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Gait variability is altered in cancer survivors with self-reported neuropathy

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ABSTRACT

Background: Falls are prevalent among cancer survivors, and neuropathy, a side effect from chemotherapy treatment, is thought to contribute to falls. While falls commonly occur during walking, there is limited information about gait function in cancer survivors with neuropathy.*Research Question:* What is the difference between gait speed and gait variability in cancer survivors with and without self-reported neuropathy and healthy controls?

Methods: Seventeen cancer survivors and 12 healthy individuals [age: 53.5 (11.8), gender: 10 females] participated in a single testing session. Cancer survivors were grouped into neuropathy [n = 9; age: 61.9 (6.1); gender: 8 females] and no neuropathy [n = 8; age: 50.75 (14.1); gender: 7 females] based on the self-reported FACT/GOG Neurotoxicity subscale questionnaire. All participants completed two walking trials at their comfortable pace across a 6 m pressure sensitive walkway. A one-way ANOVA with Tukey's post-hoc analysis and effect sizes were used to detect differences in gait speed, step length variability, and step width variability between groups.

Results: Although there were no group differences in gait speed, a significant main effect was found for step length variability ($p = 0.03$, $\eta^2 = 0.24$) between groups. Step length variability was significantly less in cancer survivors with neuropathy than healthy controls ($p = 0.05$, d = 1.30). There was a significant main effect for step width variability between groups ($p = 0.05$, $\eta^2 = 0.20$). Cancer survivors with neuropathy had significantly greater step width variability than healthy controls ($p = 0.04$, d = 1.04).

Significance: Cancer survivors with neuropathy display greater step width variability and less step length variability than healthy controls. Gait variability may be a more sensitive marker than gait speed to track mobility in cancer survivors with neuropathy symptoms. Assessing and treating gait function in cancer survivors with neuropathy symptoms may improve everyday ambulation.

1. Introduction

There are over 15.5 million cancer survivors in the United States with an expected 20.3 million survivors by 2026 [1]. With the rapidly growing number of cancer survivors, it is critical to manage symptoms from cancer treatment. Falls are common in cancer survivors, with estimates of approximately 30% of cancer survivors falling per year [2]. Falls can lead to injury, hospitalization, and even death, posing a serious health concern among this population [3].

While there are many factors that contribute to falls, neuropathy from cancer treatment is thought to be a critical risk factor [4–6]. Neuropathy, damage to one or several peripheral nerves, is a common side effect from chemotherapy treatment, affecting over 60% of cancer survivors [7,8]. Neuropathy can result in motor symptoms, such as muscle weakness or muscle cramps, sensory symptoms, such as numbness, pain, or tingling in the hands and feet, or autonomic symptoms, such as hypotension or paralytic ileus [7]. These symptoms of neuropathy can last months following cancer treatment, and it is unclear if and/or when symptoms resolve [8].

The association between neuropathy and falls in cancer survivors may result from neuropathy's deleterious effect on balance. Previous research suggests that neuropathy impairs standing balance in cancer survivors [5,9,10]. For instance, Monfort et al. [11] found static postural stability to decrease over successive chemotherapy cycles in breast cancer survivors with neuropathy. One study reported worse postural stability in cancer survivors compared to age-matched controls [12], while others found worse postural stability in cancer survivors receiving neurotoxic chemotherapy compared to healthy controls [13,14].

While evidence suggests that neuropathy impairs standing balance,

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there is limited knowledge as to whether neuropathy impacts gait in cancer survivors. Understanding how gait is impacted in cancer survivors is essential because falls are most common during walking [15]. Other clinical populations with neuropathy have demonstrated walking impairments. Diabetics with neuropathy walk with slowed gait, shorter step length, and greater gait variability than healthy controls [9,16]. Parkinson's disease patients with peripheral neuropathy walked with significantly shorter stride length, greater stride length variability, slower speed, and had a greater number of falls than Parkinson's patients without neuropathy [17]. Understanding walking behavior in cancer survivors with neuropathy may provide information on how to prevent falls and fall-related injuries.

Walking behavior is commonly identified as measures of gait speed. Slowed gait speed is associated with frailty and disability [18]. In addition to gait speed, gait variability (i.e., fluctuations in gait) provides important information regarding the control of walking. Both too much gait variability [19] and too little gait variability [20] is related to a greater number falls in older adults. Gait behavior is less understood in cancer survivors with neuropathy, and understanding their gait speed and gait variability may help reduce their risk for falling and improve ambulation. Therefore, the purpose of this pilot study was to determine differences in gait speed and gait variability in a mixed group of cancer survivors with and without self-reported neuropathy and healthy controls (i.e., age- and sex-matched). We hypothesized that cancer survivors with neuropathy will demonstrate reduced gait speed and greater gait variability compared to cancer survivors without neuropathy and healthy controls.

2. Methods

2.1. Participants

Seventeen cancer survivors and 12 healthy individuals from the community participated. The inclusion criteria for cancer survivors were as follows: a) ≥18 years of age; b) physician-confirmed diagnosis of cancer; c) received neo-adjuvant or adjuvant chemotherapy treatment; d) ability to walk with or without aid; d) understand written and spoken English. Cancer survivors were excluded if they had metastasis. Healthy controls were age- and sex-matched and were included if they: a) were ≥18 years of age; b) could walk with or without aid; c) understand written and spoken English; d) did not have cancer or other health condition. Any participant was excluded from the study if they scored more than two standard deviations from the established norms (i.e., total score < 20) on the Modified Telephone Interview for Cognitive Status (TICS-M) [21]. All procedures were approved by the Institutional Review Board, and all participants completed written informed consent prior to participation.

2.2. Procedures

In a single testing session, all participants provided demographic information including age, gender, and education. Cancer survivors completed information about their cancer history including cancer type, cancer stage, treatment type, and time since diagnosis. Participants completed the Functional Assessment of Cancer Therapy Neurotoxicity subscale (FACT/GOG-NTX), a 38-item self-report questionnaire consisting of two components, a general measure of quality of life and a neurotoxicity subscale [22]. For the purposes of this study, only the NTX subscale is reported. The NTX subscale contains 11 questions about symptoms of sensory, motor, and hearing neuropathy. NTX scores range from 0 to 44, and lower scores represent greater symptoms of neuropathy [22]. Participants also completed the Activities Balance Confidence (ABC) to measure their perceived balance confidence [23]. The ABC ranges from 0 to 100, with lower scores representing lower balance confidence [23].

After completing questionnaires, participants were instructed to walk across a 6 m Zeno™ pressure sensitive walkway at their normal, comfortable pace for two trials. Participants started walking one meter in front of the walkway and ended one meter past the walkway. Gait speed, step length, and step width mean and standard deviation were extracted from the walkway. The average of two trials for all gait measures were calculated. All participants then completed the Physiological Profile Assessment (PPA), a test to measure an individual's overall risk of falling. The PPA test measures fall risk based on vision, reaction time, leg strength, proprioception, and balance [24]. A higher PPA score represents a greater risk for falls.

2.3. Statistical analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 22 (IBM Corp, Armonk, NY). Cancer survivors were grouped into a neuropathy group and without neuropathy group based on the four sensory neuropathy items on the FACT/GOG NTX subscale [25]. These four sensory items have a 90% discriminative ability to detect neuropathy compared to a clinical assessment [25]. A one-way ANOVA with Tukey's post-hoc analysis was used to detect differences in gait speed, average step length, average step width, average step length standard deviation (i.e., step length variability), and average step width standard deviation (i.e., step width variability) between cancer survivors with neuropathy, cancer survivors without neuropathy, and healthy controls. The level of significance was set at $p \leq 0.05$. Effect sizes for ANOVA were calculated with eta squared (η^2). η^2 of 0.01 represents a small effect size, 0.06 a medium effect size, and 0.14 a large effect size [26]. Effect sizes for post-hoc analysis were calculated with Cohen's d. Cohen's d of 0.2 is considered to be a small effect size, 0.5 to be medium effect size, and 0.8 to be a large effect size [26].

3. Results

Demographic information for all participants is represented in Table 1. Per design, the cancer survivor neuropathy group had significantly higher NTX scores than cancer survivors without neuropathy group ($p < 0.001$) and healthy controls ($p < 0.001$). There were no significant differences in NTX scores between cancer survivors without neuropathy and healthy controls ($p = 0.72$). There was not a significant main effect between groups for age ($p = 0.16$). There was also not a significant main effect for PPA between groups ($p = 0.27$, $\eta^2 = 0.09$).

Average gait speed was 120.2 ± 21.2 cm/s for cancer survivors with neuropathy, 112.6 ± 15.9 cm/s for cancer survivors without neuropathy, and 133.5 ± 19.5 cm/s for healthy controls (Fig. 1). Average step length was 65.2 ± 6.6 cm for cancer survivors with neuropathy, 63.3 ± 4.7 cm for cancer survivors without neuropathy, and 70.6 ± 9.2 for healthy controls (Fig. 2A). Average step width was 7.5 ± 7.5 cm for cancer survivors with neuropathy, 6.5 ± 6.6 cm for cancer survivors without neuropathy, and 7.6 ± 7.6 cm for healthy controls (Fig. 2B). Step length variability was 2.0 ± 0.4 cm for cancer survivors with neuropathy, 2.1 ± 0.8 cm for cancer survivors without neuropathy, and 3.1 ± 1.4 cm for healthy controls (Fig. 3A). Step width variability was 2.6 ± 2.6 cm for cancer survivors with neuropathy, 2.3 ± 2.3 cm for cancer survivors without neuropathy, and 1.9 ± 2.0 cm for healthy controls (Fig. 3B).

No main effects, but borderline significance, were found for gait speed (p = 0.06, $\eta^2 = 0.19$), step length (p = 0.09, $\eta^2 = 0.17$), or step width (p = 0.73, $\eta^2 = 0.02$) between groups.

A significant main effect was found for step length variability ($p = 0.03$, $\eta^2 = 0.24$) between groups. Tukey's post-hoc analysis revealed that step length variability was significantly less in cancer survivors with neuropathy than healthy controls ($p = 0.05$, d = 1.30). No significant differences were found in step length variability between cancer survivors without neuropathy and healthy controls ($p = 0.09$, d

Table 1
Demographic and clinical variables for cancer survivors and heathy controls. Values are indicated as mean ± SD.

	Cancer Survivors with Neuropathy	Cancer Survivors without Neuropathy	Healthy Controls
Age (years)	61.9 ± 6.1	50.75 ± 14.1	53.5 ± 11.8
Gender	8 females; 1 male	7 females; 1 male	10 females; 2 males
Education, highest degree			
High School	5	1	0
Bachelor's	1	3	1
Graduate School	3	4	11
Cancer Type			N/A
Breast	8	3	
Lymphoma	0	3	
Prostate	0	1	
Leukemia	0	1	
Salivary gland	1	0	
Cancer Stage			N/A
1	4	0	
2	4	3	
3	0	3	
N/A	1	1	
Time Since Diagnosis (years)	5.8 ± 7.4	6.8 ± 2.9	N/A
Neurotoxicity Subscale	31.4 ± 3.2	39.8 ± 3.4	40.9 ± 2.3
Physiological Profile Assessment	−0.1 ± 0.5	−0.1 ± 0.6	0.4 ± 1.0
Activities Balance Confidence	86.6 ± 12.7	92.0 ± 7.7	91.8 ± 7.2

Note: N/A indicates not applicable.

= 1.02), or between cancer survivors with and without neuropathy (p = 0.97, d = 0.18). There was also a significant main effect for step width variability between groups (p = 0.05, η^2 = 0.20). Tukey's post-hoc analysis revealed that cancer survivors with neuropathy had significantly greater step width variability than healthy controls (p = 0.04, d = 1.04). There was not a significant difference in step width variability between cancer survivors without neuropathy and healthy controls (p = 0.37, d = 0.71), or between cancer survivors with and without neuropathy (p = 0.57, d = 0.48).

4. Discussion

The purpose of this pilot investigation was to determine differences in gait between cancer survivors with neuropathy, cancer survivors without neuropathy, and healthy controls (i.e., age- and sex-matched). Our results suggest that cancer survivors with neuropathy demonstrate greater step width variability and less step length variability than healthy controls. There were large between group effect sizes for gait speed and step length, but traditional levels of significance were not reached between cancer survivors and healthy controls.

Cancer survivors with sensory neuropathy had greater step width and less step length variability than healthy controls. To the best of our knowledge, this is the first study to examine step-by-step fluctuations in a cancer survivor population. Measures of gait variability are commonly used in geriatric research as markers to identify those with high fall risk [27]. There is an optimal range of variability for human movement, and falling outside this range results in poor locomotion [28]. For instance, too much or too little step width variability is associated with greater falls in older adults [20]. Because the neuropathy group reported greater sensory symptoms, it is possible that deficits in sensory integration may result in a lack of control of gait and contribute to step length and step width variability. The somatosensory system plays a vital role in receiving feedback about the environment to plan and execute of gait, and sensory neuropathy may contribute to altered gait variability. It is also possible that cancer survivors with sensory neuropathy attempt to control the length of their steps, but as a result have high fluctuations in the width of their steps as individuals can only voluntarily change either their step length or step width [29]. Step length and step width variability did not differ between cancer survivor groups. This may suggest that the combined side effects from cancer treatment (i.e., strength loss, fatigue) with neuropathy may result in greater gait variability, and not only the effects of neuropathy [30,31].

Past studies have examined changes in gait speed in cancer survivors with neuropathy. Winters-Stone et al. [32] reported that female cancer survivors with neuropathy walked slower and with shorter steps with those without neuropathy. Monfort et al. [33] followed breast cancer survivors over chemotherapy cycles and found that those with neuropathy symptoms walked at slower speeds and with shorter step length after successive treatments. While average walking speed and average step length was not did not have a significant main effect between groups, we found a large effect size (gait speed: η^2 = 0.19; step length η^2 = 0.17), and the lack of significance could be due to lack of power in the current pilot investigation. Slower gait speed and shorter step lengths are similar to those previously reported in cancer survivors [32,33]. This conservative gait pattern may be a compensatory strategy used to maintain balance while walking [6]. Future work should include a larger sample to determine whether gait speed differs among cancer survivors with neuropathy compared to cancer survivors without neuropathy and healthy controls.

Cancer survivors with neuropathy are at a high risk for falls [5,34], and gait impairments may contribute to a greater fall risk. Fluctuations in step length and step width can lead to unstable gait and poor balance, increasing the risk for falls [35]. Because gait variability is a marker for fall risk in many clinical populations [19,36,37], clinicians should track gait variability in cancer survivors with neuropathy and

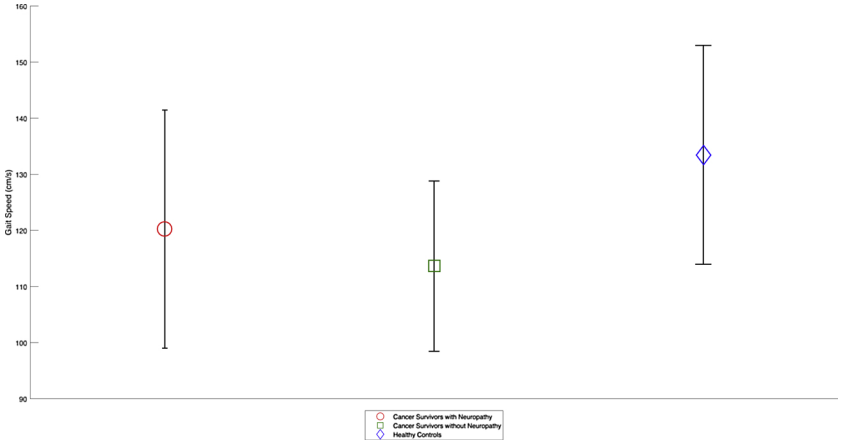

Fig. 1. Group mean ± standard deviation for gait speed (cm/s). Cancer survivors with neuropathy are indicated by the red circle, cancer survivors without neuropathy are indicated by the green square, and healthy controls are indicated by the blue diamond. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

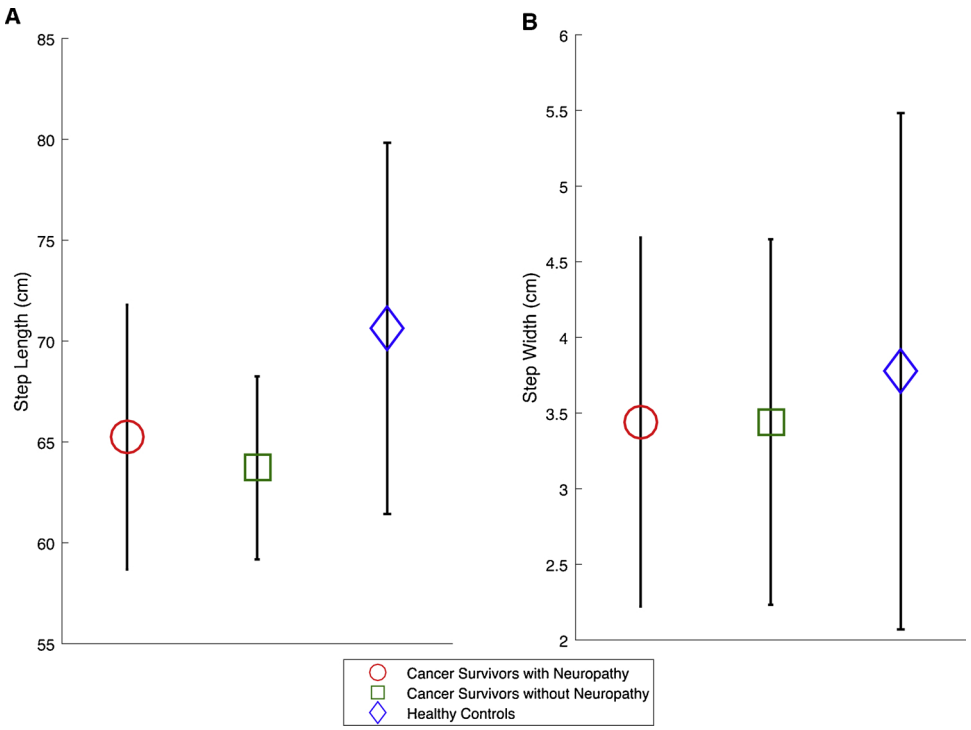

Fig. 2. Group mean ± standard deviation for (A) step length (cm) and (B) step width (cm). Cancer survivors with neuropathy are indicated by the red circle, cancer survivors without neuropathy are indicated by the green square, and healthy controls are indicated by the blue diamond. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

prescribe fall prevention strategies for those with too much or too little variability. Gait variability may serve as a sensitive early marker to track ambulation and predict falls, and it may be a more sensitive marker than gait speed. Moreover, the neuropathy group had mild symptoms of neuropathy compared to previous studies using the NTX subscale [38,39]. This suggests that gait variability is altered even in those with mild neuropathy symptoms, and gait variability may detect mobility impairment before neuropathy symptoms become severe. Detecting and treating gait and balance deficits early in the cancer treatment process may help reduce the risk of falling.

4.1. Limitations and future directions

While this study found gait impairments in cancer survivors with sensory neuropathy compared to healthy controls, the results should be interpreted within its limitations. First, the study used a mixed cancer group. While all cancer survivors received chemotherapy treatment, the varying types of cancer may influence gait function, but there is limited data as to whether cancer type influences mobility. Second, neuropathy was defined using a self-reported measure. The four sensory questions in the NTX subscale have been previously validated [25], but an

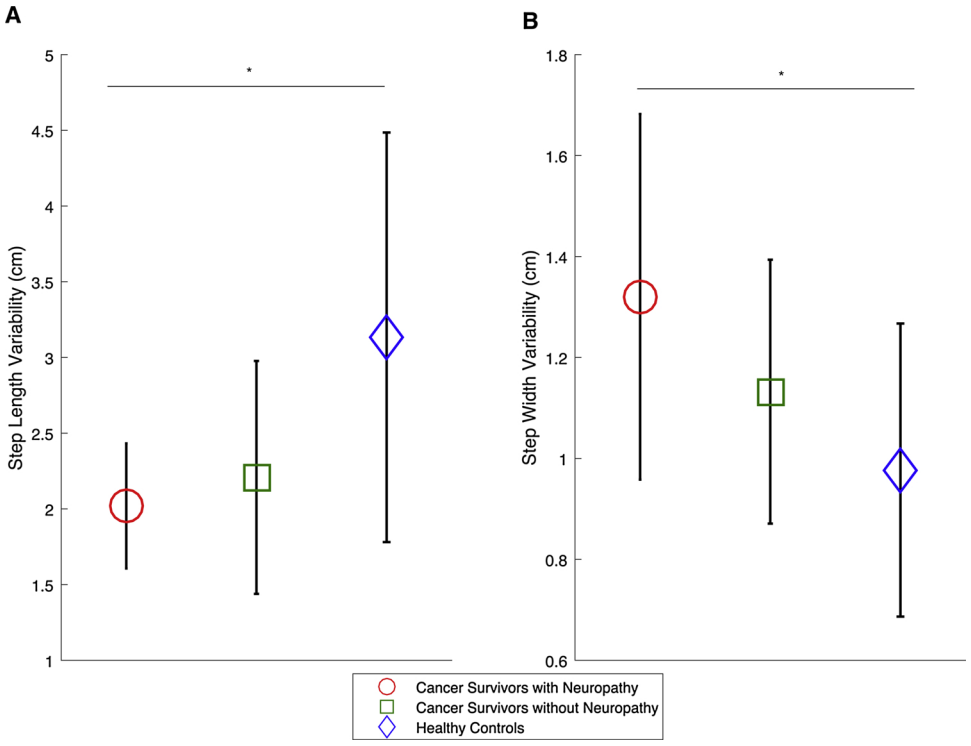

Fig. 3. Group mean ± standard deviation for (A) step length variability (cm) and (B) step width variability (cm). Step length variability was significantly less in cancer survivors with neuropathy than healthy controls ($p = 0.05$). Step width variability was significantly greater in cancer survivors with neuropathy than healthy controls ($p = 0.04$). Cancer survivors with neuropathy are indicated by the red circle, cancer survivors without neuropathy are indicated by the green square, and healthy controls are indicated by the blue diamond. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

objective measure or clinical assessment of neuropathy may provide a more accurate assessment of the presence and severity of neuropathy. Third, the majority of participants in the study were women, and results may not be generalizable to men. Future research is needed to recruit more representative samples including equal numbers of men and women. Last, there is a small sample size which limits power. This study was designed as a pilot study to determine whether gait impairments are present in cancer survivors with and without neuropathy.

Future studies should include larger samples with a single cancer group to understand the effects of chemotherapy induced neuropathy on gait function. Future studies should also include a clinical assessment of neuropathy. Samples with a range of fall risk should also be included. In the current sample, physiological fall risk as measured by the PPA did not differ between groups. This may suggest that there are alterations in gait even in highly functioning cancer survivors, or that physiological fall risk is not related to gait variability. Future longitudinal studies may also help determine whether altered gait variability predicts future falls in cancer survivors with neuropathy.

5. Conclusions

In conclusion, this study suggests that cancer survivors with self-reported sensory neuropathy demonstrate less step length and greater step width variability compared to healthy controls. Gait variability may be a more sensitive marker than gait speed or spatiotemporal measures to track fall risk in cancer survivors with neuropathy. Gait variability should be examined in cancer survivors receiving chemotherapy treatment to understand their functional level of independence. Treating cancer survivors with altered gait variability may help improve their ambulation and overall function.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.gaitpost.2019.06.014.

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