Blood Pressure Measurement as a Risk Factor for Lymphedema in Females Post Breast Cancer Treatment

Chelsea Braesch

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Abstract

Background: Lymphedema is a common complication of breast cancer treatment. And while breast cancer survivors are at an increased risk of developing lymphedema, there are various risk factors that, if avoided, might limit the incidence of arm swelling. A few national organizations have recommended that patients avoid blood pressure measurements on the affected arm. The purpose of this systematic review is to determine whether this burden is evidence-based or if it is causing unnecessary health anxiety.

Methods: An exhaustive search of available medical literature was performed using MEDLINE-PubMed, Web of Science, and CINAHL. Key words included "blood pressure" and "lymphedema" and ("breast cancer" or "breast neoplasm"). The quality of evidence was assessed using the GRADE Working Group guidelines.

Results: A total of 4 articles were included in this systematic review, all of which were prospective cohort studies. Three studies found no significantly increased risk of lymphedema with blood pressure measurements. One study measured lymphedema using 3 different techniques and found a significantly increased risk with one of the techniques but not the others.

Conclusion: This systematic review refutes the current guidelines that patients should avoid blood pressure monitoring in the affected arm. Further research that looks at how to define lymphedema and how to best diagnose it in the clinic will help with implementing earlier treatment.

Keywords: Blood pressure, lymphedema, breast cancer, and breast neoplasm

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Degree Name
Master of Science in Physician Assistant Studies

Keywords
Blood pressure, lymphedema, breast cancer, and breast neoplasm

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Blood Pressure Measurement as a Risk Factor for Lymphedema in Females Post Breast Cancer Treatment

Chelsea Braesch

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11th 2018

Faculty Advisor: Annjanette Sommers, PA-C, MS

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography
[redacted]
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Acknowledgements

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BCRL</td>
<td>Breast cancer related lymphedema</td>
</tr>
<tr>
<td>NLN</td>
<td>National Lymphedema Network</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development, and Evaluation</td>
</tr>
<tr>
<td>BIS</td>
<td>Bioimpedance spectroscopy</td>
</tr>
<tr>
<td>MFBIA</td>
<td>Multifrequency bioelectrical impedance</td>
</tr>
<tr>
<td>SOAC</td>
<td>Sum of arm circumference</td>
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</table>
Blood Pressure Measurement as a Risk Factor for Lymphedema in Females Post Breast Cancer Treatment

BACKGROUND

Lymphedema is abnormal swelling, generally in an arm or leg, which is caused by a blockage in the lymphatic system. This blockage can be caused by the removal of lymph nodes or damage to the lymphatic vessels. One of the most common risk factors for developing lymphedema is prior lymphadenectomy, a procedure often performed in conjunction with breast cancer surgery.\(^1\) Although removal of lymph nodes is vital to the initial assessment of early breast cancer, patients can try to prevent further damage to the lymphatic vessels by limiting their exposure to potentially harmful events.

However, many of the lifestyle changes that providers recommend to patients are anecdotal or based on a textbook understanding of how the body functions. Providers are operating on a “can’t hurt so why not” basis. Recommendations that are not evidence-based are causing unnecessary anxiety and fear in breast cancer survivors.\(^2\)

The theory behind the increased risk with blood pressure measurement stems from the idea that a cuff increases pressure in the arm in a focused area. This focused compression might cause further
damage to the lymphatic vessels and lead to an increase in lymph production.\textsuperscript{3} However, some research suggests that increased pressure in the affected arm should not be contraindicated because the treatment of lymphedema is in fact compression.\textsuperscript{4}

There have been many recent studies that highlight the various risk factors for developing breast cancer related lymphedema (BCRL). Despite these findings, current guidelines from the National Lymphedema Network (NLN)\textsuperscript{5} and the National Cancer Institute (NCI)\textsuperscript{6} continue to advise against blood pressure monitoring in the affected arm. The purpose of this systematic review is to resolve the question: Can measuring blood pressure post breast cancer treatment increase the incidence of lymphedema?

**METHODS**

An exhaustive literature search was conducted in June 2017 using MEDLINE-PubMed, Web of Science, and CINAHL. Keywords searched included “blood pressure” and “lymphedema” and (“breast cancer” or “breast neoplasm”). Articles that summarized relevant evidence were searched for further sources. Studies were excluded if they did not analyze BP measurement as a separate variable. The articles were assessed for quality using the Grading of
Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.\textsuperscript{7}

**RESULTS**

From the initial literature search, 40 articles were reviewed for relevance. One article was excluded because it did not analyze blood pressure measurement as a separate variable but rather as part of a group of medical procedures, which included blood draws. Two articles were selected directly from the database search and 2 articles were selected after reviewing articles that summarized relevant research. All 4 studies\textsuperscript{8-11} were prospective cohort studies published between 2005 and 2016. See Tables I-III.

**Kilbreath et al**

This multicenter, prospective cohort study\textsuperscript{8} looked at 450 women who were diagnosed with breast cancer and scheduled for axillary surgery between 2009 and 2013. The study excluded women who had a pacemaker or who were diagnosed with stage IV cancer. The women were assessed prior to surgery, within 4 weeks postoperatively, and at 6, 12, and 18 months postoperatively. Participants recorded post-surgical events that might increase the risk of lymphedema in weekly diaries. The entries were completed either online, over the phone, or using a paper diary. Lymphedema was diagnosed using bioimpedance...
spectroscopy (BIS). An impedance ratio greater than the normal threshold or increased by at least 0.1 from baseline was considered significant swelling.⁸

Of the 450 women, 241 (54%) had <5 nodes removed and 209 (46%) had ≥5 nodes removed. Only 8 (3.3%) participants with <5 nodes removed were diagnosed with lymphedema. The researchers concluded that there were insufficient events to identify risk factors for this group. The rest of the findings pertain only to the group with ≥5 nodes removed.⁸

Diaries were available for 112 participants, of which 21 were diagnosed with lymphedema at the 18-month assessment. Results showed 20.3% of women who recorded having at least 1 blood pressure measured (N=55) presented with lymphedema as compared to 16.3% of women who recorded never having blood pressure measured (N=36). The OR for blood pressure measured was 1.3 (95% CI 0.5, 3.6) with a p-value of 0.6. These results demonstrate no significant risk of lymphedema with blood pressure measurement in women with ≥5 nodes removed.⁸

**Ferguson et al**

This prospective cohort study⁹ was conducted on 632 patients who were diagnosed with breast cancer and underwent treatment at Massachusetts General Hospital between 2005 and 2014. Patients who
underwent sentinel lymph node biopsy or axillary lymph node
dissection and who were prospectively screened for lymphedema
preoperatively were included in the study. Patients who were
diagnosed with distant metastasis or wore a compression sleeve while
flying were excluded.⁹

All patients were assessed preoperatively, postoperatively, and
at regular follow-up intervals that ranged between 3 and 7 months. On
average, patients had 4 follow-up visits over a span of 24 months.
Lymphedema was diagnosed using an optoelectric Perometer, which
measures arm volume changes. A relative volume change or weight-
adjusted volume change ≥10% was determined to be significant. At
each visit, a Perometer measurement was taken and patients
completed a survey in which they were asked to recall how many
blood pressure readings they had had since the previous visit.⁹

Throughout the surveys, a total of 482 responses reported
having at least 1 blood pressure measured and 2,479 reported never
having blood pressure measured. The results showed that only 2.5%
of responses with at least 1 blood pressure measured presented with
lymphedema, as compared to 7.0% of responses that never had blood
pressure measured. The OR for blood pressure measured was 0.34
with a p-value of 0.0338 (95% CI -0.72, 0.25).

Showalter et al
This prospective sub-analysis of a randomized controlled study\textsuperscript{10} looked at 295 breast cancer survivors recruited between October 2005 and February 2007. The participants were either at risk for developing lymphedema (1-5 years post breast cancer diagnosis) or had stable lymphedema (1-15 years post breast cancer diagnosis). Participants who had undergone intensive breast cancer related lymphedema (BCRL) therapy, recorded a 10% change in volume or circumference of the arm lasting for $\geq 7$ days, at least 2 BCRL-related infections, or a BCRL exacerbation that lead to a change in daily activities, within the past 3 months were excluded from the study.$^{10}$

The original RCT aimed to assess the effects of weight lifting on BCRL. All participants were instructed to wear a compression sleeve and attend a 1-hour lecture on lymphedema education. The presence of lymphedema was measured using water volume displacement. Significant lymphedema was defined as an inter-limb volume of difference $\geq 5\%$ with a $\geq 5\%$ increase since the last measurement. Arm volume was measured at baseline (time of entry into the study) and 3, 6, and 12 months. At each visit, participants were asked to complete a questionnaire and recall if they were exposed to a blood pressure cuff within the past 3 months.$^{10}$
The study found blood pressure reading was not a significant risk factor for lymphedema. The OR was 1.47 (95% CI 0.18, 11.77) with a p-value of 0.72.\textsuperscript{10}

\textbf{Hayes et al}

This prospective cohort study\textsuperscript{11} analyzed 176 women 6 months post-breast cancer surgery. Participants residing within a 100km radius of Brisbane were randomly selected from the Queensland Cancer Registry in 2005. Women ≤75 years old diagnosed with unilateral breast cancer within the previous 6 months were included in the study.\textsuperscript{11}

One of the primary focuses of the study was to analyze the difference in lymphedema measurement techniques. The study looked at 2 objective measures, multifrequency bioelectrical impedance (MFBIA) and difference between sum of arm circumferences (SOAC), and one subjective measure, self-report. Lymphedema was defined as an impedance ratio greater than 3 standard deviations above normal, or a difference between SOAC greater than 5cm or 10%, or a “yes” response on the self-report. Due to its accurate and reliable measurements, the MFBIA technique was considered the reference standard. The self-report assessed a period of 6 months and showed the highest sensitivity. While difference in SOAC is the most popular
technique in practice, the study found it to have the lowest sensitivity and poor repeatability.11

At the time of lymphedema measurement, participants were asked to recall if they had blood pressure readings from the treated side during the previous 6 months. The results identified blood pressure readings as a significant risk factor for the presence of lymphedema. In those who had experienced blood pressure readings, the OR was 3.4 (95% CI 1.0, 11.1) when assessed using difference in SOAC >5cm. However, significance was not found with MFBIA OR 1.1 (0.2, 5.4) or self-report OR 1.5 (0.5, 4.4).11

DISCUSSION

At first glance, the results of these studies are at best eye opening but not quite practice-changing. Three of the 4 studies8-10 refute the current recommendations to avoid blood pressure measurements in the affected arm following treatment for breast cancer. One study11 claims to neither support nor refute the NLN and NCI, despite finding an increased risk of lymphedema with blood pressure measurement (See Table I).

The purpose of this systematic review is to resolve this literature conflict and determine if the burden placed on patients is evidence-
based. Each of the articles was evaluated using GRADE criteria to assess the quality of evidence, presented in Table II.

Upon reviewing the articles, there was inconsistency in the findings in regards to the outcome of lymphedema. Ferguson et al\textsuperscript{9} found significance (p=0.034) by univariate analysis, but reported that the finding was no longer significant (p=0.15) when the data was analyzed as continuous variables or by multivariate analysis. The study concluded that blood pressure measurement does not increase the risk of lymphedema. Hayes et al\textsuperscript{11} was the one study that found blood pressure measurement to be a significant risk factor for developing lymphedema. However, the study focused on how to diagnose lymphedema using 3 different methods: MFBIA, difference in SOAC >5cm, and self-report. Significance was only found when lymphedema was assessed by difference in SOAC. Yet the article states that the MFBIA technique is the ‘reference standard’ because of its accuracy. Asdourian et al,\textsuperscript{12} who also reviewed similar resources, agrees that the inconsistency limits the influence this significant finding has on the current discussion. Furthermore, measurement of arm circumference via tape measure has some degree of subjectivity and the data collectors were not blinded.\textsuperscript{11}

While the results of these studies suggest that the current guidelines need to be updated in regards to blood pressure
measurements, they also introduce new problems into the discussion on preventing lymphedema (see Table III). Throughout the 4 studies, 5 different techniques were utilized to diagnose the presence of lymphedema: MFBIA, Perometer, water volume displacement, difference in SOAC, and self-report. This methodology led to 5 different definitions of what constitutes lymphedema. The water volume displacement in Showalter et al\textsuperscript{10} did not account for changes in overall body weight nor did the difference in SOAC in Hayes et al.\textsuperscript{11} Both Ferguson et al\textsuperscript{9} and Kilbreath et al\textsuperscript{8} utilized objective measures of lymphedema, Perometer and MFBIA respectively, to define lymphedema.

Other issues that impact the outcome of these studies were the length of follow-up and the measurement of exposure to blood pressure cuff readings. The average time it takes to develop lymphedema following breast cancer treatment is 14.4 months.\textsuperscript{9} While Ferguson et al\textsuperscript{9} followed patients for 24 months and Kilbreath et al\textsuperscript{18} 18 months, Showalter et al\textsuperscript{10} only followed patients for 12 months and Hayes et al\textsuperscript{11} for only 6 months. This suggests that the latter 2 studies might underestimate the presence of lymphedema due to not long enough follow-up. The problem with measuring exposure to blood pressure cuff readings is the influence of recall bias. Hayes et al\textsuperscript{11} asked patients to recall their exposures over the past 6 months via
survey, Showalter et al\textsuperscript{10} over the past 3 months via questionnaire, and Ferguson et al\textsuperscript{9} up to 7 months via survey. Kilbreath et al\textsuperscript{8} sought to eliminate this confounding variable and asked patients to keep a diary that they filled out weekly. If at any time a diary entry was not submitted, a research assistant contacted the participant via phone.

Despite some of the differences in methodology, all of the studies evaluated breast cancer survivors status post breast cancer treatment. However, each of the studies was composed of a slightly different patient population. Hayes et al\textsuperscript{11} looked at participants from a 100km radius in Brisbane, which might limit its generalizability. Showalter et al\textsuperscript{10} was a sub-analysis of a randomized controlled study. This meant that all participants were capable of weight-lifting, attended a 1-hour educational lecture on lymphedema, and were encouraged to wear a compression sleeve. Some of the participants were 15 years post diagnosis and the study did not take into account exposures prior to the start of the study. All of these variables suggest that the study’s population might be less susceptible to developing lymphedema than the general population. Kilbreath et al\textsuperscript{8} was the only study that limited its analysis to participants with 5 or more lymph nodes removed. Even though this study was evaluating a high-risk group, it still failed to find significance with blood pressure measurements.
As prospective cohort studies, each of the studies started off as a low quality evidence meaning further research is very likely to change the estimate of effect. Both Hayes et al\textsuperscript{11} and Showalter et al\textsuperscript{10} were downgraded to a very low quality of evidence. Ferguson et al\textsuperscript{9} and Kilbreath et al\textsuperscript{8} were both published within the past 2 years and sought to address some of the methodological confounders that downgraded the other 2 studies. With ethical concerns restricting the possibility of a randomized controlled study, it is unlikely that any new research will contradict these findings. The best evidence-based research\textsuperscript{5,6} refutes the current recommendations to avoid blood pressure monitoring in the affected arm.\textsuperscript{5,6}

As a result of these recent findings, in clinical practice, patients who undergo sentinel lymph node biopsy should not be given any recommendations in regards to blood pressure monitoring. Patients who undergo axillary lymph node dissection should be encouraged to undergo normal blood pressure monitoring, unless repeated measurements are required, as in the ICU or recovery room.

\textbf{CONCLUSION}

In theory, it makes sense to avoid blood pressure measurements in order to prevent lymphedema; however, in practice, that does not seem to be the case. Even in patients with the highest risk of
developing lymphedema (≥5 nodes removed), there was no increased risk after being exposed to blood pressure readings. For patients that have undergone the stress of breast cancer and have plenty of worry and limitations, eliminating this one worry would be ethical.

These findings refute the current national guidelines that recommend patients avoid blood pressure monitoring in the affected arm. Although at very low risk, lymphedema can lead to pain, restricted function, and disfigurement and cautionary behavior should be followed, but blood pressure measurements do not appear to pose a serious risk to these patients. ¹³,¹⁴ Clinicians can protect their patients from health anxiety and stress by limiting this lifestyle restriction.
References


### Table I. Summary of Findings

<table>
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<th>Study</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
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<tr>
<td>Kilbreath et al(^8)</td>
<td>1.3</td>
<td>(0.5, 3.6)</td>
</tr>
<tr>
<td>Ferguson et al(^9)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Showalter et al(^10)</td>
<td>1.47</td>
<td>(0.18, 11.77)</td>
</tr>
<tr>
<td>Hayes et al(^11)</td>
<td>3.4</td>
<td>(1.0, 11.1)</td>
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### Table II. Quality Assessment of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
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<th>Imprecision</th>
<th>Publication Bias</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
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<td>Cohort</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Unlikely</td>
<td>None</td>
<td>Low</td>
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<tr>
<td>Ferguson et al(^9)</td>
<td>Cohort</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^a)</td>
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<td>Unlikely</td>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td>Showalter et al(^10)</td>
<td>Cohort</td>
<td>Serious(^b)</td>
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<td>Not serious</td>
<td>Unlikely</td>
<td>N/A</td>
<td>Very low</td>
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<tr>
<td>Hayes et al(^11)</td>
<td>Cohort</td>
<td>Serious(^c)</td>
<td>Not serious</td>
<td>Serious(^d)</td>
<td>Not serious</td>
<td>Unlikely</td>
<td>N/A</td>
<td>Very low</td>
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\(^a\) Significance with univariate analysis but not with multivariate analysis

\(^b\) Cohort is not generalizable (lymphedema education, compression sleeve, capable of weight lifting), does not consider exposures prior to the start of the study (some are 15 years post diagnosis)

\(^c\) Lack of blinding of data collectors – significant finding was based on arm measurements; and high risk of recall bias influencing data collection

\(^d\) Reference standard did not prove significance
Table III. Summary of Significant and Non-significant Risk Factors for Lymphedema

<table>
<thead>
<tr>
<th>Kilbreath et al\textsuperscript{8}</th>
<th>Ferguson et al\textsuperscript{9}</th>
<th>Showalter et al\textsuperscript{10}</th>
<th>Hayes et al\textsuperscript{11}</th>
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<tr>
<td><strong>Significant</strong></td>
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<tr>
<td>≥5 nodes removed</td>
<td>BMI ≥25</td>
<td># of nodes removed</td>
<td>BP measurement</td>
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<td>Axillary LN dissection</td>
<td>Radiation therapy</td>
<td>Tx on non-dominant side</td>
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<td>Taxane-based chemo</td>
<td>Cellulitis</td>
<td>Asian race</td>
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<td>Arm swelling at 6mos.</td>
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<tr>
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<td>BP measurement</td>
<td>BP measurement</td>
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Revised 07Dec2009