 12(Suppl.), 2788-97
- [7] Mortimer P.S., The pathophysiology of lymphedema, *Cancer*, 1998, 83, 12(Suppl.), 2798-802
- [8] Kissin M.W., Querci della Rovere G., Easton D., Westbury G., Risk of lymphedema following the treatment of breast cancer, *Br. J. Surg.*, 1986, 73, 580-84
- [9] Werner R.S., McCormick B., Petrek J., Cox L., Cirincione C., Gray J.R., et al., Arm edema in conservatively managed breast cancer: Obesity is a major predictive factor, *Radiology*, 1991, 180, 177-84
- [10] Segerstrom K., Bjerle P., Graffman S., Nystrom A., Factors that influence the incidence of brachial edema after treatment of breast cancer, *Scand. J. Plast. Recons. Hand Surg.*, 1992, 26, 223-7
- [11] Mozes M., Papa M.Z., Karasik A., Reshef A., Adar R., The role of infection in postmastectomy lymphedema, *Ann. Surg.*, 1982, 14, 73-83
- [12] Soran A., D'Angelo G., Begovic M., Ardic F., Harlak A., Samuel Wieand H., et al., Breast cancer-related lymphedema--what are the significant predictors and how they affect the severity of lymphedema? *Breast J.*, 2006, 12, 536-43
- [13] Sullivan S.R., Fletcher D.R., Isom C.D., Isik F.F., True incidence of all complications following immediate and delayed breast reconstruction, *Plast. Reconstr. Surg.*, 2008, 122, 19-28
- [14] Stillwell G.K., Treatment of postmastectomy lymphedema, *Mod. Treatment*, 1969, 6, 396-412
- [15] Standard Occupational Classification 2000. Bureau of Labor Statistics <http://www.bls.gov/SOC/>
- [16] Johansson K., Ohlsson K., Ingvar C., Albertsson M., Ekdahl C., Factors associated with the development of arm lymphedema following breast cancer treatment: a match pair case-control study, *Lymphology*, 2002, 35, 59-71
- [17] Fernandez J.C., Serin D., Bauges S., Fre'quence des lymphoedemes du membre supe'rieur apre's traitement du cancer du sein. Facteurs du risque. A propos de 683 observations, *Bull Cancer*, 1996, 122, 536-41
- [18] Mozes M., Papa M.Z., Karasik A., Reshef A., Adar R., The role of infection in postmastectomy lymphedema, *Ann. Surg.*, 1982, 14, 73-83
- [19] Woo P.C., Lum P.N., Wong S.S., Cheng V.C., Yuen K.Y., Cellulitis complicating lymphoedema, *Eur. J. Clin. Microbiol. Infect. Dis.*, 2000, 19, 294-7
- [20] Brewer V.H., Hahn K.A., Rohrbach B.W., Bell J.L., Baddour L.M., Risk factor analysis for breast cellulitis complicating breast conservation therapy, *Clin. Infect. Dis.*, 2000, 31, 654-9
- [21] Hayes S.C., Janda M., Cornish B., Battistutta D., Newman B., Lymphedema after breast cancer: incidence, risk factors, and effect on upper body function, *J. Clin. Oncol.*, 2008, 26, 3536-42
- [22] Suami H., Pan W.R., Taylor G.I., Changes in the lymph structure of the upper limb after axillary dissection: radiographic and anatomical study in a human cadaver, *Plast. Reconstr. Surg.*, 2007, 120, 982-91
- [23] Deutsch M., Land S., Begovic M., Sharif S., The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone, *Int. J.*

- Radiat. Oncol. Biol. Phys., 2008, 70, 1020-4
- [24] Kronowitz S.J., Kuerer H.M., Hunt K.K., Ross M.I., Massey P.R., Ensor J.E., et al., Impact of sentinel lymph node biopsy on the evolution of breast reconstruction, *Plast. Reconstr. Surg.*, 2006, 118, 1089-99
- [25] Jhaveri J.D., Rush S.C., Kostroff K., Derisi D., Farber L.A., Maurer V.E., et al., Clinical Outcomes of Postmastectomy Radiation Therapy after Immediate Breast Reconstruction, *Int. J. Radiat. Oncol. Biol. Phys.*, 2008, 72, 859-865
- [26] Temple C.L., Strom E.A., Youssef A., Langstein H.N., Choice of recipient vessels in delayed TRAM flap breast reconstruction after radiotherapy, *Plast. Reconstr. Surg.*, 2005, 115, 105-13
- [27] Figus A., Ramakrishnan V., Rubino C., Hemodynamic changes in the microcirculation of DIEP flaps, *Ann. Plast. Surg.*, 2008, 60, 644-8
- [28] Heitland A.S., Markowicz M., Koellensperger E., Schoth F., Feller A.M., Pallua N., Duplex ultrasound imaging in free transverse rectus abdominis muscle, deep inferior epigastric artery perforator, and superior gluteal artery perforator flaps: early and long-term comparison of perfusion changes in free flaps following breast reconstruction, *Ann. Plast. Surg.*, 2005, 55, 117-21