

Medical Procedures Safety for Breast Cancer Survivors Considering Lymphedema: A Systematic Review

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Introduction: Lymphedema is one of the most disturbing complications of breast cancer treatment and some routine medical procedures such as blood pressure (BP) monitoring or injections have been reported to be the major risk factors for lymphedema. This systematic review aimed to shed light on the safety of some medical procedures among breast cancer survivors with and without lymphedema.

Methods: An electronic systematic search in Pubmed and Scopus was undertaken from 1 January 1992 to 12 May 2020 and all relevant studies were summarized in a table based on the PRISMA guideline.

Results: Twenty-three articles were included from which 11 and 8 articles were prospective and retrospective original studies, respectively. The remaining 4 articles were case reports. BP measurement, injections, blood draw, and hand surgeries were the medical procedures of interest. Most of the included studies have reported that these medical procedures did not result in lymphedema initiation or worsening in breast cancer survivors; however, case reports of the harmful effects of these procedures were also included in this systematic search.

Conclusions: Although recent well-designed prospective studies did not show any significant side effects from medical procedures in breast cancer survivors, concerns exist for both healthcare staff and patients. Additionally, it seems that there are specific aspects that have not been investigated properly in previous studies and should be considered in future studies.

INTRODUCTION

Breast cancer-related lymphedema (BCRL) is one of the complications following breast cancer (BC) diagnosis or treatment such as biopsy, surgery, or radiotherapy which results in edematous upper limb and affects the patient's quality of life in a great deal [1, 2]. One out of five BC patients undergoing surgery eventually develops BCRL during the first 2 years [3]. However, since there is no definitive consensus on lymphedema definition and diagnosis, the incidence of BCRL is obscure. Risk factors for BCRL initiation are studied in the context of BC characteristics, its treatment and especially the surgical technique and body mass index (BMI) [2, 4]. Some medical procedures including phlebotomy, skin puncture, and hand surgery have been considered as risk factors for BCRL and guidelines have recommended avoiding such procedures in BC survivors [5]. Although evidence regarding these medical procedures is lacking and there are limited publications on the safety of such procedures in BC survivors with or without lymphedema, healthcare practitioners make decisions for these patients based on current guidelines. This systematic review aimed to study the existing evidence of medical procedures safety in BC survivors with or without BCRL to determine which medical procedures have been reported to be safe in BC survivors, and shed light on the research gap in this field.

METHODS

The "Medical Procedure" is a wide term used to address many different efforts intended for health delivery and all of the treatment modalities of BC can be assumed as a medical procedure. Historically, there has been fear toward using some routine procedures such as blood pressure (BP) monitoring or injections in BC survivors among the healthcare professionals since the early reports had indicated such procedures increase the risk of BCRL. Previous reviews have studied the risk factors of BCRL including air travel, BMI, and even drug prescriptions, yet it is important to investigate medical procedures exclusively since this topic brings its specific clinical importance. It should be noted that in this systematic review the emphasis was mostly on routine procedures such as BP monitoring, blood draws and injections, and

orthopedic procedures such as carpal tunnel release (CTR) since carpal tunnel syndrome (CTS) has clinical importance in BCRL. Altogether, the use of medical procedures in this review was mostly intended to address procedures in routine clinical practice that have been avoided by healthcare professionals.

Pubmed and Scopus were searched based on the PRISMA guideline [6] from 1 January 1992 to 12 May 2020. The search protocol of this systematic review is registered in PROSPERO (ID: CRD42020197044 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=197044). Searched keywords included the following MeSH terms: "medical procedures", "phlebotomy", "blood pressure measurement", "injections", "skin puncture", "hand surgery", "trauma", "lymphedema" and "breast cancer-related lymphedema". The search strategy in Scopus was as follows:

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((TITLE-ABS-KEY (medical AND procedures) OR TITLE-ABS-KEY (phlebotomy) OR TITLE-ABS-KEY (blood AND pressure AND measurement) OR TITLE-ABS-KEY (injections) OR TITLE-ABS-KEY (skin AND puncture) OR TITLE-ABS-KEY (hand AND surgery) OR TITLE-ABS-KEY (trauma))) AND ((TITLE-ABS-KEY (lymphedema) OR TITLE-ABS-KEY (breast AND cancer-related AND lymphedema)))
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After excluding duplicates, the search result was independently screened by two investigators. In the first phase, titles unrelated to lymphedema were excluded. In the second phase of screening, abstracts were reviewed and those articles that have not investigated risk factors of lymphedema in BC survivors or safety of medical procedures in BCRL patients were excluded. Books, animal studies, letters, and review articles were not included. There was no limitation on the year of publication and all relevant articles were included until the day of search (12/5/2020). Articles in English and Persian were included and those in other languages were excluded. Finally, in the third phase, full texts were screened and original articles that have studied the following medical procedures were included: blood draw, BP measurement, injections, skin puncture, hand surgery, and any other reported medical procedure.

Trauma was also added to this list, although it is not a medical procedure, it is similar to invasive orthopedic surgery and therefore articles about trauma were also included. References of included studies were also screened for related articles. After included studies were determined, two investigators extracted the following data of each study: name of the first author, the year of publication, design of the study (prospective or retrospective), population characteristics (number and type of surgery if available), follow-up period (only for prospective studies), studied medical procedures, and lymphedema definition and diagnosis. The procedure was not mentioned clearly in some articles and therefore even though an important surgery among BCRL patients is CTR, the procedure was considered as hand surgery. The statistical significance of the relationship between medical procedures and the risk of lymphedema development or worsening was also extracted. Any disagreement between two investigators was solved by a third investigator and then extracted data were summarized into a table. The quality of included studies was assessed based on the quality assessment tool for studies with diverse designs (QATSDD) which is based on 15 questions for quantitative studies with answers ranged from 0 to 3 [7]. The score of each article and its percentage of the total possible score (45) was calculated. The quality of 4 case reports was not assessed.

RESULTS

The search provided 2725 titles from which 2408 articles remained after excluding the duplicates. Excluding 2367 irrelevant titles/abstracts resulted in 41 full texts that were reviewed and finally 23 articles were included of which 11 were prospective studies, 8 were retrospective articles, and 4 were case reports. Most of the studies used circumference measurement for lymphedema diagnosis and follow-up. Figure 1 shows the PRISMA diagram for the included studies. The quality of 19 articles (case reports were not considered for quality assessment), ranged from 33.3% to 97.7% with a mean quality of 63.4%. A total of 12 articles had a quality of more than 50%. The characteristics of included studies is presented in Table 1.

Table 1: Included Studies Characteristics ^a

Author [Reference]	Design (Year)	Population; Time Since Surgery	Risk Factors	Lymphedema Measurement	Quality Assessment (%)
Lee [8]	prospective (2019)	19 BCRL; 4, y (1-10)	• Arthroplasty ^b	• questionnaire	25 (55.5)
Ribeiro Pereira [9]	prospective (2017)	964 BC ALND; 10, y	• chemotherapy infusion ^b	• circumference measurements	42 (93.3)
Asdourian [10]	prospective (2017)	327 bilateral BC surgery; 6.1 to 68.2, mo	• BP measurement • blood draws • injections • trauma	• clinical examination • perometry	44 (97.7)
Baltzer [11]	retrospective cohort (2017)	103 BC undergone ALND, SLNB, or RT; N/A	• hand surgery	• circumference measurements	30 (66.6)
Ferguson [12]	prospective (2016)	632 BC survivors; 6 to 60, mo	• BP measurements • blood draws • injections • trauma	• perometry	45 (97.7)
Kilbreath [13]	prospective (2016)	450 BC survivors with removed lymph nodes; 18, mo	• BP measurement ^b • blood drawn • injection • trauma	• circumference measurements • bioimpedance spectroscopy	43 (95.5)

Gunnoo [14]	prospective (2015)	32 BCRL; 33, mo	• CTR	• circumference measurements	20 (44.4)
Lee [15]	retrospective (2015)	22 BC ALND; 9.2, mo	• hand surgery	• N/A	25 (55.5)
Showalter [16]	prospective (2013)	295 BC axillary surgery; 1, y	• BP measurement • blood draw • surgical procedure • change of breast prosthesis • cut ^b • trauma	• water volume displacement measures	42 (93.3)
Lee [17]	case study (2012)	1 BC mastectomy; 26, y	• injections ^b (vaccine)	• bioelectric impedance	N/A
Winge [18]	retrospective (2010)	311 BC ALNC; N/A	• injection	• questionnaire	20 (44.4)
Haddad [19]	retrospective (2009)	355 BC survivors; 4, y	• BP measurement • blood draws • injections • trauma	• circumference measurements	20 (44.4)
Swenson [20]	retrospective (2009)	188 BC axillary dissection; N/A	• drainage tube	• circumference measurements	16 (35.5)
Mak [21]	retrospective (2009)	202 BC ALND; N/A	• drainage tube ^b • trauma	• circumference measurements	29 (64.4)
Hershko [22]	retrospective (2007)	25 BC surgery and ALND; N/A	• hand surgery	• N/A	17 (37.7)
Clark [23]	prospective (2005)	251 BC axillary nodes biopsy; 3, y	• skin puncture ^b • surgical procedure	• circumference measurements	38 (84.4)
Hayes [24]	prospective (2005)	176 BC survivors; 6, mo	• BP measurement ^b • injection • trauma	• circumference measurements • bioelectric impedance	33 (73.3)
Assmus [25]	prospective (2004)	52 BC mastectomy; N/A	• CTR	• N/A	25 (55.5)
Donachy [26]	case study (2002)	1 BCRL; 6, mo	• CTR	• circumference measurements	N/A
Smith [27]	case study (1999)	1 BC mastectomy; 12, y	• hand surgery ^b	• N/A	N/A
Smith [28]	prospective (1998)	10 BC axillary dissection; N/A	• blood draw	• N/A	15 (33.3)
Dawson [29]	retrospective (1995)	15 BCRL; N/A	• CTR	• N/A	15 (33.3)
Brennan [30]	case study (1992)	1 BC mastectomy; 30, y	• blood draws ^b (diabetes finger stick)	• N/A	N/A

^a Abbreviations: ALND, axillary lymph node dissection; ALNC, axillary lymph node clearance; BC, breast cancer; BCRL, breast cancer-related lymphedema; BP, blood pressure; CTR, carpal tunnel release; N/A, not available/appreciable; RT, radiation therapy; SLNB, Sentinel lymph node biopsy

^b The mean difference is significant at the 0.05 level.

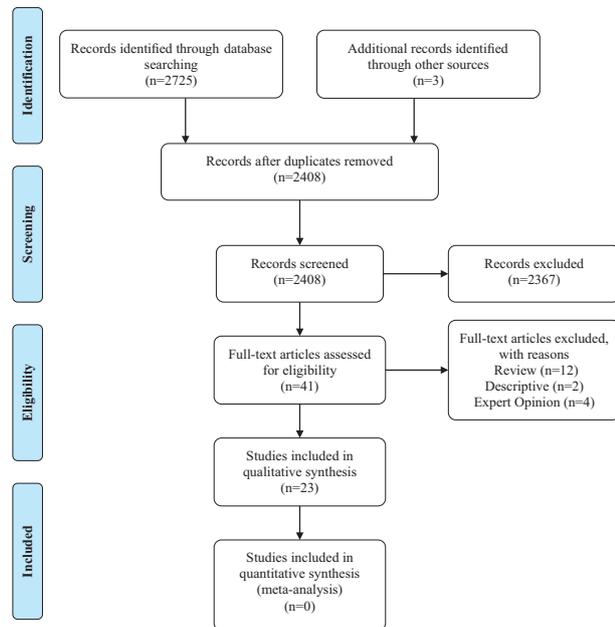


Figure 1: PRISMA Diagram for Included Studies

BP and Blood Draw

Two included articles reported that BP measurement resulted in lymphedema in BC survivors with 6 to 18-month follow-up [13, 24]; however, 4 other articles did not show a significant risk of BP measurement for lymphedema [10, 12, 16, 19]. Except for one case report [30], the other articles reported that blood draw in BC survivors with or without BCRL did not result in any significant edema or worsening of the condition [10, 12, 13, 16, 19, 28]. The case was a BC survivor with a history of mastectomy 30 years ago that developed lymphedema following finger stick for diabetes management [30].

Injections

The injection was considered safe in 6 articles [10, 12, 13, 18, 19, 24], while 1 study reported a case of a BC survivor treated with mastectomy 26 years ago who developed lymphedema after vaccination [17]. Two included retrospective studies investigated the risk of the drainage tube in BC survivors. In one study, drainage tubes significantly increased the risk of BCRL in BC patients who underwent axillary lymph node dissection (ALND) [21], however, there was no significant risk in the other study [20]. Additionally, one prospective study reported that chemotherapy was a risk factor for BCRL in BC patients treated with ALND [9].

Trauma, Cut, and Skin Puncture

In all 7 included studies that have investigated trauma in BC survivors with or without BCRL, there was no significant association with lymphedema development or worsening of the condition [10, 12, 13, 16, 19, 21, 24]. Cut and skin puncture were reported in two prospective studies to increase the risk of lymphedema in BC survivors [16, 23]. Changing breast prosthesis and surgical procedures (not declared what kind of surgery) were not risk factors for BCRL [16, 23].

Hand Surgery

Hand surgery resulted in lymphedema in one case with a history of mastectomy 12 years ago [27]; however, 3 retrospective studies showed no significant change in limb volume following hand surgery in BC patients undergoing ALND or other treatments [11, 15, 22]. One prospective study reported that arthroplasty worsened BCRL [8]. CTR was exclusively studied in 4 articles and none have reported any long-term changes in limb volume [14, 25, 26, 29].

DISCUSSION

In this systematic review, some medical procedures were investigated regarding their risk for the development of BCRL or its worsening in BC survivors. Although recent well-designed cohort studies have indicated that procedures such as BP measurement, blood draw, and injections are not risk factors for BCRL [10, 12], there are high precautions in clinical practice. Cellulitis and infection are complications with great importance in BCRL [31]. It has been reported that cellulitis increases the risk of BCRL and recurrent infections affect the edematous limb which may lead to fibrosis and worsen BCRL [2]. Some of the studied procedures can cause cut, wounds, and infection however these risks are not well studied in the literature. There is not enough evidence that injection and blood draw, for instance, significantly increase the risk of cellulitis in BCRL and most of the included studies have only reported changes in BCRL volume or incidence in BC survivors. It seems that there is a lack of evidence for mechanisms of procedures that lead to harmful outcomes in BCRL. The association of these procedures with wounds and infection is important to be studied in future researches. Historically, the

hand surgery procedures such as CTR are avoided; based on the very first reports. Ever since there are different published articles in this field and especially for surgical treatment of CTS and it seems that there may be slight swelling and edema after the surgery, it reverses after a short while. Interestingly, most of these studies did not have long-term follow-ups which should be an important point to be evaluated in future investigations. The recent recommendations indicate that hand surgery is safe in BC survivors without BCRL and it may increase a minimal chance of infection and worsen the condition in survivors that have already developed BCRL [32]. There is an important point in the included studies in terms of diagnosing lymphedema. Although diagnostic tools were different, most of them have used circumference measurement. This type of measurement with the meter is a practical, easy, and cheap way of BCRL detection; however, other methods such as bioelectric impedance spectroscopy are suggested to be more accurate in the detection of subclinical BCRL. This condition puts BC survivors at more risk of infections and inflammation [33]. So, medical procedures after BC treatment may result in subclinical lymphedema and therefore these patients may be prone to develop BCRL. On the other hand, there should be more cautious in using such procedures in these subclinical patients since they can trigger processes that may eventually lead to BCRL. Although some of the included studies have used bioelectric impedance spectroscopy, none of them have investigated subclinical BCRL. Future research is suggested to focus on the role of medical procedures on the risk of subclinical BCRL initiation or worsening of the condition. As far as this systematic search shows, there are many questions needed to be investigated. Based on the recent well-designed cohorts, some of these procedures seem to be safe, however, in clinical practice, the precautionary behaviors of healthcare staff are not something easy to be changed. Additionally, physicians and nurses may deal with harmful events in daily practice after procedures such as BP measurement, injection, blood draw, and hand surgery that may worsen BCRL. However, this observation is not reported in well-designed publications. There is a call for research on ways that harmful events of medical procedures can be prevented. For example, strict skincare and reducing BMI before hand surgery, as an important risk factor for BCRL, may be beneficial strategies

to minimize the side effects of procedures resulting in BCRL. The limitation of this systematic review is that there may be some publications that have not been included since we only searched PubMed and Scopus, however, we screened references of included studies and review articles to maximize the number of included studies. Also, only articles in English and Persian were considered eligible to be included and there may be some articles that have been missed due to their language.

This systematic review aimed to gather evidence for the side effects of medical procedures such as blood draw, BP measurement, injections, and hand surgery regarding BCRL. Most of the included studies have concluded that these procedures seem to be safe, however, in daily practice, there are hesitations and cautions towards using these procedures. As limiting unnecessary medical procedures in BC survivors should be considered by both patients and healthcare staff, further research with new methods and objectives is needed to improve current guidelines.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

Not applicable.

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