RESEARCH ARTICLE

Correlates of Lymphedema in Women with Breast Cancer: a Case Control Study in Shiraz, Southern Iran

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Abstract

Globally, the burden of breast cancer (BC) continues to increase. BC related lymphedema (BCRL) is currently non curable and as a life time risk it affects at least 25% of BC patients. Knowing more about BCRL and appropriate control of its modifiable risk factors can improve quality of life (QOL) of the affected patients. In this case control study to detect factors, 400 women with BCRL (as the case group) and 283 patients with BC without lymphedema (as the control group) that were referred to Shiraz University of Medical Sciences affiliated BC clinic center were assessed. The data were analyzed in SPSS. The mean age of the case group was 52.3±11.0 years and of the control group was 50.1±10.9 years. In patients with BCRL, 203(50.7%) had left (Lt) side BC and in non- lymphedema group 151 (53.3%) had Lt side BC. Out of all BCRL patients, 204 (51%) had lymphedema in all parts of their affected upper extremities, 100 (25%) had swelling in the arm and forearm and 23 (5.7%) had edema in both the upper extremity and trunk. Edema, heaviness, concern about changing body image, pain and paresthesia were the most common signs/ symptoms among patients with BCRL. In BCRL patients, the difference of circumference between the affected upper limb and non-affected limb was 4.4±2.5 cm and the difference in volume displacement was 528.7±374.4 milliliters. Multiple variable analysis showed that moderate to severe activity (OR; odds ratio =14, 95% CI :2.6-73.3), invasiveness of BC (OR =13.7, 95% CI :7.3-25.6), modified radical mastectomy (OR=4.3, 95% CI :2.3-7.9), BMI =>25 (OR=4.2, 95% CI :2-8.7), radiotherapy (OR=3.9, 95% CI :1.8-8.2), past history of limb damage (OR=1.7, 95% CI :0.9-3.1) and the number of excised lymph nodes (OR=1.06, 95% CI :1.02-1.09) were the significant predictors of lymphedema in women with BC. Modifiable risk factors of BCRL such as non-guided moderate to severe physical activity, high BMI and trauma to the limb should be controlled as early as possible in BC patients to prevent development of BCRL and improve QOL of these patients.

Keywords: Breast cancer - determinants - lymphedema - QOL

Introduction

Globally, burden of breast cancer (BC) continues to increase. BC is the second most common cancer among all cancers and the most frequent cancer among women worldwide including 140 of 184 countries and Eastern Mediterranean Region countries (EMRO). It caused 1 in 4 of all cancers in women with 1.7 million new diagnosed patients in 2012. BC is also the fifth cause of death from cancer with 522,000 deaths in 2012 (Naderimagham et al., 2014).

In Iran, with an age-standardized death rate from cancer of 69.8 per 100,000 for females (Lankarani et al.,2013), BC is the most frequent cancer in women, the 1st cause (14.2%) of death due to cancer among women and the 5th common cause of death in Iranian women while women of 41-50 years of age group are more affected by it (Afsharfard et al., 2013). The age-standardized incidence rate of BC has increased from 16.2 in 1996-2000 to more than 25-30 per 100,000 in 2001-2006, meanwhile the age of incidence is about 10 years lower than western countries (Sadjadi et al., 2009). The general mortality rate of BC increased from 0.9 to 4.3 per 100,000 and more invasive form of BC is seen among younger age groups (Afsharfard et al., 2013).The Standardized mortality ratios (SMRs) for Iranian women with BC at 5-15 year intervals after diagnosis is 6.7- 1.3 (Haghighat et al., 2012). BC patients suffer from many problems, among these, BC related lymphedema (BCRL) as one of the most important sequelae of the treatment of BC affects at least 1 in 5 women with BC (Michael et al., 2011; Disipio et al., 2013). BCRL continues to challenge

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clinicians worldwide and it has remained a potentially life-time and irreversible complication that is leaving chronic physical, psychological and emotional consequences for BC patients (Merchant and Chen., 2015). Quality of life (QOL) is impaired remarkably in women with BCRL via inducing pain, heaviness, tightness, decreased range of motion, restriction at work or home, personal care functions and by imposing anxiety, depression, and emotional distress on these patients (Disipio et al., 2013; Taghian et al., 2014; Merchant and Chen., 2015). Some reports showed that lymphedema may also shorten survival (Afsharfard et al., 2013; DiSipio et al., 2013). Therefore, considering increased incidence of BC and improved 5-year survival of BC patients, more attention should be focused on QOL of these patients. This study was aimed to improve understanding of correlation between lymphedema in Iranian women with BC to provide more evidences for preventive strategies targeting disabling and distressing disorder.

Materials and Methods

In this Case Control study, during an 8- month period from February 2014 to September 2015, 400 women with BC and lymphedema (as the case group) and 283 patients with BC without lymphedema (as the control group) that referred to Shiraz University of Medical Sciences (SUMS) affiliated breast cancer clinic center were assessed. The sample size in the case group was calculated with presumption of 50% incidence of secondary lymphedema in treated BC patients, a 5% precision level, and a confidence level of 95%. Patients were selected through a systematic randomized sampling. Data were extracted from the medical records of patients. Excluded patients were non treated BC patients, patients with bilateral BC, and patients who were not followed after their treatment. We did not match two groups of case and control, due to presumption of effect of all studied variables in development of lymphedema. Acquired data included demographic characteristics, body mass index (BMI), physical activity (mild, moderate or severe), right versus left side BC, pathologic tumor report (tumor size, being invasive or non-invasive, histological grading), number of lymph nodes that were excised or affected, receptor status of tumor (estrogen, progesterone and human epidermal growth factor receptor (HER2)) , presence of metastasis, type of treatment of BC (modified radical mastectomy, conservative surgery, chemotherapy, radiotherapy, hormone therapy), duration and frequency of chemotherapy, radiotherapy, and hormone therapy. Pattern of distribution and signs/symptoms of lymphedema, past medical history (history of limb damage, lymphangitis, previous lymphedema treatment, diabetes mellitus (DM), hypertension (HTN), congestive heart failure (CHF), family history of lymphedema and treatment for lymphedema (in the case group)) were also acquired. Diagnosis of lymphedema in upper limb was made by measuring the difference of circumference of both upper limbs by the same investigator and with the same procedure. If the circumference differences were 2 centimeters (cm)

or higher in any corresponding point, the patient was considered a lymphedema case. Another method of detection of lymphedema of upper extremity was volumetric measurement test through determining water volume displacement and volume reduction by affected limb with lymphedema compared to non- involved limb (McNeely et al.,2004). Volumes were measured in two specially-constructed cylindrical plexi-glass tanks that both have two drainage taps. The main (internal) tank measured 70 cm in height by 21 cm in diameter. The external tank measured 60 cm in height and 31 cm in diameter. The internal tank has section area about 330 cm² and was filled with water to a height of 70 cm. The external tank's outer wall was marked in millimeters (ml) and cm to show the height of the water that over-flowed from the inner tank. While standing next to the device, the patient immersed her straightened healthy arm and hand into the inner tank up to a point 15 cm above the olecranon. The height of the displaced water and amount of water spilled into the outer tank were measured in centimeters. Then the patient removed her healthy upper limb and immerses the affected arm and hand into the internal tank, and the height of the displaced water was recorded. To calculate the volume of water displaced by the arm with lymphedema compared to the unaffected limb in ml, the difference between the two measurements was multiplied by the section area of the inner tank (330 cm) (Mcneely et al.,2004). Moreover, Stemmer's test results were collected. To perform this test, skinfold at the base of the second toe or middle finger should be pinched and lifted. Failure to pinching and lifting the skin means that Stemmer's sign is positive and is the sign of lymphedema (Iuchi et al.,2015).

All data were analyzed in the SPSS version 20 software (SPSS, Chicago, IL, USA). The accuracy of data entry was ensured by randomly selecting and checking data against their corresponding data in the SPSS software. Chi squared and t tests were used as appropriate. After single variable analysis, multiple analysis was done by including variables with p values <0.2 in the logistic regression (Enter method). P values less than 0.05 was considered significant.

Ethics

The protocol of this research was approved by research ethics committee of health policy research center affiliated with SUMS.

Results

Out of 683 studied women with BC, 400(58.6%) had BCRL compared to 283(41.4%) who had only BC. The mean age of case group was 52.3±11 years compared to the control group that was 50.1±10.9 years (P=0.01) (Table 1). In patients with lymphedema, 203(50.7%) had left (Lt) side BC and in non-lymphedema group 151(53.3%) had Lt side BC (P=0.5). In BCRL patients 204 (51%) had lymphedema in all parts of the affected upper extremity, 100(25%) had swelling in the arm and forearm and 23 (5.7%) had edema in both upper extremity and trunk, while the rest had a different pattern of distribution

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Table 1 . Single Variable Analysis in Patients with Breast Cancer and Lymphedema (Case Group, n=400) Compared to Patients with Breast Cancer without Lymphedema (Control Group, n=283) (Mild: Sitting, Standing Still or Lying Down, Moderate:Routine Walking, House Working or any Other Activity More than Mildly but to Highly Demanding, High: Aerobic Exercise, Hard House Working, Climbing Stairs or any Other Activity Causing Sweating or Increased Heart Rate.

Type	Variable		Mean± SD,N(%)	P value	OR (95%CI)
Demographic , Anthropometri and Activity level	Age	Case	52.3 ± 11 (Yrs)	0.01	-
		Control	50.1 ± 10.9		
	BMI	Case	340.0(85%)/60.0(15%)	<0.01	2.5(1.7-3.7)
	(=>25 /<25)	Control	195.0(68.9%)/88.0(31.1%)		
	Education	Case	319.0(79.7%) /81.0 (20.3 %)	0.90	0.9(0.6-1.4)
	(=<12 / >12yrs)	Control	225.0 (79.5%) /58.0(20.5 %)		
	Marital status(Married/Single)	Case	298.0 (74.5%) /102.0 (25.5%)	0.20	0.8(0.5-1.1)
		Control	221.0 (78 %) / 62.0(22 %)		
	Physical Activity	Case	377.0(94.2%)/4(1%)	<0.01	4.9(1.6-15.1)
	(Moderate or Severe/ Mild)†	Control	268(94.6%)/14(4.9%)		
	Involved Breast	Case	197 (49.2%) / 203 (50.8	0.50	1.1(0.8-1.5)
	(Right / Left)	Control	%)132 (46.6%) / 151 (53.4%)		
Diagnostic	Pathology	Case	258 (64.5%)/ 142(35.5%)	<0.01	3.7(2.7-5.2)
	(Invasive / Non Invasive)	Control	92 (32.5 %) / 191 (67.5 %)		
	Tumor Size	Case	341 (85.2%)/59 (14.8%)	0.04	1.5(1-2.2)
	(2cm< / =<2 cm)	Control	220 (77.8%)/63(22.2 %)		
	Number of Lymph nodes excised	Case	20.1 ± 9.5	<0.01	-
		Control	12.9 ± 9.7		
	Number of Lymph nodes affected	Case	5.7 ±7.8	<0.01	-
		Control	2.1± 4.1		
	Receptor(positive / negative)	Case	266(66.5 %) /42(10.5 %)	0.20	1.2(0.8-2)
		Control	195(68.9 %) /40 (14.1 %)		
	Metastasis(Yes/No)	Case	33(8.2 %)/225(56.2%)	FE=0.04	0.2(0.09-0.9)
		Control	5(1.7 %)/10(3.5 %)		
Therapeutic	Surgery	Case	251(62.7%)/126(31.5%)	<0.01	3.2(2.3-4.4)
	(Modified Radical Mastectomy /Conservative surgery)	Control	107(37.8%)/174(61.4%)		
	Chemotherapy	Case	391(97.7%)/5(1.2%)	<0.01	11.3(4.4-29.4)
	(Yes/No)	Control	247(87.2%)/36(12.7%)		
	Chemotherapy duration(week)	Case	17.8±4.1	<0.01	-
		Control	16.7±4.2		
	Chemotherapy sessions	Case	7.2±1.4	0.04	-
		Control	6.9±1.9		
	Radiotherapy	Case	341(85.2%)/51(12.7%)	<0.01	3.5(2.4-5.2)
	(Yes/No)	Control	184(65%)/99(34.9%)		
	Hormone therapy	Case	281(70.2%)/113(28.2%)	<0.01	1.6(1.1-2.2)
	(Yes/No)	Control	170(60%)/113(39.9%)		
Past History	Previous history limb damage	Case	110(27.5%)/28(7%)	<0.01	1.5(1.1-2.1)
	(Yes/No)	Control	107(37.8%)/175(6.8%)		
	Previous history of lymphangitis	Case	47(11.7%)/340(85%)	<0.01	1.1(1-1.1)
	(Yes/No)	Control	0(0%)/282(99.6%)		
	Previous history of lymphedema treatment	Case	36(9%)/360(90%)	<0.01	1.1(1-1.1)
	(Yes/No)	Control	0(0%)/283(100%)		

of lymphedema. Moreover, in the case group 185 (46.2%) had concern about their body image. In BCRL patients, the difference of circumference between affected upper limb and non-affected limb was 4.4±2.5 cm and the difference in volume displacement by volumetric measurement test was 528.7±374.4 ml. Most of patients with BCRL (258; 64.5%) had invasive BC compared to the majority of non-lymphedema group (191;67.4%) that had non-invasive types of BC (P<0.01). Similarly, chemotherapy was 11.3 times, moderate to severe physical activity was 4.9 times, radiotherapy was 3.5 times, modified radical mastectomy was 3.2 times, BMI was 2.5 times, hormone therapy was 1.6 times, tumor size larger than 2 cm was 1.5 times and number of excised or affected lymph nodes were more frequent in the lymphedema group (P<0.05) (Table1).Moreover, edema was 36.4 times, paresthesia was 5.6 times, sense of heaviness was 5.5 times, moderate to severe pain was 4.7 times, lymphostasis was 3 times, Stemmer's sign was 2.8 times, previous history of upper limb damage was 1.5 times, limited range of motion of upper extremity was 1.3 times and history of lymphangitis was 1.1 times more common in BCRL group. However, education, having job, marital status, frequency of right (Rt) versus Lt hand dominancy, histological grading of BC, existing receptors in involved tissues, Rt vs. Lt mastectomy, comorbidities, markers of cancers (CA 15-3,CA 125, CEA; carcino embryogenic antigen) were not different among BC patients with or without lymphedema (P>0.05). Multiple variable analysis showed that moderate to severe activity (OR; odds ratio =14), invasiveness of tumor (OR =13.7), modified radical mastectomy (OR=4.3), BMI =>25(OR=4.2), radiotherapy (OR=3.9), past history of limb damage (OR=1.7) and the number of excised lymph nodes (OR=1.1) were significant predictors of

Table 2. Multiple Variable Analysis (Logistic Regression: Enter Method) in Patients with Breast Cancer and Lymphedema

Variable	OR	CI 95%	P value
Physical Activity	14.0	2.6 -73.3	<0.01
(Moderate-Severe, Mild)			
Pathology	13.7	7.3-25.6	<0.01
(Invasive , Non Invasive)			
Surgery	4.3	2.3-7.9	<0.01
(Modified Radical Mastectomy , Conservative Surgery)			
BMI	4.2	2-8.7	<0.01
(>=25 , <25)			
Radiotherapy	3.9	1.8-8.2	<0.01
(Yes, No)			
History of Limb damage	1.7	0.9-3.1	0.05
(Yes, No)			
Number of Lymph nodes excised	1.1	1-1.1	<0.01

lymphedema in women with BCRL (Table 2).

Discussion

BC has an increasing trend and involves the younger ages more than before. On the other hand, mortality among BC patients is decreasing , however, there are many issues such as BCRL, changed body image, depression, anxiety, stress, changes in relationships with husband and children, dealing with any ongoing side effects and the fear of BC recurrence that these women are chronically challenging (Fu MR., 2014; Jassim et al.,2015). Among these problems, BCRL develops within three years of a BC diagnosis but can occur much later (Fu.,2014). BCRL affects more than one in five women and is currently non curable (Disipio et al., 2013; Iuchi et al.,2015). BCRL imposes physical, psychological and heavy cost consequences upon BC patients (Alcorso and Sherman.,2015; Fu., 2014). Our study revealed that edema, heaviness, concern about body image, pain and paresthesia are the most common signs/symptoms among patients with BCRL. These may be the earliest alarming signs of BCRL as was noted by another study and therefore physicians should be educated about them. (Fu MR., 2014). However, knowing about risk factors of BCRL is more important and may help its prevention. Different studies showed a more and less variant picture of BCRL related risk factors. One study found that breast surgery (lumpectomy or mastectomy), sentinel lymph node biopsy or dissection of axillary lymph nodes, radiotherapy, or chemotherapy, obesity or weight gain after diagnosis, even minor upper extremity infections, trauma to the affected limb, or overuse of the limb are involved in development of BCRL (Fu MR., 2014). Another survey detected that in addition to axillary lymph node dissection (OR=3.7), hypertension (OR=1.8), high body mass index (OR=1.8), chemotherapy (OR=1.3) and radiotherapy (OR=1.3) were effective in BCRL developing (Zhu et al., 2014).More radical axillary surgery, more affected axillary nodes, a postoperative axillary hematoma, seroma, infection, and nodal radiation were also found to be related to BCRL (Golshan M and Smith B.,2006). According to other evidence, correlation of the BMI ≥30 kg/m^2 (OR 1.6),removal of greater number of lymph nodes (OR =1.1) and longer interval since surgery (OR =2.3 at 18 months) were known as correlates of BCRL (Voss et al.,2015).It was shown that overweight BC patients treated with tamoxifen were also at risk of lymphedema and a weight reduction in these patients helps to treat them (Das et al., 2015).On the other hand, T classification (OR=0.5) and stage (OR=0.6) were protective against lymphedema, while age, number of positive lymph nodes, and number of lymph node dissection did not show an obvious correlation (Zhu et al., 2014). In our study, moderate to severe physical activity, invasiveness of BC, modified radical mastectomy, BMI =>25, radiotherapy, past history of limb damage and number of excised lymph nodes were the most significant predictors of lymphedema in women with BCRL respectively. These findings are compatible with other

studies, except that there are contradictory evidences about the effect of physical activity in development or protection of lymphedema. Several studies recommend a guideline based physical exercise in BCRL patients (Fu MR., 2014; Zhu et al., 2014; Voss et al.,2015) . Moreover, reduction of BMI in obese BC patients, prevention of infection or trauma have a protective role against BCRL (Fu MR., 2014; Voss et al.,2015).

Our limitation in this study was that if we could follow the BC patients in a prospective manner, the risk of development of BCRL in relation to the time could also be measured. Moreover, we should not have overlooked the role of well informed physicians that can empower BC patients by presenting or reinforcing risk reduction information to them (Fu MR., 2014). The role of education of people as well as primary care physician to prevent or at least improve the care for BCRL has been proved in another study (Mete Civelek et al.,2015).Therefore, recently launched family physician program in Fars province of Iran should be considered as a golden opportunity to integrate preventive and supportive care of patients with BCRL in this program (Honarvar et al.,2015). Expanding the lymphedema clinics that provide a more specialized diagnostic and therapeutic services for BCRL patients is also needed.

In conclusion, modifiable risk factors of BCRL such as non -guided moderate to severe physical activity, high BMI and trauma to the limb should be controlled as early as possible in BC patients to improve their QOL.

Acknowledgements

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