Systematic Review and Meta-Analysis

Gait and Balance Impairments in Breast Cancer Survivors: A Systematic Review and Meta-analysis of Observational Studies

Katherine L. Hsieh, BS a, Tyler A. Wood, MS, MAT, ATCa, Ruopeng An, PhD a, Linda Trinh, PhD b, Jacob J. Sosnoff, PhD a

a Department of Kinesiology and Community Health, University of Illinois at Urbana Champaign, Urbana, IL
b Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada

KEYWORDS
Breast neoplasms; Mobility limitation; Gait; Postural balance; Rehabilitation

Abstract
Objective: To systematically review and quantitatively synthesize gait and balance impairments in breast cancer survivors compared with age-matched controls or normative values for adults who never had breast cancer.

Data Sources: PubMed, Cumulative Index of Nursing and Allied Health, and Web of Science was searched using terms associated with breast cancer, mobility, and adult until November 2018.

Study Selection: Studies were included if they were randomized control trials, cross-sectional, prospective, pre-post, or case-control by design, included adult breast cancer survivors, reported gait and/or balance metrics as primary or secondary outcomes, were peer-reviewed publications, and were written in English. The search yielded 2117 results with 29 studies meeting the inclusion criteria.

Data Extraction: Two reviewers assessed study quality by the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies to determine the strength of evidence for each study that met the inclusion criteria. Basic descriptors of each study, study protocol, and balance and gait measures were extracted. Meta-analysis was performed for the single leg stance, functional reach, center of pressure velocity, gait speed, and timed up and go.

Data Synthesis: For quality assessment, 3 studies were rated good, 16 fair, and 10 poor. The meta-analysis indicated that there were no significant differences in single leg stance between breast cancer survivors and those who never had breast cancer (\( P = .33 \)). Pooled values of the functional reach task (22.16cm; 95% CI, 8.98-35.33) and center of pressure velocity (1.2cm/s;...
Breast cancer is the most commonly diagnosed cancer in women. Approximately 1 in 9 women will be diagnosed as having breast cancer in the United States before the age of 85. The current 5-year survival rate for breast cancer is 93%. While breast cancer survivors (BCSs) have a high survival rate, they are still faced with acute and chronic adverse effects from cancer treatments. These adverse effects, such as fatigue, muscle weakness, and neuropathy, are associated with gait and balance impairments. Neuropathy, for instance, affects up to 44% of BCSs at least 2 years post diagnosis and is associated with worse balance and greater risk of falls. Gait and balance are fundamental for activities of daily living and maintaining functional independence, and throughout clinical populations, impairments in gait and balance are associated with a high rate of falls. Understanding gait and balance function in BCSs is critical to reduce their risk of fall-related injuries.

It is unclear how prevalent gait and balance impairments are in BCSs, which may be because of lack of understanding of these impairments. Past studies have focused primarily on clinical measures of balance and gait, such as the functional reach task or timed Up and Go (TUG). More recently, studies have investigated changes in balance and gait function as they relate to impairment. For instance, Monfort et al found gait speed and postural stability decreased after successive chemotherapy cycles. Winters-Stone et al also found slower gait speed and shorter step length in BCSs with neuropathy, which was associated with an increased fall risk and greater disability. These studies suggest that not only is cancer treatment related to impairment, but impairment is also related to decreased quality of life. These novel studies further highlight growing scientific evidence on gait and balance impairments in BCSs compared with those who never had breast cancer or normative values of healthy adults. We hypothesized that BCSs display worse gait and balance compared with age-matched persons who never had breast cancer or compared with normative values.

Methods

Study selection criteria

Studies that met the following criteria were included in the review: (1) had a study design of RCT, prospective, post, case-control, or cross-sectional; (2) were of adults diagnosed as having breast cancer; (3) objectively measured gait and/or balance as primary or secondary measures; (4) were published peer-reviewed articles; and (5) were published in English. Studies were excluded if they were nonoriginal articles (ie, study protocols, reviews, or editorials).

Search strategy

The systematic review and meta-analysis was aligned to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses process. A keyword search was performed in PubMed, Cumulative Index to Nursing and Allied Health Literature, and Web of Science (table 1). Two reviewers (K.H. and T.W.) independently conducted title and abstract screening and jointly determined the list of articles for full-text review through discussion. Any disagreements or ties were resolved by a third independent reviewer (A.R.).

A cited reference search (ie, forward reference search) and reference list search (ie, backward reference search) were conducted on the full-text articles that met the study eligibility criteria from the keyword search. Titles and abstracts of all articles were screened based on the eligibility criteria. Articles meeting the eligibility criteria were retrieved for full-text evaluation. Articles identified through a forward/backward search were further screened using the same selection criteria. The reference search was
repeated on all newly identified articles until no additional relevant article was identified. Articles up to November 14, 2018, were identified.

Data extraction

A standardized data extraction form was used to collect the following methodological and outcome variables from each included study: country of study, author(s), publication year, study design, sample size, participant characteristics (ie, age, body mass index [calculated as weight in kilograms divided by height in meters squared], education, race, cancer stage, treatment type, time since treatment, and adverse effects), and gait and/or balance measures. Gait measures included the 8-ft and 3-m TUG, usual and fast gait speeds, and the short physical performance battery gait score. To control for varying methodologies, fast gait speed was categorized into short distances (<10m) and long distances (≥100m or ≥6min). Balance measures included single leg stance time, overall stability index, short physical performance balance battery score, functional reach, center of pressure (COP) displacement, velocity, root mean square, 95% confidence ellipse, and the sensory organization test (SOT). For pre-post and RCT studies, only pretest data were extracted in order to avoid the intervention effect on gait or balance measures. Two gait parameters (ie, gait speed and TUG) and 3 balance parameters (ie, single leg stance time, functional reach, and COP velocity) were included in the meta-analysis. These measures were selected during the review and were chosen because at least 2 studies reported these outcome measures. Four studies were excluded from the meta-analysis. The gait and/or balance outcome measures reported in these 4 studies were overall stability index, COP displacement reported as median values, COP velocity reported as median values, and gait speed during backward walking. Because only 1 study reported 1 of these outcome measures, a meta-analysis could not be performed. Meta-analysis also could not be performed on measures that were reported as median values.

Data synthesis

Meta-analysis was performed on single leg stance time, functional reach distance, center of pressure (COP) velocity, usual gait speed, fast gait speed, 8-ft TUG time, and 3-m TUG time for BCSs. Meta-analysis was also performed to estimate the differential single leg stance time between BCSs and persons who never had breast cancer. Study heterogeneity was assessed using the $I^2$ index. The level of heterogeneity represented by the $I^2$ index was interpreted as modest ($I^2$ ≤25%), moderate (25%<$I^2$ ≤50%), substantial (50%<$I^2$ ≤75%), or considerable ($I^2$ >75%). A fixed-effect model would be estimated when modest to moderate heterogeneity was present, and a random-effect model would be estimated when substantial to considerable heterogeneity was present. All statistical analyses were conducted using the Stata, 14.2 SE version (StataCorp). All analyses used 2-sided tests, and $P$ values >.05 were considered statistically significant.

Study quality assessment

Study quality for all included studies was assessed by the National Institute for Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies because 19 of the studies are either cohort or cross-sectional. Study quality was assessed with 14 questions that were answered as "yes," "no," "cannot determine," "not applicable," or "not reported." All responses other than "yes" indicate risk of bias. Two reviewers assessed all articles, and any discrepancies were resolved by a third reviewer. Study quality scores helped measure the strength of evidence but were not used to determine the inclusion of studies.

Results

Study selection

Figure 1 shows the study selection flow chart. A total of 2117 articles were identified through the keyword search, with 3 articles identified from the forward/backward search. After removing duplicates, 2041 articles underwent title and abstract screening, and 1994 articles were excluded. The remaining 47 articles were read in full text, and 18 were excluded for not meeting the study selection criteria. Studies were excluded because they included multiple cancer types, did not measure gait or balance parameters, did not specify cancer type, or were an inappropriate study design. The remaining 29 articles were included in the review.
Basic characteristics of the included studies

Table 2 reports the basic characteristics of the 29 articles included in the review. Fifteen studies were conducted in the United States, 11,12,36,37,39,41,44-48,50,57,60 2 in Finland,40,43 and 2 in Turkey.35,51 For study design, 11 studies were cross-sectional,35,37,38,40,42,43,45,47-49,52 11 were RCTs,14,39,44,46,50,51,54,55,57-59 and 3 were pre-post.11,36,60 Six studies included a control group who had never had breast cancer.35,38,42,45,47,52 Seventeen of the studies measured gait and/or balance as the primary outcome,11,12,35-38,40-42,44-46,48,49,51,53,58 while 12 analyzed gait and/or balance as secondary outcomes.14,39,43,47,50,52,54-57,59,60 The total sample size was 2025 BCSs and 138 persons who never had breast cancer. Average age was 53.8 years among BCSs and 52.3 years among those who never had breast cancer. The majority of BCSs were overweight, with a body mass index over 25. Most BCSs completed at least high school, and almost all were white. Cancer stage ranged from stage 0 to stage III, with most diagnosed as having stage II. Surgery and chemotherapy were the most common treatments. The most common adverse effects from treatment were lymphedema, neuropathy, and menopause. Six studies included participants with ongoing breast cancer treatment,12,40,41,49,54,55 whereas 9 studies included participants 1 month following completion of cancer treatment.35,36,42-44,46,47,56,60

Table 3 reports gait and balance measures examined by the studies included in the review. Eleven studies analyzed only gait metrics,36,39,43,49-51,53-55,57,59 10 studies analyzed only balance metrics,33,35,38,41,42,44,47,52,58,60 and 8 studies analyzed both gait and balance metrics.11,14,34,37,40,45,46,48 Of the balance metrics studies, 5 reported the single leg stance task,11,40,46,47,52 4 reported the functional reach test,11,14,33,60 3 reported COP velocity,31,42,45 2 reported COP displacement,38,42 2 reported balance scores from the short form physical performance test,34,37 2 reported outcomes of the SOT,45,47 1 reported an overall stability score measure,35 and 1 reported backward walking speed as a measure of dynamic balance.60 Of the gait metrics studies, 16 reported gait speed11,12,37,40,43,46,48-51,53-56,59 and 5 reported TUG,11,13,40,43,46,48,51,52,55,59 and 5 reported COP velocity.11,42,45

Meta-analysis

Balance measures among BCSs are depicted in figure 2 for the single leg stance (fig 2A), functional reach (fig 2B), and COP velocity (fig 2C). The forest plot for single leg stance included studies that stopped the test after reaching 60 s. Meta-analysis estimated the duration of single leg stance time with eyes open on a firm surface to be 23.75 s (95% CI, 22.10-25.39) among BCSs, which is less than that of normative values (36±12s).61,62 The estimated distance of the functional reach test was 22.16 cm (95% CI, 8.98-35.33), which is less than those of adults who never had breast cancer (38.08±6.53 cm).51 The estimated COP velocity was 1.2 cm/s (95% CI, 0.87-1.55), which is greater than values of individuals who never had breast cancer (0.72 cm/s), suggesting worse postural control.63,64
| Author          | Study ID | Country | Type of Study | Control Group Who Never Had Breast Cancer | Sample Size | Mean Age ± SD (y) | Stage (%) | Mean BMI ± SD | Education, Level (%) | Race (%) | Treatment Type (No.) | Time Since Treatment ± SD | Adverse Effects |
|-----------------|----------|---------|---------------|------------------------------------------|-------------|------------------|-----------|---------------|----------------------|-----------|---------------------|-----------------------------|-----------------|
| Anderson et al  | 01       | USA     | RCT           | No                                       | 104         | 40% between 50-65| I (49)    | 71%>25        | High school or less (17) | White (88.5) | MAS (52)             | NR                          | NR              |
| Besar et al     | 02       | Turkey  | Cross-sectional | Yes                                      | 24 BCSs 22 CON 29 | BCSs 57.4±7.2 CON 55.1±6.6 | I-II (49) | BCSs 28.3±4.9 | CON 28.3±4.4 | NR                   | NR                   | NR                         | -6 mo            | LD (24)         |
| Damush et al    | 03       | USA     | Pre-post      | No                                       | 56          | 70±3.9           | I-III     | 30.1±0.9      | NR                   | NR                   | CT (62)             | 3.1 y                       | NR              |
| Eyigor et al    | 04       | Turkey  | RCT           | No                                       | 56          | 70±3.9           | I-III     | 30.1±0.9      | NR                   | NR                   | CT (62)             | 3.1 y                       | NR              |
| Extermann et al | 05       | USA     | Cross-sectional | No                                       | 12          | 59               | I-III     | 30.1±0.9      | NR                   | NR                   | CT (62)             | 3.1 y                       | NR              |
| Foley et al     | 06       | USA     | Pre-post      | No                                       | 56          | 70±3.9           | I-III     | 30.1±0.9      | NR                   | NR                   | CT (62)             | 3.1 y                       | NR              |
| Fong et al      | 07       | China   | Pre-post      | Yes                                      | 17 BCSs 36 CON 57 BCSs 36 CON | BCSs 54±7 CON 56.9±8.3 | I-II (49) | BCSs 21.5±3.7 | CON 24±4.7 | NR                   | NR                   | NR                         | PostM (12), LD (8)         |
| Galantino et al | 08       | USA     | Pre-post      | No                                       | 12          | 59               |                   | NR                   | College (60%) | White (90) | Breast conserving Sx (41) | CT (8), RT (10), MAS (1), Lump (2) | NR             | PostM (12), LD (8) |
| Galantino et al | 09       | USA     | Pre-post      | No                                       | 12          | 59               |                   | NR                   | High school or less (8.3) | White (91.6) | African American (10% | CT (8), RT (10), MAS (1), Lump (2) | NR             | PostM (12), LD (8) |
| Galiano-Castillo et al | 10 | Spain   | Cross-Sectional | No                                      | 87          | 48.3±8.5         | I (36.8)  | NR            | NR                   | CT (4)               | RT (4)                     | LD (10)                     |
| Haines et al    | 11       | Australia| RCT           | No                                       | 81          | 55.1±10.9        | II (42.5) | NR            | NR                   | CT (32)              | RT (82)                    | Ongoing                 |
| Husebo et al    | 12       | Norway  | RCT           | No                                       | 60          | 52.2±9.3         | II (56.7) | NR            | NR                   | MAS (45)             | CT (60)                    | Ongoing                 |
| Kneis et al     | 18       | Germany | Cross-sectional | Yes                                      | 20 BCSs 16 CON 128 | BCSs 48.8±4.5 CON 46.5±5.4 | I-II (37.1) | BCSs 26.3 | CON 27.0 | High school (17.9) | College (19.3) | University (6.5) | CT (20) | NR | CIPN (20) |
| Kokkonen et al  | 14       | Finland | Cross-sectional | Yes                                      | 40 BCSs 40 CON 13 | BCSs 51.5±6.5 CON 50.5±7.9 |                   | NR                   | NR                   | NR                   | CT (122)              | Ongoing                 | NR              |
| Montezuma et al | 15       | Brazil  | Cross-sectional | No                                       | 40 BCSs 40 CON 13 | BCSs 51.5±6.5 CON 50.5±7.9 |                   | NR                   | NR                   | NR                   | MAS (40)              | Ongoing                 | NR              |
| Mascherini et al | 16      | Italy   | Cohort        | No                                       | 40 BCSs 40 CON 13 | BCSs 51.5±6.5 CON 50.5±7.9 |                   | NR                   | NR                   | NR                   | CS (5.2)              | Ongoing                 | NR              |

(continued on next page)
| Author          | Study ID | Country | Type of Study | Control Group Who Never Had Breast Cancer | Sample Size | Mean Age ± SD (y) | Stage (%) | Mean BMI ± SD | Education, Level (%) | Race (%) | Treatment Type (No.) | Time Since Treatment ± SD | Adverse Effects |
|-----------------|----------|---------|---------------|-------------------------------------------|-------------|-------------------|------------|---------------|-----------------------|-----------|----------------------|--------------------------|----------------|
| Monfort et al   | 17       | USA     | Prospective   | No                                        | 32          | 47.6 ± 11.2       | II (50)    | 27.9 ± 7.8    | NR                    | NR        | CT (32)              | Ongoing                  | NR            |
| Monfort et al   | 18       | USA     | Prospective   | No                                        | 33          | 47.8 ± 11.2       | III (50)   | 28.9 ± 9.4    | NR                    | NR        | CT (33)              | Ongoing                  | NR            |
| Penttinen et al | 19       | Finland | Cross-sectional | No                                       | 537         | 52.4              | NR         | >25 57%       | 13.9 (3.4)            | NR        | MAS (277), CT (492), RT (421) | >4 mo                  | PostM (284)   |
| Reis et al      | 20       | USA     | RCT           | No                                        | 41          | 56.1 ± 11         | I (51)     | 29.6 ± 6.3    | High school (29), Associate’s (29), Bachelor’s (27), Master’s (12) | White (90), African American (7) | NR        |                     |                          |               |
| Twiss et al     | 21       | USA     | RCT           | No                                        | 223         | 58.7 ± 7.5        | NR         | 26.77 ± 4     | White (98.7), African American (0.87), American Indian (0.43%) |                     |                       | 5.95 ± 6.1 y          | LD (42), PostM (223) |
| Vollmers et al  | 22       | Germany | RCT           | Yes                                       | 36          | 49.8 ± 11.1       | BCSs 50.4 ± 9.3, CON 49.6 ± 9.1 | NR         | NR         | BCs 25.0                | NR        | NR                   | NR                      | CIPN (20)     |
| Wampler et al   | 23       | USA     | Cross-sectional | Yes                                      | 20 BCSs 20 CON | 72          | I (22.2), II (77.8) | NR       | NR        | CON 25.61                | NR        | NR                   | NR                      | CT (20)       |
| Wang et al      | 24       | Taiwan  | RCT           | No                                        | 59          | 58.5 ± 9.7        | BCSs 50.4 ± 9.3, CON 49.6 ± 9.1 | NR         | NR        | BCs 26.6 ± 5.4, CON 24.1 ± 3.9 | NR        | NR                   | NR                      | PostM (35)   |
| Winters-Stone et al | 25       | USA     | Cross-sectional/ prospective | Yes                                 | 35 BCSs 26 CON | 44.9 ± 3.2     | I (31.4), II (57.1), III (19) | NR         | NR        | BP 25.0                | NR        | NR                   | NR                      | Amenorrhea (35) |
| Winters-Stone et al | 26       | USA     | Case-control/ cross-sectional | No                                    | 59          | 58.5 ± 9.7        | BCSs 50.4 ± 9.3, CON 49.6 ± 9.1 | 0 (5), I (29), II (30), III (19) | 28.3 ± 7.2 | NR        | CON 25.0                | NR        | CT only (17), ET (19), CT with estrogen inhibitor (23) | 6-24 mo          | NR           |
| Winters-Stone et al | 27       | USA     | RCT           | No                                        | 37          | 62.1 ± 6.7        | O (5.6), I (39.6), II (41.5), III (5.7) | 29.5 ± 5.7 | NR        | CON 25.0                | NR        | CT (32), RT (46), PostM (37) | >1 y            | NR           |
| Yuen and Sword  | 28       | USA     | RCT           | No                                        | 22          | 53.9 ± 12.8       | NR         | NR        | High school (13.5), Some college (86), Secondary (40.5), University (16.8) | White (77), African American (23) | NR        | Sx (22), CT (18), RT (17) | NR                      | NR           |
| Zak et al       | 29       | Poland  | Cross-sectional | No                                      | 102         | 70.2 ± 4.3        | NR         | 27.3 ± 4.3    | Sx (102), CT (7), RT (2) HT (27), RT + CT (23), HT + CT + RT (26) | Sx (22), CT (18), RT (17) | Ongoing         | NR                      | NR           |

Abbreviations: CIPN, chemotherapy induced peripheral neuropathy; CON, controls (never had breast cancer); CT, chemotherapy; HT, hormone therapy; LD, lymphedema; MAS, mastectomy; NR, not reported; RT, radiation therapy; PreM, premenopause; PostM, postmenopause; Sx, surgery.
Gait measures among BCSs for usual gait speed, fast gait speed at a short distance, and fast gait speed at long distance are shown in figure 3. Meta-analysis estimated the usual gait speed to be 0.91 m/s (95% CI, 0.2-1.6), fast gait speed at a short distance to be 1.2 m/s (95% CI, 0.31-2.1), and fast gait speed at a long distance to be 1.65 m/s (95% CI, 1.64-1.66), which are slower than normative values (usual gait speed = 1.1-1.2 m/s; fast gait speed short = 2.0-2.6 m/s; fast gait speed long = 1.7-1.8 m/s). For the TUG, 2 studies used an 8-ft course\(^\text{36,49}\) while 3

| Study ID | Gait Measures | Mean Outcome ± SD | Balance Measures | Mean Outcome ± SD |
|----------|---------------|-------------------|------------------|-------------------|
| 01       | Fast gait speed–long (m/s) | 1.49±0.28         |                  |                   |
| 02       | Overall Stability Index EO | 0.47±0.32         |                  |                   |
| 03       | Overall Stability Index EC | 2.64±0.93         |                  |                   |
| 04       | Short Physical Performance Battery Score | 3.82±0.49         |                  |                   |
| 05       | TUG (s) | 8.05±2.39          |                  |                   |
| 06       | Fast gait speed–long (m/s) | 1.16±0.23         |                  |                   |
| 07       | Single leg stance time (s) | 26.8±20.9         |                  |                   |
| 08       | Functional reach (cm) | 29.7±7.4          |                  |                   |
| 09       | Functional reach (cm) | 12.6±6.10         |                  |                   |
| 10       | Median COP displacement (cm) | 63.1          |                  |                   |
| 11       | Median COP velocity EO (cm/s) | 1.8           |                  |                   |
| 12       | Median COP velocity EC (cm/s) | 2.0           |                  |                   |
| 13       | COP root mean square (cm) | 0.48±0.03         |                  |                   |
| 14       | COP 95% confidence ellipse area (cm) | 2.113±0.305     |                  |                   |
| 15       | COP medial-lateral root mean square (cm) | 0.33±0.11       |                  |                   |
| 16       | Backward walking velocity (m/s) | 0.43           |                  |                   |
| 17       | Single leg stance EO sway area (cm²) | 21.03±5.9       |                  |                   |
| 18       | Sensory Organization Test–Composite | 69±10          |                  |                   |
| 19       | Single leg stance time EO (s) | 60.6±46.5        |                  |                   |
| 20       | Single leg stance time EC (s) | 15.7±16.4        |                  |                   |
| 21       | Sensory Organization Test–Visual | 80.35±14.61     |                  |                   |
| 22       | Single leg stance time (s) | 23.52±9.60        |                  |                   |
| 23       |                  |                  |                  |                   |
| 24       |                  |                  |                  |                   |
| 25       |                  |                  |                  |                   |
| 26       |                  |                  |                  |                   |
| 27       |                  |                  |                  |                   |
| 28       |                  |                  |                  |                   |
| 29       |                  |                  |                  |                   |
| 30       |                  |                  |                  |                   |

NOTE. Values are mean ± SD or as otherwise indicated.

Abbreviations: EC, eyes closed; EO, eyes open; NR, not reported.
The estimated 8-ft course time was 7.14 s (95% CI, 3.27–11.01; fig 4), and the estimated 3-m course time was 7.65 s (95% CI, 6.25–8.87; see fig 4), which is greater than normative reported values (6.44±0.17s).53

There were no differences for the single leg stance time between BCSs and those who never had breast cancer (P=.33; fig 5).

Study quality assessment

Study quality assessment using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies is provided for each study in supplemental table S1. Overall, 3 studies were rated good, 16 were rated fair, and 10 were rated poor. Because most studies are cross-sectional studies, breast cancer and gait and/or balance outcomes were assessed at the same time point, providing weak evidence as to whether breast cancer and its treatment cause gait and balance impairments or if gait and balance impairments precede cancer diagnosis. Therefore, it is possible that gait and balance impairments in BCSs may be influenced by factors apart from breast cancer. Additionally, 8 studies provided justification for their sample size,44,46,47,52,54,55,58,59 and no studies reported assessors blinded to breast cancer diagnosis.

Discussion

This study systematically reviewed and quantitatively synthesized existing scientific evidence on gait and balance characteristics of individuals diagnosed as having breast cancer. A total of 21 out of 29 studies provide evidence that BCSs display gait and balance impairments. Specifically, there is some form of gait or balance impairment as measured by the functional reach task, COP velocity, gait speed, or TUG.

Maintaining standing balance involves the complex interplay of multiple physiological components, and deficits in any processes will lead to balance impairment.55 Balance impairments in BCSs may result from reduced muscle strength and loss in proprioception from neuropathy, which are common adverse effects from breast cancer treatment.64 One study that found BCSs with functional reach impairments also found worse leg strength than normative values.11 Additionally, proprioceptive deficits may also contribute to poor balance. Proprioception involves the somatosensory systems sending and receiving information about the body’s orientation to keep the center of mass stabilized.67 Four studies included in the review found balance impairments in BCSs treated with neurotoxic chemotherapy, which is associated with peripheral neuropathy that may lead to proprioceptive loss.34,38,41,45 Recent evidence suggests walking and resistance exercise may reduce neuropathy symptoms, suggesting that future work should explore the impact of exercise on gait and balance in BCSs receiving neurotoxic chemotherapy.15 Additionally, because taxane- and platinum-based chemotherapy are common treatments for BCSs, clinicians should assess gait and balance with tests such as the functional reach or standing balance with a force plate.58

From the 3 different balance tasks analyzed in the meta-analysis, BCSs display balance impairment when compared with normative values of adults who never had breast cancer. Additionally, BCSs appear to have worse balance in the absence of visual feedback and when proprioception is challenged. For instance, 2 studies42,45 found greater COP velocity in BCSs than those who never had breast cancer when without visual feedback during a standing balance task. Furthermore, Besar et al35 found that BCSs have worse overall postural stability when visual information was not present compared with those who never had breast cancer. Wampler et al15 also found worse balance performance during the no-visual component of the SOT. Moreover, BCSs also demonstrated worse balance than those who never had
breast cancer when standing on a foam surface\textsuperscript{52} and worse balance when standing on a compliant surface without visual feedback.\textsuperscript{45} Collectively, these investigations suggest BCSs heavily rely on visual feedback to maintain upright posture, which may be because of the loss of proprioception commonly displayed after cancer treatment. When assessing balance, clinicians should rely on tests that challenge balance through the absence of visual feedback or with challenging proprioceptive conditions. Furthermore, clinicians should use caution using the single leg stance test because there are mixed results when comparing with those who never had breast cancer and normative values.

This review also found evidence of gait impairments in BCSs, as indicated by impairments in usual and fast gait speeds and TUG performance. Pamoukdjian et al\textsuperscript{69} found that usual gait speed under 0.8 m/s was an independent predictor of death in older cancer survivors. While the population in this review is well below the age of older adults, this highlights the importance of maintaining gait function with age after cancer treatment. While more studies used longer walking tests to assess endurance, our results suggest that walking tests at shorter distances will also capture changes in gait. There was large variability in gait speed between studies that may result from varying sampling methods and cancer treatment. Further work should identify which factors contribute to slow gait speed because exercise interventions may only benefit a subgroup of BCSs.

Gait impairments may result from fatigue and proprioceptive deficits. Fatigue is the most common adverse effect following breast cancer treatment.\textsuperscript{70} In older adults, greater fatigue has found to be significantly associated with slower
walking speed. Therefore, it may also be possible that cancer-related fatigue contributes to slowed walking. While 2 of the studies that measured gait speed also measured fatigue, neither of the studies explored the possibility of an association. Furthermore, proprioceptive deficits due to neuropathy may also influence gait speed because they inhibit information reaching the central nervous system to coordinate gait and maintain a constant speed. Three studies in the review that analyzed gait included BCSs with neuropathy, suggesting that symptoms of neuropathy may impair normal walking patterns. Future work should continue to identify which factors contribute to slow gait speed and explore whether exercise improves these factors and, consequently, gait function in BCSs.

The timescale of mobility impairment recovery following breast cancer treatment is poorly understood. While 3 of the studies tested BCSs during treatment, no overall conclusion could be determined if mobility is worse during or after treatment because of inconsistent findings. Conversely, 2 studies followed BCSs over consecutive treatments and found impaired postural stability and gait speed over time, indicating that postural stability and gait worsened with continuous chemotherapy. It is also evident that gait and balance impairments persist up to 5 years post treatment. Further work should determine when gait and balance impairments first appear with cancer treatment and if they resolve over time. This may help determine when an intervention is most effective to improve mobility.

For the studies included in the review, heterogeneity was substantial, indicating large variations between studies. This may be a result of differences in age range and cancer severity between studies. For instance, some studies included older women with breast cancer, and mobility has shown to decline with advanced age. Some studies recruited postmenopausal women, and loss of estrogen has been associated with declines in balance function. Furthermore, treatment types differed across studies and adverse-effects differences related to...
particular treatments may influence mobility outcomes. Collectively, these variations may confound the pooled effect and effect size results.

This study provides evidence of gait and balance impairments in BCSs. While current exercise interventions in BCSs have shown to improve quality of life and decrease fatigue and pain, few studies have examined whether exercise can improve gait and balance in this population. Because aerobic and resistance training can improve leg strength, fatigue, and proprioception in cancer survivors, it is possible that exercise can improve gait and balance. Feasibility studies have found improvements in balance with yoga and tai chi, but future steps should implement RCTs to determine if exercise interventions will improve gait and balance impairment. Because poor gait and balance are linked to a greater risk of falls and worse quality of life, successful interventions have potential to enhance functional independence, improve gait and balance impairment, and prevent falls and fall-related injuries.

This review provides important information for BCSs and clinicians. BCSs should report any noticeable changes in their gait or balance to clinicians because early detection may prevent long-term impairment. Clinicians should also assess gait and balance at the clinic both during and following treatment. Assessing balance with a force plate will better detect changes in stability, but the functional reach test can also be quickly administered and detect balance impairments. To assess gait speed, clinicians should assess usual and fast gait speed over 10 m or use TUG because a shorter distance appears to be able to detect changes in gait. Assessing and tracking their gait and balance can help identify BCSs in need of rehabilitation to improve their mobility. Improving gait and balance may reduce fall risk and prevent fall-related injuries such as hip fractures. Future research is also needed to help clinicians identify the type, intensity, and frequency of exercises that may improve gait and balance and reduce fall risk tailored for BCSs.

**Study limitations**

While this is the first study to systematically review mobility impairments in BCSs, it is not without limitations. The single leg balance was the only task that studies used to compare BCSs and those who never had breast cancer. Given the numerous measures of balance, overall conclusions about balance cannot be drawn from a single measure. Additionally, only 7 of the studies included a control group who never had breast cancer. Therefore, most of the findings among BCSs were compared with normative values. Furthermore, because of the high risk of bias from the included studies, the identified gait and balance impairments should be interpreted with caution. Many of the studies did not aim to understand balance or gait in BCSs as their primary purpose, which limits findings compared with those who never had breast cancer or over multiple time points. The high number of fair and poor quality studies also suggest that many of these studies are not suited to understand gait and balance impairments in BCSs. While some RCTs may be well-designed and lack study bias, these exercise interventions were not designed to understand mobility and, therefore, may not have a representative sample. There is a need for future work to better understand gait and balance impairments in BCSs. Moreover, the small number of studies included in the meta-analysis prevented an assessment of publication bias.

Of the balance tests in the review, the majority were static balance tests. Although important, adverse events related to poor balance such as falls typically occur during dynamic movements. Therefore, future studies should analyze both dynamic and static stability. For gait measures, studies reported gait speed and TUG times, but no studies reported spatial-temporal measures of gait (ie, step time, width, and length). Gait speed is an important component of gait, but characterizing spatiotemporal parameters of individual steps provides additional information about overall mobility. Future studies should further understand gait function.

**Conclusion**

This study systematically reviewed and quantitatively synthesized gait and balance measures in BCSs. The results suggest that BCSs have balance impairment and declines in gait speed. The pooled estimates for functional reach scores, COP velocity, gait speed, and TUG times based on the meta-analysis were all lower than their respective normative values, indicating potential balance and gait impairments in BCSs. Specifically, it was found that BCSs demonstrated worse stability in the static balance tasks...
when the visual and proprioceptive systems were challenged. Both usual and fast gait speed at short and long distances were also slower than adults who never had breast cancer. Clinicians should consider assessing changes in gait and balance in BCSs to identify those at risk for falls. Future interventions should target walking and balance exercises to improve mobility in BCSs.

Supplier

a. Stata, version 14.2 SE; StataCorp.

Corresponding author

Katherine L. Hsieh, BS, Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, 906 S Goodwin Ave, Urbana, IL 61801. E-mail address: klhsieh3@illinois.edu

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.

2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71-96.

3. Ferlay J, He´ry C, Autier P, Sankaranarayanan R. Global burden of breast cancer. In: Breast cancer epidemiology. New York: Springer; 2010. p 1-19.

4. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Engl J Med 2001;344:1997-2008.

5. Mustafa Ali M, Moeller M, Rybicki L, Moore HCF. Long-term peripheral neuropathy symptoms in breast cancer survivors. Breast Cancer Res Treat 2017;166:519-26.

6. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. Support Care Cancer 2012;20:583-9.

7. Hirvensalo M, Rantanen T, Heikkinen E. Mobility difficulties and physical activity as predictors of mortality and loss of independence in the community-living older population. J Am Geriatr Soc 2000;48:493-8.

8. Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. J Clin Oncol 2012;30:1829-34.

9. Allet L, Armand S, De Bie R, et al. The gait and balance of patients with diabetes can be improved: a randomised controlled trial. Diabetologia 2010;53:458-66.

10. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing 2006;35(Suppl 2):i37-41.

11. Foley MP, Hasson SM. Effects of a community-based multimodal exercise program on health-related physical fitness and physical function in breast cancer survivors: a pilot study. Integr Cancer Ther 2016;15:446-54.

12. Monfort SM, Pan X, Patrick R, et al. Gait, balance, and patient-reported outcomes during taxane-based chemotherapy in early-stage breast cancer patients. Breast Cancer Res Treat 2017;164:69-77.

13. Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. J Clin Oncol 2017;35:2604-12.

14. Galantino ML, Callens ML, Cardena GJ, Piela NL, Mao JJ. Tai chi for well-being of breast cancer survivors with aromatase inhibitor-associated arthralgias: a feasibility study. Altern Ther Health Med 2013;19:38-44.

15. Kleckner IR, Kamen C, Gewandter JS, et al. Effects of exercise during chemotherapy on chemotherapymduced peripheral neuropathy: a multicenter, randomized controlled trial. Support Care Cancer 2018;26:1019-28.

16. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

17. Littell JH, Corcoran J, Pillai V. Systematic reviews and meta-analysis. New York: Oxford University Press; 2008.

18. Almstedt HC, Grote S, Perez SE, Shoepe TC, Strand SL, Tarleton HP. Training-related improvements in musculoskeletal health and balance: a 13-week pilot study of female cancer survivors. Eur J Cancer Care 2017;26.

19. Bennett JA, Lyons KS, Winters-Stone K, Nall LM, Scherer J. Motivational interviewing to increase physical activity in long-term cancer survivors: a randomized controlled trial. Nurs Res 2007;56:18-27.

20. Croarkin E, Huang MH. Screening balance deficits in older individuals diagnosed with cancer. Top Geriatr Rehabil 2011;27:244-51.

21. Ihira H, Mizumoto A, Makino K, et al. Physical functions, health-related outcomes, nutritional status, and blood markers in community-dwelling cancer survivors aged 75 years and older. Asian Pac J Cancer Prev 2014;15:3305-10.

22. Klepin HD, Geiger AM, Tooze JA, et al. Physical performance and subsequent disability and survival in older adults with malignancy: results from the health, aging and body composition study. J Am Geriatr Soc 2010;58:76-82.

23. Mina DS, Au D, Brunet J, et al. Effects of the community-based Wellspring Cancer Exercise Program on functional and psychosocial outcomes in cancer survivors. Curr Oncol 2017;24:284-94.

24. Schmitt AC, Repka CP, Heise GD, Challis JH, Smith JD. Comparison of posture and balance in cancer survivors and age-matched controls. Clin Biomech 2017;50:1-6.

25. Swartz MC, Lewis ZH, Lyons EJ, et al. Effect of home- and community-based physical activity interventions on physical function among cancer survivors: a systematic review and meta-analysis. Arch Phys Med Rehabil 2017;98:1652-65.

26. Bennett JA, Winters-Stone KM, Dobek J, Nail LM. Frailty in older breast cancer survivors: age, prevalence, and associated factors. Oncol Nurs Forum 2013;40:E126-34.

27. Cheville AL, Troxel AB, Basford JR, Kornblith AB. Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer. J Clin Oncol 2008;26:2621-9.

28. Glowacka I, Nowikiewicz T, Siedlecki Z, Hagner W, Nowacka K, Zegarski W. The assessment of the magnitude of disability and survival in older adults with breast cancer. Pathol Oncol Res 2018;24:284-94.

29. Hanuszkiewicz J, Malicka I, Barczyk-Pawelec K, Wozniewski M. Late Breast Cancer Patients: The Assessment of the Magnitude of Disability and Survival in Older Adults with Breast Cancer. Breast Cancer Res Treat 2018;26:2621-9.

30. Huang MH, Righter A, Shilling T. Self-reported balance confidence relates to perceived mobility limitations in older cancer survivors. Rehabil Oncol 2016;34:64-71.
31. Niederer D, Schmidt K, Vogt L, et al. Functional capacity and fear of falling in cancer patients undergoing chemotherapy. Gait Posture 2014;39:865-9.
32. Rostkowski E, Bak M, Samborski W. Body posture in women after mastectomy and its changes as a result of rehabilitation. Adv Med Sci 2006;51:287-97.
33. Galantino ML, Greene L, Daniels L, Dooley B, Muscatello L, O’Donnell L. Longitudinal impact of yoga on chemotherapy-related cognitive impairment and quality of life in women with early stage breast cancer: a case series. Explore (NY) 2012;8:127-35.
34. Hile ES, Fitzgerald GK, Studenski SA. Persistent mobility disability after neurotoxic chemotherapy. Phys Ther 2010;90:1649-57.
35. Basar S, Basar S, Bakar Y, et al. Does lymphedema affect the postural stability in women after breast cancer? Top Geriatr Rehabil 2012;28:287-94.
36. Damush TM, Perkins A, Miller K. The implementation of an oncology referred, exercise self-management program for older breast cancer survivors. Psychooncology 2006;15:884-90.
37. Extermann M, Leeuwenburgh C, Samiljan L, et al. Impact of chemotherapy on medium-term physical function and activity of older breast cancer survivors, and associated biomarkers. J Geriatr Oncol 2017;8:69-75.
38. Kneis S, Wehrle A, Freyler K, et al. Balance impairments and neuromuscular changes in breast cancer patients with chemotherapy-induced peripheral neuropathy. Clin Neurophysiol 2016;127:1481-90.
39. Yuen HK, Sword D. Home-based exercise to alleviate fatigue and improve functional capacity among breast cancer survivors. J Allied Health 2007;36:e257-75.
40. Kokkonen K, Saarto T, Makinen T, et al. The functional capacity and quality of life of women with advanced breast cancer. Breast Cancer 2017;24:128-36.
41. Monfort SM, Pan X, Patrick R, et al. Natural history of postural instability in breast cancer patients treated with taxane-based chemotherapy: a pilot study. Gait Posture 2016;48:237-42.
42. Montezuma T, de Oliveira Guirro EC, Leite MMDOL, Vernal S. Changes in postural control in mastectomized women. J Cancer Ther 2014;5:493.
43. Penttinen HM, Saarto T, Kellomäki-Lehtinen P, et al. Quality of life, body composition and physical activity of breast cancer patients after adjuvant treatments. Psychooncology 2011;20:1211-20.
44. Twiss JJ, Waltman NL, Berg K, Ott CD, Gross GJ, Lindsey AM. An exercise intervention for breast cancer survivors with bone loss. J Nurs Scholarsh 2009;41:20-7.
45. Wampler MA, Topp KS, Miaskowski C, Byl NN, Rugo HS, Hamel K. Quantitative and clinical description of postural instability in women with breast cancer treated with taxane chemotherapy. Arch Phys Med Rehabil 2007;88:1002-8.
46. Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. J Cancer Surviv 2012;6:189-99.
47. Winters-Stone KM, Nail L, Bennett JA, Schwartz A. Bone health and falls: fracture risk in breast cancer survivors with chemotherapy-induced amenorrhea. Oncol Nurs Forum 2009;36:315-25.
48. Winters-Stone KM, Torgrimson B, Horak F, et al. Identifying factors associated with falls in postmenopausal breast cancer survivors: a multi-disciplinary approach. Arch Phys Med Rehabil 2011;92:646-52.
49. Zak M, Biskup M, Macek P, Krol H, Krupnik S, Opuchlik A. Identifying predictive motor factors for falls in postmenopausal breast cancer survivors. PLoS One 2017;12:e0173970.
50. Anderson RT, Kimmick GG, McCoy TP, et al. A randomized trial of exercise on well-being and function following breast cancer surgery: the RESTORE trial. J Cancer Surviv 2012;6:172-81.
51. Eijigor S, Karapolat H, Yesil H, Uslu R, Durmaz B. Effects of pilates exercises on functional capacity, flexibility, fatigue, depression and quality of life in female breast cancer patients: a randomized controlled study. Eur J Phys Rehabil Med 2010;46:481-7.
52. Fong SS, Choi AWM, Luk WS, Yam TTT, Leung JCY, Chung JYW. Bone mineral density, balance performance, balance self-efficacy, and falls in breast cancer survivors with and without qigong training: a randomized study. Integr Cancer Ther 2018;17:124-30.
53. Galantano-Castillo N, Arroyo-Morales M, Ariza-Garcia A, et al. The six-minute walk test as a measure of health in breast cancer patients. J Aging Phys Act 2016;24:508-15.
54. Haines TP, Sinnammon P, Wetzig NG, et al. Multimodal exercise improves quality of life of women being treated for breast cancer, but at what cost? Randomized trial with economic evaluation. Breast Cancer Res Treat 2010;124:163-75.
55. Husebo AM, Dyrstad SM, Mjaaland I, Soreide JA, Bru E. Effects of scheduled exercise on cancer-related fatigue in women with early breast cancer. ScientificWorldJournal 2014;2014:271828.
56. Mascherini G, Giannelli C, Ghelarducci G, Dei-Innocenti S, Petri C, Galanti G. Active lifestyle promotion with home-based exercise in breast cancer survivors. J Hum Sport Exerc 2017;12:119-28.
57. Reis D, Walsh ME, Young-McCaughan S, Jones T. Effects of Nia exercise in women receiving radiation therapy for breast cancer. Oncol Nurs Forum 2013;40:E374-81.
58. Vollmers PL, Mundhenke C, Maass N, et al. Evaluation of the effects of sensorimotor exercise on physical and psychological parameters in breast cancer patients undergoing neurotoxic chemotherapy. J Cancer Res Clin Oncol 2018;144:1785-92.
59. Wang YJ, Boehmke M, Wu YW, Dickerson SS, Fisher N. Effects of a 6-week walking program on Taiwanese women newly diagnosed with early-stage breast cancer. Cancer Nuts 2011;34:E1-13.
60. Galantino ML, Desai K, Greene L, Demichele A, Stricker CT, Mao JJ. Impact of yoga on functional outcomes in breast cancer survivors with aromatase inhibitor-associated arthralgias. Integr Cancer Ther 2012;11:313-20.
61. Bohannon RW, Larkin PA, Cook AC, Gear J, Singer J. Decrease in timed balance test scores with aging. Phys Ther 1984;64:1067-70.
62. Springer BA, Marin R, Cyhan T, Roberts H, Gill NW. Normative values for the unipedal stance test with eyes open and closed. J Geriatr Phys Ther 2007;30:8-15.
63. Isles RC, Choy NL, Steer M, Nitz JC. Normal values of balance tests in women aged 20-80. J Am Geriatr Soc 2004;52:1367-72.
64. Lafond D, Corriuval H, Hébert R, Prince F. Intraobserver reliability of center of pressure measures of postural steadiness in healthy elderly people. Arch Phys Med Rehabil 2004;85:896-901.
65. Winter DA. Biomechanics and motor control of human movement. Hoboken: John Wiley & Sons; 2009.
66. Visovsky C. Muscle strength, body composition, and physical activity in women receiving chemotherapy for breast cancer. Integr Cancer Ther 2006;5:183-91.
67. Horak FB. Clinical assessment of balance disorders. Gait Posture 1997;6:76-84.
68. Sereny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain 2014;155:2461-70.
69. Pamoukdjian F, Lévy V, Sebbane G, et al. Slow gait speed is an independent predictor of early death in older cancer patients.
outpatients: results from a prospective cohort study. J Nutr Health Aging 2017;21:202-6.

70. Mortimer JE, Barsevick AM, Bennett CL, et al. Studying cancer-related fatigue: report of the NCCN scientific research committee. J Natl Compr Canc Netw 2010;8:1331-9.

71. Manty M, de Leon CF, Rantanen T, et al. Mobility-related fatigue, walking speed, and muscle strength in older people. J Gerontol A Biol Sci Med Sci 2012;67:523-9.

72. Frigon A, Rassignol S. Experiments and models of sensorimotor interactions during locomotion. Biol Cybern 2006;95:607-27.

73. Steffen TM, Hacker TA, Mollinger L. Age-and gender-related test performance in community-dwelling elderly people: six-minute walk test, Berg Balance Scale, Timed Up & Go test, and gait speeds. Phys Ther 2002;82:128.

74. Armstrong AL, Oborne J, Coupland CA, MacPherson MB, Bassey EJ, Wallace WA. Effects of hormone replacement therapy on muscle performance and balance in postmenopausal women. Clin Sci 1996;91:685-90.

75. Murtezani A, Ibraimi Z, Bakalli A, Krasniqi S, Disha ED, Kurtishi I. The effect of aerobic exercise on quality of life among breast cancer survivors: a randomized controlled trial. J Cancer Res Ther 2014;10:658-64.

76. Schmidt ME, Wiskemann J, Armbrust P, Schneeweiss A, Ulrich CM, Steindorf K. Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: a randomized controlled trial. Int J Cancer 2015;137:471-80.

77. Kampshoff CS, Chinapaw MJ, Brug J, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise After ChemoTherapy (REACT) study. BMC Med 2015;13:275.

78. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. Maturitas 2013;75:51-61.

79. Chen Z, Maricic M, Bassford TL, et al. Fracture risk among breast cancer survivors: results from the women’s health initiative observational study. Arch Int Med 2005;165:552-8.

80. Centers for Disease Control and Prevention. Fatalities and injuries from falls among older adults—United States, 1993-2003 and 2001-2005. MMWR Morb Mortal Wkly Rep 2006;55:1221-4.

81. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. Arch Phys Med Rehabil 2001;82:1050-6.