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Exploring the Effects of Yoga Therapy on Heart Rate Variability and Patient-Reported Outcomes After Cancer Treatment: A Study Protocol

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Abstract

Background: Following cancer treatment, adults commonly report worsened patient-reported outcomes (PROs) such as anxiety, stress, depression, persistent and upsetting cognitive complaints, unrelenting fatigue, and reduced quality of life. Poorer PROs are associated with disrupted autonomic nervous system functioning as measured by heart rate variability (HRV), both of which have been associated with greater morbidity and mortality. Interventions to improve HRV and PROs among adults following cancer treatment are needed. Yoga therapy holds promise as an intervention to improve HRV and PROs. Therefore, we conducted a single-subject exploratory experimental study to investigate the effects of yoga therapy on HRV and specific PROs (ie, cancer-related fatigue, anxiety, cognitive function, depression, stress, quality of life) in adults treated for cancer. To reduce publication bias, improve reproducibility, and serve as a reference for forthcoming reporting of study results, we present the study protocol for this study herein. **Methods:** Participants were adults who completed cancer treatment that were recruited from the Ottawa Integrative Cancer Centre. Consenting and eligible participants received one 1:1 yoga therapy session (ie, 1 participant, 1 Yoga Therapist) and 6 weekly group-based yoga therapy sessions (ie, 2-3 participants, 1 Yoga Therapist). Participants completed assessments 7 times: 3 times prior to the program (ie, −6 weeks, −3 weeks, immediately prior to the 1:1 yoga therapy session), immediately following the 1:1 yoga therapy session, prior to the first group-based yoga therapy session, after the last group-based yoga therapy session, and at a 6-week follow-up. Hierarchical linear modeling will be used to test the average effects of the yoga therapy program across participants. **Discussion:** This study will explore several novel hypotheses, including whether yoga therapy can improve HRV and/or specific PROs among adults treated for cancer acutely (ie, during a 1:1 yoga therapy session) and/or through repeated exposure (ie, after completing 6 weeks of group-based yoga therapy). Although the findings will require confirmation or refutation in future trials, they may provide initial evidence that YT may benefit adults treated for cancer. **Trial registration:** ISRCTN registry, ISRCTN64763228. Registered on December 12, 2021. This trial was registered retrospectively. URL of trial registry record: https://www.isrctn.com/ISRCTN64763228

Keywords

autonomic function, heart rate variability, yoga, cancer

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Background

Cancer is a leading cause of morbidity and mortality worldwide.[1] Though the 5-year survival rate has increased due to improved early detection and treatment protocols,[2] multiple studies describe heightened anxiety, stress, depression, persistent and upsetting cognitive complaints, unrelenting fatigue, and worsened quality of life (QoL) following treatment.[3-6] This is problematic because when such symptoms and distress go untreated, adults may be less adherent to surveillance and treatment protocols, which can result in worse disease outcomes, comorbidities, and early mortality.[7]

Additionally, adults with a history of cancer have a heightened risk for cardiovascular disease[8] and are 10 times more likely to die from cardiovascular disease than the

general population.[9] The pathways through which cancer increases the risk of developing cardiovascular disease are complex and multifactorial; however, dysregulated autonomic nervous system (ANS) functioning is one proposed mechanism.[10] Analysis of heart rate variability (HRV)—the variation in the time interval between consecutive heartbeats—is widely used for the assessment of ANS functioning. HRV is a quantitative, multidimensional, non-invasive, non-specific marker of ANS functioning.[11] Generally, increased HRV is reflective of well-regulated ANS functioning and associated with decreased health risks. Adults diagnosed with cancer have decreased HRV.[12,13] In comparison to matched controls, women diagnosed with breast cancer have a significantly faster heart rate, and significantly decreased HRV as indicated by lower values for standard deviation of normal-to-normal interval, square root of mean squared differences of successive normal-to-normal interval, HRV index, and high-frequency power.[12] A decreased HRV is concerning as it signifies an inability to reduce sympathetic activation of the heart,[14] which can render the heart vulnerable to arrhythmia, lead to sudden death, and accelerate the development of atherosclerotic coronary artery disease.[15,16] Moreover, a decreased HRV is an independent predictor of cardiac events and mortality in healthy adults and adults with a history of myocardial infarction,[14,17] as well as in adults diagnosed with cancer.[18] Beyond being implicated in the risk for cardiovascular disease and survival, a decreased HRV is associated with stress, depression, and fatigue among adults with and without a history of cancer.[19-21] If not dealt with, a decreased HRV can significantly reduce survival and QoL. Thus, strategies to improve HRV have the potential to reduce cardiovascular disease and improve several patient reported outcomes (PROs) among adults diagnosed with cancer.

Yoga Interventions

Yoga is classified by the National Institutes of Health as a form of Complementary and Alternative Medicine,[22] and it represents one of the most commonly used complementary therapies among adults with cancer.[23] Yoga is a mind-body practice that typically includes meditation and relaxation techniques, breath practices, and physical postures.[24] Yoga has become widely popular in recent years,[25] leading to an increasing interest in the scientific evaluation of yoga for promoting health and managing certain lifestyle-related diseases such as cancer.[26] Among adults with and without a history of cancer, different styles of yoga (eg, Hatha, Iyengar, Vinyasa, Ashtanga, Sivananda, Restorative) with different lineages that offer specific practices and varying combinations of duration and frequency (ie, dosage) have been found to improve psychosocial outcomes including anxiety, depression, and stress, enhance markers of ANS functioning including heart rate, increase exercise capacity, and reduce cardiovascular disease risk.[27-36] Additionally, different yoga styles (practiced at varying dosages) have been shown to improve ANS functioning and several PROs.[28,37-39] For example, there is evidence supporting the positive effects of different yoga styles (practiced at varying dosages) on QoL, psychosocial outcomes (eg, anxiety, depression, negative affect, fatigue, spiritual wellbeing), and HRV among adults with a history of cancer.[33,39-41]

Despite yoga's value, its practice is often focused on strengthening and stretching the body and improving fitness via physical postures (ie, asanas) and breathing exercises (ie, pranayamas) in many Western countries. However, asanas and pranayamas are only two aspects of yoga. Consequently, questions remain about how a more extensive, inclusive, personalized, and therapeutic practice that focuses on ANS response and regulation can help to improve HRV and specific PROs among adults with a history of cancer. Yoga Therapy (YT), reflecting advanced education as certified by the International Association of Yoga Therapy, warrants particular attention due to its: (1) non-prescriptive kosha-based assessment and practices; (2) understanding of the person as an integrated body–mind system that can function optimally when there is a state of dynamic balance; (3) respect of individual differences; (4) ability to assess ANS response and regulation, and; (5) ability to adapt to the needs of people with different health conditions.[42,43] YT is "the professional application of the principles and practices of yoga to promote health and wellbeing within a therapeutic relationship that includes personal assessment, goal setting, lifestyle management, and yoga practices for individuals and small groups."[43] Accordingly, the yoga therapist assists participants in

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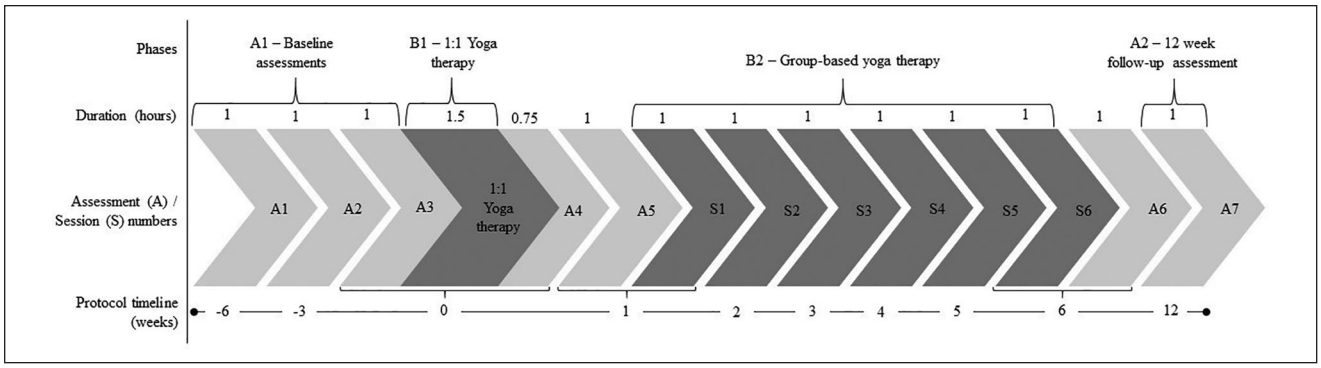

Figure 1. Study timeline depicting duration of each phase and assessment schedule. Notes. 1:1 = one on one. 1:1 yoga therapy session was set as week 0 (intervention start date) and timeline was adjusted accordingly.

implementing a dynamic, individually tailored practice to manage their condition and alleviate suffering in a progressive, non-invasive manner.[43] Core components of YT are designed to help participants regulate their ANS functioning and involve yogic philosophy and lifestyle education, physical postures, somatic movement, breathing practices, guided imagery, and relaxation techniques to suit participants' bio-psycho-social-spiritual needs. Although the evidence base for using YT to prevent and treat health issues ranging from anxiety to cardiovascular diseases is growing,[26,44,45] studies are needed to test the effects of YT on HRV and PROs among adults following cancer treatment before it can be recommended.

Current Study

We developed a single-subject experimental exploratory study to assess the effects of YT on HRV (primary outcome) and a range of secondary outcomes including specific PROs related to physical symptoms (ie, cancer-related fatigue), psychosocial problems (ie, anxiety, depression, stress), cognitive function (ie, perceive cognitive impairments, perceived cognitive abilities, impact of perceived cognitive impairment on QoL and comments from others on cognitive function), and QoL among adults who have completed cancer treatment (aim 1). We hypothesize that YT will lead to improvements in HRV, and furthermore that YT will lead to reduced cancer-related fatigue, anxiety, depression, and stress, and improved cognitive function and QoL. Changes in slopes for HRV and specific PROs across the transition from one phase to another phase (ie, when 1:1 YT is introduced, when group-based YT is introduced, and when the YT program is completed) will also be examined to determine if there is a difference in level of change across phases (aim 2). We have no hypothesis for this aim given its exploratory nature. In this manuscript, we present the protocol for this study to reduce publication bias, improve reproducibility, and serve as a reference for forthcoming reporting on study results.

Methods/Design

Study Design

Given the potential for idiosyncratic patterns of responses to YT, a single-subject experimental design was adopted for this exploratory study because it helps to preserve and describe the variability within and between individuals.[46] Using the participant as their own control can be very useful for analyzing data from heterogenous samples often recruited in oncology settings. Single-subject experimental design studies have been described in detail elsewhere.[47-51] Briefly, single-subject experimental design studies are methodologically robust and seek to answer questions about the effect(s) of an intervention (eg, YT) on an outcome or outcomes of interest (eg, HRV, PROs) using systematic measurement strategies. Defining features of single-subject experimental design studies are that data are gathered, analyzed, and interpreted for 1 entity (ie, 1 participant or a group of participants), and that each is observed repeatedly during baseline and treatment phases allowing each to serve as their own control by establish a pattern for the outcome(s) of interest at baseline before the intervention is introduced. In other words, each participant serves as their own control for purposes of comparison within single-subject experimental design studies.[50] Single-subject experimental design studies are advantageous as they provide detailed information about the variations in the effect(s) of an intervention, which tends to be lost in group-comparison designs because they focus on averages and effect sizes for the entire group. Other advantages of single-subject experimental design studies are that they can be implemented in their natural settings to reduce the gap between research and practice,[52] and they allow researchers to conduct research with populations that have a relatively low prevalence because they require a small sample size.[50]

The usual convention is to have at least 3 assessments to establish a baseline for each participant. To this end, each participant completed 3 assessments prior to any YT sessions (Figure 1, A1 phase). Participants then received a 1:1 YT

session (ie, 1 participant, 1 Yoga Therapist; Figure 1, B1 phase; intervention phase 1) and 6 weeks of group-based YT (ie, 2-3 participants, 1 Yoga Therapist; Figure 1, B2 phase; intervention phase 2) with assessments taking place immediately following the 1:1 yoga therapy session, prior to the first group-based yoga therapy session, and after the last group-based yoga therapy session. Finally, participants completed an assessment at 6-week follow-up (ie, 12 weeks after they first received their 1:1 YT session; Figure 1, A2 phase). The duration of each phase and assessment schedule was established to assess if any changes in outcomes occurred. Moreover, the repeated assessments were to help rule out threats to internal validity (eg, passage of time, life events, medication changes) and afford dynamic changes in the outcomes over short periods of time to be captured, enabling questions about how the outcomes change as the program shifts from 1:1 YT to group-based sessions to be asked and answered.

Ethical Principles

The study reported on herein was designed and carried out in accordance with the principles of the Declaration of Helsinki. Participants were provided with both oral and written information regarding the study prior to obtaining their informed consent. The ethics committees at the University of Ottawa and at the Canadian College of Naturopathic Medicine approved the study protocol on March 14, 2017 (#H01-17-04). The study was registered retrospectively in a publicly accessible registry for clinical trials (https://www.isrctn.com/ISRCTN64763228).

Participants

Adults were recruited using 3 strategies. First, adults who had agreed to be contacted for research through the Ottawa Integrative Cancer Centre (OICC; now known as the Centre for Health Innovation) institutional "permission to contact" registration process were contacted by OICC staff and invited to participate. Second, naturopathic doctors and OICC staff referred interested adults to the research team. Third, study recruitment posters were placed throughout the OICC inviting interested adults to contact the research team.

Eligibility criteria. Adults were eligible to participate if they: (1) were ≥18 years of age; (2) had received a diagnosis of cancer (regardless of time since diagnosis); (3) had not undergone conventional cancer treatments (ie, chemotherapy, radiotherapy, surgery) within the past 3 months and had none scheduled for the next 5 months; (4) were not currently on any cardiac medication; (5) self-reported no YT practice since their cancer diagnosis, but may have participated in yoga classes; (6) were cleared for physical activity as indicated by physical activity readiness questions, and; (7) were willing and able to provide informed consent in English.

Sample Size

A priori, the target sample size was set to a minimum of 25 participants based on the primary outcome of HRV with a moderate effect size ($d=0.50$) and 80% power at the 5% level of significance. With an expected loss to follow-up rate of 20%, the goal was to recruit 30 participants. However, recruitment ceased after 28 months (May 2017-September 2019) once 25 participants were recruited. This sample size is in line with sample sizes for single-subject experimental design studies, which are generally small (eg, range from 1 to 13, $M=3.64$).[53] In addition, repeated assessments were conducted to ensure a sufficiently large number of observations to perform well-powered statistical (idiographic, within-person) analyses even with a small sample size.[54]

Procedures

As mentioned above, participants were screened for eligibility and informed consent was obtained. Repeated assessments were conducted at the OICC before, during, and after the YT program was introduced. Twenty-four hours prior to each assessment, participants were instructed to abstain from alcohol, caffeine, heavy meals, and strenuous exercise. Upon arrival, participants were asked to change into a Hexoskin Smart Shirt (Carre Technologies Inc.; https://www.hexoskin.com/) selected and programed to match their height, weight, date of birth, and sex. Once participants were wearing the shirt, the built-in textile electrocardiography (ECG) and respiratory sensors, as well as the Bluetooth recording device were activated. Participants were then asked to complete a series of questionnaires and sit calmly for 30 minutes. This allowed for participants' vital signs to be recorded continuously. At each assessment, the same procedures were followed, with the exception of the assessments that occurred immediately before, during, and immediately after the 1:1 YT session wherein participants completed these assessments during the same visit and thus wore the shirt continuously. Data from the questionnaires were entered into SPSS and raw data from the Hexoskin Smart Shirts were uploaded to the Hexoskin Online Dashboard following each assessment.

YT program

Paramount to describing the study protocol is the description of the YT program to enhance readers' ability to understand what was done. As such, the 2021 CLARIFY guidelines,[55] which provide a template for the reporting of the providers, content, and delivery of practices used in yoga research interventions, were used for the reporting of the YT program and its details (Supplemental File 1). Participants completed a single 90-minute 1:1 YT session and 6 weekly 60-minute group-based sessions at the OICC over a 7 week period. No specific strategies were used to

promote participants' attendance, which was tracked by the Yoga Therapists. The 7 sessions were delivered by experienced yoga teacher volunteers who were actively completing their practicum competency to become Certified Yoga Therapists at the School of Embodied Yoga Therapy in Ottawa, ON (Canada). Beyond their regular YT coursework, all student Yoga Therapists participated in a 2-day education specific to yoga and cancer, where they studied the bio-psycho-social-spiritual impact of medical treatments, and how to modify movement and breath for persistent side effects (eg, lymphedema). They also received an addendum (Supplemental File 2). Sessions and clinical notes were regularly supervised and reviewed by an experienced, expert Yoga Therapist who designed the YT program using a combination of lineage (eg, Hatha), post-lineage (eg, somatic movement), and modality focused (eg, restorative) practices designed to help participants regulate their ANS functioning. The 1:1 YT session offered empathetic listening, co-assessment of participants' concerns (including persistent side effects of cancer treatment), yogic education with regard ANS response and regulation, and yoga practices (ie, physical, energetic, emotional, mental, and connection/meaning/spiritual) specific to the participants' needs and responses. Information about each participant's abilities and preferences for practice were carried over from the 1:1 YT session to the group practice by the Yoga Therapist. Generally, participants had the same Yoga Therapist for all sessions; however, there was one instance when the Yoga Therapist changed from the 1:1 YT session to the group practice due to therapist availability, and in that case, the new Yoga Therapist was informed by notes and verbal communication of participants' abilities and preferences. The small group-based YT sessions were offered once a week and included a group check in, yogic ANS functioning education, gentle Hatha poses, lateral somatic movement, breath awareness practice (and possible practice of breath extension), full body relaxation, and a check out to share responses to the practice. Yoga practices were delivered in English using an established modifiable protocol (including lying prone practices, seated, "table top" and standing poses, ending with "savasana" or corpse pose relaxation), but continually tailored to meet participants' abilities and preferences, gleaned from the 1:1 YT sessions and as they arose during the group sessions. Participants were encouraged to modify the practices themselves, ask for help, imagine the practices (rather than completing them physically), and/or rest anytime they wanted. Soft background music was employed (ie, "Bija" by Todd Norian). See Table 1 for examples of posture and breathwork practices along with approximate durations for the group sessions.

Additional information as required by the 2021 CLARIFY guidelines,[55] are that: (1) participants were encouraged to practice any techniques (eg, movements, breath work) they found helpful at home, though no specific homework was given; (2) participants were made aware of ongoing yoga classes for individuals with cancer (free of charge) and ongoing YT at the OICC (at a cost that could be supplemented at 50% by the OICC foundation, if needed), and; (3) home practice, if done voluntarily, was not measured.

Assessments

The assessment schedule is presented in Table 2.

Self-Reported Questionnaires

Sociodemographic, behavioral, and medical characteristics. To describe the sample, participants were asked to self-report their date of birth, sex, civil status, cultural and racial background, education level, annual household income, employment status, health conditions (eg, stroke, diabetes), characteristics of their most recent cancer diagnosis (ie, type, stage, treatments received, date of diagnosis), height, and weight. Body mass index was computed using the following formula: weight in kilograms divided by height in meters squared. Participants also completed the 2-item Godin Leisure Time Exercise Questionnaire (GLTEQ)[56] wherein they self-reported their physical activity behavior. Using the first item, total weekly scores can be calculated by multiplying the reported weekly frequencies of strenuous, moderate, and mild activity by 9, 5, and 3 respectively, which provides a total metabolic equivalent intensity level. Alternatively, reported weekly frequencies of strenuous, moderate, and mild activity can be analyzed separately. Using the second item, overall frequency in which participants engaged in regular activity during a typical 7-day period that results in a fast heartbeat and sweating that ranges from 1 (*often*) to 3 (*never*) can be computed. After reverse scoring responses, higher scores reflect greater engagement in regular physical activity.

Patient reported outcomes (secondary outcomes)

Trait and State Autonomic Regulation (aR) scales. The 19-item trait version of the self-report aR scale was used to assess participants' general state of regulation for different autonomic functions, namely orthostatic-circulatory, rest/activity, and digestive regulation.[57] The state version of the aR scale was also used. It includes items adapted from the trait version to reflect state of regulations in relation to the preceding week. Although an 18-item state version has been published,[58] only the 14 items that could be adapted and that were not too specific were used. Each trait aR item was scored on a 3-point scale (though the anchors differed across items) whereas each state aR item was scored on a 5-point scale (with different anchors across items). The scales are scored such that higher scores (after removing item 12 for the trait aR scale and reverse scoring negative items for both

Table 1. General Group-Based Yoga Therapy Session Outline, Including Examples of Teachings and Yogic Practices.

Phases	Approximate duration	Sample teachings and yoga practices (all modifiable for side effects and accessibility, including utilizing supports of chair, wall, bolsters, block)
Open/check in/ education	10 min	Open-ended questions to the group: *How are you? What are you noticing in your body these days and in this moment? Is there anything else* you'd *like to say about your experience?*
Supine (or seated with support)	10 min	Lateral spinal movements (ventral vagal rolling practice) Spinal warm-up (eg, bridge pose or Setu Bandhasana) Natural breath awareness Slow extension of exhalation, if comfortable
Seated	5 min	Spinal twists (eg, easy twist pose or Parivrtta Sukhasana) Lateral flexions (eg, side bend pose or Parsva Sukhasana) Seated forward bends (eg, wide-angled seated forward bend or Upavistha Konasana) Seated backbends (eg, reclining pose or Supta Sukhasana) Natural breath awareness Slow extension of exhalation, if comfortable
Table top	10 min	Flexions and extensions (eg, cat pose or Marjaryasana) Spinal extensions (eg, child's pose or Balasana) Twists (eg, thread the needle pose or Parsva Balasana) Natural breath awareness Slow extension of exhalation, if comfortable
Standing	10 min	Warrior I (or Virabhadrasana I) Tree poses (or Vrksasana) Extended triangle/side angle pose (or Utthita Trikonasana/Utthita Parsvakonasana) Standing backbend (or Anuvittasana) Natural breath awareness Slow extension of exhalation, if comfortable
Seated (continuation of seated poses practices, as described above)	5 min	Spinal twists Lateral flexions Seated forward bends Seated backbends Natural breath awareness Slow extension of exhalation, if comfortable
Final resting pose	10 min	Corpse pose or Savasana Natural breath awareness Slow extension of exhalation, if comfortable
Closing/check out/ questions and support		Seated comfortably Natural breathing Slow extension of exhalation, if comfortable

Notes. All aspects of the yoga practice were modified for individual preference and need, including changes of position and addition of supports (blocks and bolsters). Participants were encouraged to change movements/breath work at any time, visualize the practices instead or rest, depending on their interoceptive awareness. As well, as the study was designed to explore yoga therapy (not yoga instruction), the Yoga Therapists delivered the agency of practice back to participants. Practices were offered, individualized for participants' abilities and preferences, and participants choses the content and duration of their practice. Min = minutes.

scales) indicate better autonomic-regulation.[59] Scores have been shown to have adequate-to-good internal consistency, test-retest reliability, and validity among adults with a range of medical conditions, including cancer.[57-59]

Functional Assessment of Cancer Therapy-Fatigue scale (FACT-F). The FACT-F is a 13-item questionnaire used to assess fatigue and its influence on global QoL in people with cancer over a 7-day period.[60] It has been used in trials designed to test the impact of yoga on fatigue among adults diagnosed with cancer.[41] Each item was scored on a 5-point scale ranging from 0 (*not at all*) to 4 (*very much*). The FACT-F is scored such that higher scores indicate less fatigue. FACT-F scores have demonstrated strong internal consistency (alpha coefficient ranges = 0.93-0.95) and good stability (test-retest reliability, $r = 0.87$).[60]

Functional Assessment of Cancer Therapy-Cognitive Function Version 3 (FACT-Cog v.3). The FACT-Cog v.3 is a 37-item measure designed to assess impairment of cognitive abilities and its impact on QoL during the past 7 days.[61] It allows cancer survivors to assess their memory, attention, concentration, language, and thinking abilities, and consists of 4 subscales: perceived cognitive impairments, comments from others, perceived cognitive abilities, and impact on QoL. It has been used in trials designed to test

Table 2. Data Collection Timeline.

Outcomes (Data collection instrument)	Assessment number						
	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]
HRV (Hexoskin Smart Shirt)	x	x	x[h]	x	x	x	x
Sociodemographic, behavioral, and medical characteristics	x						
Perceptions of regulation for different autonomic functions (aR scales)	x	x	x		x	x	x
Physical activity behavior (GLTEQ)	x	x	x		x	x	x
Cancer-related fatigue (FACT-F)	x	x	x		x	x	x
Cognitive function (FACT-Cog v.3)	x	x	x		x	x	x
Depressive symptoms (CES-D)	x	x	x		x	x	x
Perceived stress (PSS)	x	x	x		x	x	x
Anxiety (STAI)	x	x	x	x	x	x	x
Quality of life (FACT-G v.4)	x	x	x		x	x	x
Group identification (GIS)						x	x

Notes: HRV = heart rate variability; aR scales = Trait and State Autonomic Regulation scales; GLTEQ = Godin Leisure Time Exercise Questionnaire; FACT-F = Functional Assessment of Cancer Therapy-Fatigue scale; FACT-Cog v.3 = Functional Assessment of Cancer Therapy-Cognitive Function Version 3; CES-D = Center for Epidemiologic Studies Depression short-form scale; PSS = Perceived Stress Scale; STAI = State-Trait Anxiety Inventory; FACT-G v.4 = Functional Assessment of Cancer Therapy General Version 4; GIS = Group Identification Scale.

[a]6 weeks prior to the one-on-one yoga therapy (1:1 YT) session.

[b]3 weeks prior to the 1:1 YT session.

[c]Immediately prior to the 1:1 YT session.

[d]Immediately following the 1:1 YT session.

[e]Prior to the first group-based YT session.

[f]After the last group-based YT session.

[g]At 6-week follow-up.

[h]Assessment was continuous between assessments 3 and 4 (ie, throughout the 1:1 YT session).

the impact of aerobic and resistance training on cognition among adults with a history of cancer.[62,63] Items were rated on a 5-point scale ranging from 0 (*never* or *not at all*) to 4 (*several times a day* or *very much*). To score the FACT-Cog v.3, negatively worded items are reverse scored and all individual item scores are summed such that it yields 4 summary scores whereby higher scores reflect fewer cognitive problems and better QoL. FACT-Cog scores have shown high reliability and validity with cancer survivors.[64,65]

The Center for Epidemiologic Studies Depression (CES-D) short-form scale. The CES-D short-form scale is a 10-item questionnaire used to assess depressive symptomatology during the past week.[66] It has been used in trials designed to test the impact of physical activity on depressive symptoms among adults with a history of cancer.[67] Each item was scored on a scale ranging from 0 (*rarely or none of the time* (*< 1 day*)) to 3 (*all of the time* (*5-7 days*)). The 2 positive mood items receive a reverse score and then all responses are summed with higher scores indicating more severe depressive symptoms. The measurement properties of this scale have been assessed, with satisfactory test-retest reliability and good predictive accuracy as compared to the full-length 20-item version of the CES-D.[66]

Perceived Stress Scale (PSS). The 10-item PSS[68] is one of the most widely used questionnaires for assessing perceptions of stress and it has been used in trials designed to test the impact of yoga on perceived stress among adults with a history of cancer.[69] It consists of 10 questions that tap into one's ability to feel in control of their emotions and everyday problems during the past month. Participants responded using a scale ranging from 0 (*never*) to 4 (*very often*). The 4 positive mood items receive a reverse score and all responses are summed with higher scores reflecting higher degrees of perceived stress. PSS scores have shown adequate reliability (alpha coefficient ranges = 0.78-0.87)[70,71] and high predictive validity.[72,73]

The State-Trait Anxiety Inventory (STAI). The STAI is a widely validated questionnaire that consists of 40 items divided equally into 2 distinct subscales to measure subjective level of anxiety in specific situations (ie, state anxiety) and in general (ie, trait anxiety).[74] Responses can range from 1 (*almost never*) to 4 (*almost always*). After reverse scoring appropriate items, state and trait anxiety responses are summed separately, with higher scores indicating more anxiety symptoms. The STAI has been found to have high intercorrelation between subscale items, high test re-test reliability for the trait subscale and low for the state scale, and high concurrent validity as compared to other measures of anxiety.[75,76]

The Functional Assessment of Cancer Therapy General Version 4 (FACT-G v.4). The FACT-G v.4 is a past 7-day

health-related QoL questionnaire with 27 items covering 4 dimensions: physical, social, emotional, and functional wellbeing. Each item was scored on a 5-point scale ranging from 0 (*not at all*) to 4 (*very much*).[77] It yields 4 summary scores and a total score computed from the combination of the subscales, and it is scored such that higher scores indicate better QoL. FACT-G scores have shown good validity and acceptable reliability among adults with a history of cancer.[78,79]

The Group Identification Scale (GIS). Given that the extent to which participants identify with their group during the group sessions may influence outcomes, the GIS was administered. It is a 4-item questionnaire designed to assess one's sense of belonging to the group and one's sense of commonality with in-group members.[80] Each item was reported on a 7-point scale ranging from 1 (*I strongly disagree*) to 7 (*I strongly agree*). Higher scores reflect greater group identification. GIS scores have been found to have acceptable reliability and validity in the general population.[81,82]

Objective Assessments

HRV (primary outcome). Hexoskin Smart Shirts (Carre Technologies Inc.; https://www.hexoskin.com/), which are compression shirts for men and women with ECG sensors, were worn by participants to collect real-time vital signs for set periods of time. A number of studies have assessed the validity and reliability of the Hexoskin Smart Shirts (see https://www.hexoskin.com/pages/scientific-publications, for a list). Further, the accuracy of these shirts in outpatient settings has been previously validated among adults without a history of cancer during activities of daily living[83] and moderate-to-vigorous intensity aerobic activity.[84] Hexoskin Smart Shirts contain 5 sensors: 2 respiratory loops and 3 cardiac dry textile electrodes. Activity, respiratory, and heart sensors measure data in real time and record data for up to 14 hours through a small Bluetooth recording device that enabled data transmission to an application on the research team's tablet. The data collected were then downloaded into password-protected Excel spreadsheets directly from the Hexoskin online dashboard for analysis.

A multitude of parameters or features can be derived from the Hexoskin Smart Shirt data, including heart rate, HRV, heart rate recovery, respiratory sinus arrhythmia, and changes in the duration of different activation phases (eg, changes in the ST-segment or T-wave amplitude). Respiration (or breathing rate) can also be extracted and used to compute several breathing characteristics (eg, respiration variability, respiratory rate, tidal volume, and in/expiratory duration change). Acceleration, activity level, step counts, and energy expenditure (in kilocalories) are also possible outputs of the shirt. Common linear and nonlinear HRV metrics that can be derived from these data and analyzed include: standard deviation of the normal-to-normal interval (an estimate of overall HRV), square root of the mean squared differences of successive normal-to-normal intervals (an estimate of short-term components of HRV), mean heart rate, and entropy measures.[85] These specific linear and nonlinear HRV metrics will be analyzed.

Data Analysis

Preliminary analyses. In relation to the sociodemographic, behavioral, and medical characteristics, as well as the study outcomes (ie, HRV, PROs), descriptive statistics will be computed using means and standard deviations for continuous variables (or medians and interquartile ranges when the observed variables do not follow a normal distribution) and frequencies and percentages for categorical variables. Additionally, a CONSORT flow chart will be developed to summarize the process of recruitment and follow-up of participants in the study.

Main analyses. Van den Noortgate and Onghena's[86,87] 2-level hierarchical linear modeling (HLM) approach will be used to address the main objective of the study and test the average effects of the YT program across participants. The HLM approach is similar to other approaches proposed for analyzing single-subject experimental design study data (eg, ordinary least squares regression analysis, generalized regression analysis, piecewise regression analysis). However, it allows for combining data from multiple participants and accounts for the dependencies that may result from the hierarchical clustering of the data that occurs because assessments are nested within participants.[88] In contrast, the other approaches typically serve for the analysis of data from a single participant, which makes them inefficient to estimate several parameters of primary interest (eg, average effects of YT on HRV metrics and PROs). Furthermore, the HLM approach is very flexible and can be extended to account for linear and nonlinear trends, autocorrelations, unequal within-phase variances, and non-normal data. Further, the HLM approach has been validated with small sample sizes,[89] and predictors such as age can be included in level-2 to examine and explain variability between participants variability. Finally, dummy variables can be added to estimate changes in trends between the phases of interest; details on extensions of the basic 2-level HLM can be found elsewhere.[90]

Briefly, we will apply the 2-level HLM approach for each outcome (ie, HRV metrics, PROs) to estimate the average estimated baseline level, the average estimated effect across time (ie, trend across all phases), the average estimated effect across each phase, the average change in level

across adjacent phases, the between-person variance of these estimates, and the covariance between these estimates along with the within-person variance; details on the approach can be found elsewhere.[86,87] The restricted maximum likelihood estimation approach in SPSS will be used to obtain the aforementioned estimates. Given the importance of statistical considerations when specifying multilevel models, a description of the multilevel model building process will be presented alongside results.

Additional analyses. The amount and richness of data collected facilitate additional exploratory analyses. Indeed, after the main analyses are conducted to address the study aims, it is envisaged that further research questions will be asked. In these cases, more exploratory analyses may be undertaken to address these subsequent research questions.

Discussion

Adults diagnosed with cancer endure a range of negative effects from diagnosis onward. Cancer-related fatigue, impaired cognitive function, anxiety, stress, depression, and reduced QoL are the most prevalent and distressing PROs, and dysregulated ANS functioning (as indicated by a decreased HRV) may contribute to these PROs while increasing the risk of morbidity and early mortality. There is an urgent need to identify feasible and effective interventions to improve HRV and PROs. Research shows that different yoga styles are effective in improving HRV and several PROs.[28,37,38] As YT adapts the practice of yoga to the needs of people with specific illnesses such as cancer,[42] it may be an ideal offering for adults with a history of by cancer. Emerging evidence supports its use among adults diagnosed with cancer.[26,44,45] This exploratory study will generate evidence on the effects of a YT program targeting ANS functioning to determine if it improves HRV and related PROs (ie, cancer-related fatigue, cognitive function, depression, stress, anxiety, and QoL), though results will have to be tested in further confirmatory trials. In addition to examining the effects of the YT program (ie, the average estimated effects across the program), we hope to contribute to addressing gaps in knowledge in the field. In particular, considering resources are generally limited, short interventions and group-based sessions are preferable options. However, empirical data are needed to conclude if: (1) a single 1:1 YT session may be effective, and (2) group-based sessions may be effective. Therefore, we will estimate the average estimated effects across each phase and the average change in level across adjacent phases to examine the potential differential effects of the specific phases (ie, 1:1 YT session, weekly group-based sessions), and thus gain a better understanding of the effects of 1:1 YT versus group-based YT, which will require confirmation or refutation in future trials.

A key strength of this study is its design. Although single-subject experimental design studies have become increasingly popular in recent years, studies focused on yoga (or YT specifically) using such designs are rare. The advantage of this design is that repeated measurements are compared for each participant, which allows each participant to serve as their own control and helps to account for potential confounds. Another strength of this study is the close collaboration between various stakeholders, enabling the implementation of the YT program in a "real world setting." Indeed, special attention was given to involve a large number of professionals in this study. By including researchers and healthcare professionals from multiple domains and delivering the program in the community through an ongoing program and partnership, we aimed to enhance the likelihood that our results would be transferable to practice. A final strength of this study is the methodology applied and the breadth of outcomes assessed, which will allow us to uncover links among the outcomes and refine theoretical propositions regarding relationships between HRV and PROs.

Nevertheless, there are challenges that were encountered during the conduct of this study that are worth mentioning to provide others with the ability to prevent or plan for these challenges if they arise. These include: problems with the scheduling of the YT sessions and assessments, limited room availability at the OICC for assessments, technical issues that occurred when recording data from the Hexoskin Smart Shirts, and dropouts (n = 6). These challenges should be addressed by others interested in this type of research as they could affect study conduct and ultimately results. In addition, others should take into account the length of assessment in future studies. The combination of multiple measures may facilitate a more comprehensive assessment of the impact of YT on HRV and PROs while maximizing the resources invested; however, it is necessary to carefully consider participant burden, sample size, and adjustments for multiple testing. While efforts were made to reduce respondent burden (eg, questionnaire versions with the fewest number of items were selected), the assessments may still have been too long. Additionally, it is important to recognize that HRV is a limited measure of ANS functioning. HRV does not reflect the autonomic state of the whole body because the autonomic functions reflected in HRV are those regulating the pace-making function of the sinoatrial node, and as such the autonomic functions of other organ systems cannot be known from HRV.[91] As well, the recruitment strategies may limit the generalizability of the results to the greater population of interest. Finally, the main drawback of using a single-subject experimental design is that it does not control for secular trends in improvement; maturation may cause improvements in HRV and PROs regardless of the YT program.

To conclude, in this manuscript, we describe the protocol for an exploratory study investigating the effects of a YT program, comprising one 1:1 YT session and 6 weekly group YT sessions, on HRV (primary outcome) and specific PROs (secondary outcomes) in adults diagnosed with cancer. We anticipate that the findings will provide initial evidence that YT may benefit adults treated for cancer. However, given the exploratory nature of this study, findings may require additional testing in a confirmatory trial prior to encouraging other centers to develop similar programs for a growing segment of the population. Besides, the data collected could be used to address other research questions (eg, point to factors [other than the YT program itself; eg, sociodemographic characteristics] potentially associated with the primary or secondary outcomes). In turn, results from these exploratory analyses can be used to generate hypotheses that can be confirmed in further independent studies. All results will be reported transparently alongside appropriate interpretations in forthcoming publications.

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Author Contributions

JB and DS conceived the study. JB, AW, AP, JKE, and DS made substantial contributions to the conception and design of the study. AP made substantial contributions to the conception and design of the yoga therapy program, as well as oversaw the delivery of the yoga therapy program. CLH made substantial contributions to the data collection and analysis protocol. JB, AW, JH, AP, EC, JKE, and DS participated actively in the execution of the study reported on. JB drafted the manuscript. AW and JH drafted certain sections of the manuscript. AW, JH, AP, EC, JKE, CLH, AJES, and DS critically reviewed the manuscript for intellectual content and approved the final version to be published.

Availability of Data and Materials

The data cannot be shared as participants were assured that their data would be kept private and confidential to the extent permitted by law and that only the research team would have access to the data.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

Approval of the study protocol was granted by the ethics committees at the University of Ottawa and at the Canadian College of Naturopathic Medicine. Written informed consent was obtained from all participants to participate.

Consent for Publication

Informed consent was obtained from all participants for results to be published.

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Supplemental Material

Supplemental material for this article is available online.

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