Effects of High-Intensity Aerobic Interval Training on Cardiovascular Disease Risk and Health-related Quality of Life in Testicular Cancer Survivors: The HIITTS Trial

By

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Abstract

Background

Testicular cancer (TC) survivors (TCS) are an understudied, high-risk group susceptible to late-onset treatment-related cardiovascular disease (CVD), psychosocial, and health-related quality of life (HRQoL) deficits in the years following treatment. Importantly, despite having the second highest cure rate of all solid tumors, improvements in overall survival from testicular cancer are being off-set by treatment-related CVD. Aerobic exercise training prevents the development and mitigates the severity of cardiovascular and psychosocial deficits, similar to those experienced by TCS, in healthy and clinical populations including some cancer survivor groups. However, no studies to date have assessed the effects of aerobic exercise training on cardiovascular, psychosocial, and HRQoL deficits in TCS. High-intensity aerobic interval training (HIIT) is a modality of aerobic exercise training which involves alternating periods of vigorous- and light-intensity aerobic exercise; and, compared to moderate-intensity continuous aerobic exercise training (MCT), evidence suggests that HIIT may cause greater improvements in exercise capacity, cardiac and vascular health, metabolic and lipid-profile changes, antioxidant defenses, and possibly even HRQoL.

Purpose

The purpose of my dissertation was to evaluate the effects of a 12-week aerobic HIIT program on traditional and novel CVD risk factors, surrogate markers of cardiovascular and overall mortality, psychosocial function, and HRQoL in a population-based sample of TCS.

Methods

The High-Intensity Interval Training in Testicular cancer Survivors (HIITTS) trial was a randomized controlled trial. Recruited through the Alberta Cancer Registry and the surveillance clinic at the Cross Cancer Institute, 63 TCS were randomly allocated to either HIIT or a wait-list control usual care (UC) group. All HIIT and the UC participants were asked to maintain the low-to-moderate intensity physical activity they were performing at baseline throughout the duration of the 12-week intervention/observation period. Participants in the HIIT group were asked to attend thrice-weekly supervised exercise sessions for 12 weeks. The HIIT intervention consisted of four 4-minute work periods involving uphill walking/jogging on a treadmill between 75% and 95% of VO_{2peak} which were separated by three 3-minute active recovery periods performed at a lower intensity, for a total of 35 minutes per session (*including a 5-minute warm-up and 5-minute cool-down*). Participants in the UC group were invited to participate in a 6-week condensed version of the HIIT protocol after the 3-month follow-up period. Assessments were made at baseline, immediately postintervention, and at 3-month follow-up [patient-reported outcomes (PROs) only]. Participants' general and cardiovascular health were assessed using a maximal exercise protocol, non-invasive measures of vascular structure and function, resting and post exercise autonomic nervous system function, blood-based biomarkers, as well as self-report questionnaires (i.e., PROs) pertaining to physical activity, HRQoL, cancer-related fatigue (CRF), sleep quality, depression, anxiety, stress, and self-esteem.

Results

Postintervention data were available in ≥97% of participants for our primary outcome (VO_{2peak}) and 37 out of 45 (82%) secondary cardiovascular and PROs. HIIT participants completed 99% of all exercise sessions and achieved 98% of their target exercise intensity. Analysis of covariance (ANCOVA) revealed that, compared to UC, HIIT caused improvements

in the primary outcome of VO_{2peak} (3.7 mL O_2/kg/min; 95% CI: 2.4 to 5.1; p<0.001) and numerous secondary outcomes including Framingham CVD Risk Score (FRS) (p=0.011), arterial-thickness (p<0.001), arterial-distensibility (p=0.049), arterial-stiffness (p<0.001), microvascular reactivity (p=0.039), resting heart rate (p=0.012), parasympathetic reactivity (p=0.033); post-exercise parasympathetic reactivation (p<0.001), inflammation (p=0.045), low-density lipoprotein (p=0.014), CRF (p=0.003), self-esteem (p=0.029), the mental component score (p=0.034), role-physical (p=0.048), general health (p=0.016), vitality (p=0.001), and social functioning (p=0.011). Moreover, the effects of HIIT on CRF (p=0.031) and vitality (p=0.015) persisted at 3-month follow-up. Exploratory analyses also provided preliminary evidence that changes in VO_{2peak} may have partially mediated the postintervention improvements in the mental component score, vitality, and mental health; and the 3-month follow-up improvements in CRF and vitality. There were no HIIT-related adverse events.

Conclusions

The HIITTS trial provides the first randomized evidence that 12 weeks of supervised HIIT causes significant and potentially clinically meaningful improvements in traditional and novel CVD risk factors, surrogate markers of cardiovascular and overall mortality, and patient-reported CRF, self-esteem, and HRQoL in TCS. If confirmed, the HIIT-related mitigation of treatment-related sequalae may lead to subsequent improvements in the quality and length of life in TCS. Further investigation of HIIT to reduce cardiovascular morbidity/mortality and improve both psychosocial function and HRQoL in TCS is warranted.

Preface

This doctoral dissertation is the original work of myself, Scott C. Adams. The HIITTS trial received research ethics approval from the Health Research Ethics Board of Alberta – Cancer Committee (Trial ID# 14-0183) and the University of Alberta. The introduction (**Chapter 1**), discussion (**Chapter 5**), and **Appendices B – F** are my original work.

Chapters 2 (primary paper) and **3** (online supplement) of this dissertation are *in press* as Scott C. Adams, MSc, Darren S. DeLorey, PhD, Margie H. Davenport, PhD, Michael K. Stickland, PhD, Adrian S. Fairey, MD, MSc, Scott North, MD, Alexander Szczotka, and Kerry S. Courneya, PhD. (*2017 – in press*), **Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: a phase II randomized controlled trial**, *Cancer*, pp. XXX-XX. I was responsible for the trial conception, design, intervention and control group supervision, data collection, data analyses and interpretation, and wrote the first draft of the manuscript. Drs. Courneya, DeLorey, and Davenport made important contributions to the study conception, design, and data analyses. Drs. Courneya and DeLorey provided equipment for and supervised the data collection. All coauthors provided important feedback on aspects of data interpretation and provided critical appraisals of the manuscript content.

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the study conception, design, and data analyses. Drs. Courneya and DeLorey provided the equipment for and supervised the data collection. All coauthors provided important feedback on aspects of data interpretation and provided critical appraisals of the manuscript content.

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Key Dissertation Abbreviations

- CI: confidence interval
- CID: clinically important difference
- CRF: cancer-related fatigue
- CVD: cardiovascular disease
- ECG: electrocardiogram
- FACT-F: Functional Assessment of Cancer Therapy-Fatigue
- FRS: Framingham risk score
- HIIT: high-intensity aerobic interval exercise training
- HIITTS: high-intensity interval training in testicular cancer survivors
- HR: heart rate
- HRQoL: health-related quality of life
- HRR: one-minute heart rate recovery
- hsCRP: high-sensitivity C-reactive protein
- MCS: mental component score
- MCT: moderate-intensity continuous aerobic exercise training
- PCS: physical component score
- PROs: patient-reported outcomes
- PWV: pulse wave velocity
- RCTs: randomized controlled trials
- SD: standard deviation
- TC: testicular cancer
- TCS: testicular cancer survivors
- UC: usual care
- VO_{2peak}: cardiorespiratory/aerobic fitness

Chapter I – Introduction

1.1 Testicular Cancer

In North America, testicular cancer (TC) is the most commonly diagnosed malignancy in men 20 to 40 years of age.[1-3] TC accounts for 1% to 1.5% of all male cancers[1-3] with approximately 1,000 Canadians[1] and 8,000 Americans[3] diagnosed annually. The incidence of TC has risen over the past two decades[4] and is predicted to continue to rise.[5] Although several factors have been proposed as potential contributors to the increasing incidence of TC (e.g., testicular dysgenesis syndrome, increasing rates of in utero or perinatal exposure to endocrine disrupting factors, low birth weight, low gestational age, and high maternal age)[6,7] the exact causes remain poorly understood.[5,8]

The majority of TC diagnoses are germ cell tumors (90 – 95%)[9] presenting as painless unilateral masses in the scrotum.[10] Although certain serum markers can be used to inform the diagnosis and staging of TC (e.g., include α-fetoprotein, lactate dehydrogenase and human chorionic gonadotrophin), the presence or absence of these markers are not necessarily requisite markers of disease status. Rather, TC diagnoses are based on i) direct testicular examination, ii) regional examination, and iii) ultrasound-based confirmation of a testicular mass.[10]

Frontline TC therapies involve single or multi-modality regimes (i.e., surgery, radiotherapy, and chemotherapy). Surgical interventions involve the removal of one or both testicles (i.e., unilateral or bilateral orchiectomy) and, if metastases are suspected, may also involve retroperitoneal lymph node dissection. Radiotherapy is exclusively used in the treatment of seminoma (i.e., a radiotherapy sensitive subtype of TC) and, if local metastases are detected via computerized tomography scan, retroperitoneal lymph node dissection may be used to arrest or limit disease progression.[11] Chemotherapeutic treatments involve multi-agent "cocktails" of anticancer drugs used synergistically to oblate and prevent the spread of cancerous cells.

Common chemotherapy drugs used to treat TC patients include cisplatin, bleomycin, etoposide, paclitaxel, ifosfamide, and vinblastine.[12] Unfortunately, each of the described TC treatment modalities contributes to an increased risk of subclinical and overt cardiovascular disease (CVD)[13-24] as well as impaired psychosocial function and health-related quality of life (HRQoL).[25-30] Importantly, TC has the second highest cure rate of all solid tumors (5-year relative survival rate 97%)[1] and is highly curable even in the advanced disease setting.[31]

1.2 Treatment-Related Risks in Testicular Cancer Survivors

As described earlier, TC is typically diagnosed at an age (i.e., 20-40 years) and life-stage (i.e., young adulthood) that is associated with significant social-, emotional-, physical-, and cognitive-development.[30] Despite their high survival rates,[1] the treatment-related improvements in TC-specific survival rates come at a price.[32] TC survivors (TCS) are susceptible to a variety of HRQoL- and survival-compromising conditions related to their treatments including secondary cancers,[33,34] cancer-related fatigue (CRF),[26,28] anxiety,[29] infertility,[35] hypogonadism,[36] peripheral and autonomic neuropathies,[37,38] ototoxicity,[39] renal dysfunction,[11] metabolic syndrome,[21] and multiple forms of CVD.[14,20,40] Importantly, the combination of TCS' younger average age at diagnosis and high survival rates results in a prolonged period of increased susceptibility to treatment-related risks; and, together, these factors likely contribute to the increased mortality risks associated with the development of treatment-related CVD and secondary cancers in TCS, which persist beyond 15 years posttreatment.[41,42] Traditional CVD risk screening practices in oncology primarily focus on cardiac dysfunction (i.e., left-ventricular ejection fraction changes).[43] However, the available evidence suggests that left-ventricular ejection fraction lacks the sensitivity to detect early cardiac damage and fails to account for the subclinical injuries in

the periphery.[44] Accordingly, a more comprehensive approach to characterizing CVD risk in TCS should incorporate peripheral and circulating markers of subclinical cardiovascular injury/dysfunction. The following sections contain brief reviews of the treatment-related cardiovascular, psychosocial, and HRQoL deficits in TCS. Supplemental reviews of cardiovascular assessment methods and psychosocial/HRQoL assessment methods are provided in **Appendices B** and **C**, respectively. Furthermore, an expanded literature review on CVD risk screening and treatment-related CVD risks in TCS is provided in **Appendix D**.

1.2.1 Treatment-Related Risks: Cardiovascular Disease

In general, TCS demonstrate low to normal testosterone levels, with the prevalence of below normal testosterone levels in TCS ranging from 11% to 34%.[36,45,46] Provided TCS retain the normal functioning of the contralateral testicle, the serum testosterone levels in TCS treated with unilateral orchiectomy-only often remain relatively unaffected.[47] However, hypogonadism develops if the remaining testicle is unable to compensate and maintain adequate levels of testosterone production. A multicenter survey of 1235 TCS reported an elevated age-adjusted odds ratio for hypogonadism of 3.8 (95% CI, 2.0-7.3) compared to controls, which increased with treatment intensity and was highest in patients who had received cumulative doses of cisplatin >850 mg (*odds ratio*: 7.9; 95% CI, 3.6-17.4).[48] Hypogonadism-related risks may include CVD, metabolic syndrome, osteoporosis, type II diabetes, premature aging and decreased HRQoL.[49]

Patients with disseminated seminoma-based disease often receive external-beam radiotherapy and have been identified as being at a particularly high-risk of CVD. Individuals receiving radiotherapy, alone or in combination with chemotherapy and especially with mediastinal involvement, are reported to have an approximately doubled CVD risk, owing to

direct radiotherapy-related injury to coronary vasculature and microvasculature.[50-53] Although mediastinal radiotherapy is no longer common in TC treatment, elevated CVD risk has also been identified in patients treated with infradiaphragmatic radiotherapy[11] such as increased risks for peripheral vascular disease (i.e., vascular stenosis, thromboembolism and accelerated or premature atherosclerosis)[54] and renal dysfunction.[55-57] In addition to the localized conduit vessel damage within the involved field of radiation, abdominal irradiation, involving one or both kidneys, has been shown to cause nephropathy-related hypertension[55-57] through what is believed to be a reno-vascular effect involving the renin-angiotensin system.[55,56,58]

Of the six chemotherapeutic agents listed previously, bleomycin and cisplatin are known to cause a variety of acute and long-term cardiovascular complications in TCS. Bleomycin belongs to a family of anticancer drugs called "antitumor antibiotics." Although the exact mechanisms of action for this drug are partially unknown, bleomycin induces apoptosis by causing DNA strand breaks through targeted DNA binding and free radical production.[59,60] Bleomycin, like other cytoskeletal-disrupting agents, has anti-angiogenic effects (decreases endothelial growth and induces apoptosis).[61] Bleomycin, either alone or in combination with cisplatin, etoposide or vinca alkaloids, may cause pulmonary fibrosis,[62] and is associated with myocardial ischemia and infarction, Raynaud's phenomenon and thromboembolic events.[15,63,64] Notably, Raynaud's phenomenon often involves, and reflects, endothelial dysfunction and has been reported in approximately one third of patients treated with bleomycin.[65,66] Cisplatin is a platinum compound belonging to a family of anticancer drugs called alkylating agents.[67] Through DNA binding, cisplatin's antitumor effect involves the disruption of cellular transcription and replication mechanisms.[68] Although the introduction of cisplatin-based therapy in the 1970's led to a dramatic increase in TC survival,[31,69] reactive forms of the agent remain detectable in the plasma beyond 20 years posttreatment.[70-72] Cisplatin is thought to contribute to late-onset

occlusive vascular disease by triggering a degenerative process in vessel walls (medium-thickness);[18] and, it is biologically plausible that ongoing platinum-induced vascular damage extends well into survivorship by promoting endothelial injury and atherosclerotic plaque development – representing the greatest treatment-related contributor to the elevated CVD risk in TCS.[18,70,72]

Overall, the available evidence suggests that TCS have significantly elevated risks of treatment-induced subclinical vascular (e.g., endothelial dysfunction, arterial stiffness and chronic inflammation)[17,20] and parasympathetic nervous system (e.g., decreased respiratory sinus arrhythmia)[73] dysfunction and overt CVD (e.g., coronary artery disease and metabolic syndrome)[15,48] (***please see full review in*** **Appendix D**). Importantly, this premature development of CVD limits the overall survival of TCS and poses a serious threat to their HRQoL.

1.2.2 Treatment-Related Risks: Psychosocial and HRQoL Impairments

TCS are also susceptible to a number of psychosocial- and HRQoL-related impairments including poor mental HRQoL, anxiety, cognitive impairments, stress, and, to a lesser extent, depression[25,27-30,74-76] which are often related to other commonly-reported physical and psychosocial deficits like CRF[27,28] or a fear of recurrence.[77,78]

Compared to healthy controls, early observational studies reported little-to-no HRQoL impairment in TCS regardless of treatment exposure.[79-81] More recently, however, cross-sectional and prospective studies have identified both short-term[76] and long-term mild-to-moderate[30,75] HRQoL deficits. Smith et al.[30] found that, compared to the general population, TCS had poorer HRQoL in all domains except physical functioning. Moreover, compared to the smaller and clinically insignificant impairments observed in the more *physical* aspects of HRQoL, Smith et

al. found that the magnitude of impairment in the *mental* aspects of HRQoL in TCS were more than double the minimal clinically important difference thresholds.[30] Given TCS's generally good prognosis, the lack of HRQoL impairment reported in early cross-sectional research may be partially explained by TCS having undergone a state response shift,[82-84] wherein survivors regain a mainly positive outlook in the years after being cured of a life-threatening disease. In fact, evidence suggests that TCS rate their health as good, or better, than healthy controls despite living with an increased number of adverse health conditions.[85]

Increased anxiety,[25,29,30] stress,[30] and depressive[27,30] symptoms have also been reported in TCS. Dahl et al.[29] compared anxiety and depression levels of 1,408 TCS (mean 44.6 years of age) to data from 23,837 individuals in the general population (mean 43.8 years of age) and found an increased severity (4.6 vs. 4.1; $p<0.001$), prevalence (19.2% vs. 13.5%; $p<0.001$), and relative risk for anxiety (1.49; 95% CI, 1.31 to 1.69; $p<0.05$) but not depression. These findings are somewhat in contrast to a more recent TCS study (n=244) wherein approximately 50% of participants were at least 2 years posttreatment and the majority (77%) treated with orchidectomy plus some form of adjuvant therapy.[30] Compared to Dahl et al., the authors reported similarly-increased anxiety symptom severity (50.73 vs. 48.3; $p=0.007$) and prevalence (19% vs. 13%; $p<0.007$) but further reported an increase in depressive symptom severity (51.1 vs. 48.6; $p=0.003$) and prevalence (20% vs. 13%; $p=0.001$) as well as an increased prevalence of stress (17% vs. 13%; $p<0.001$).[30]

Finally, CRF is one of the most highly distressing and frequently reported symptoms in TCS.[26] According to the National Comprehensive Cancer Network, CRF is defined as "a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning".[86] CRF is more prevalent in TCS than fatigue is in the general population (17-30% vs. 9.7-12.2%, respectively) and the prevalence is reported to increase approximately 2-fold

from 12-19 years posttreatment, independent of treatment exposure.[27,28] A comparison of 1,431 TCS to 1,080 age-matched healthy controls found that TCS with CRF had significantly greater levels of anxiety and depression, and that CRF was associated with poor HRQoL.[27] Considering the life-stage and treatment-related risks described herein, the CRF experienced by TCS is complex and likely results from a combination of both physical and psychosocial factors. One study identified low-grade inflammation as a potential contributor to the pathogenesis of CRF in TCS.[87] Whereas other studies have demonstrated a high degree of association between CRF and hypogonadism, neuropathy, poor HRQoL, psychological distress, anxiety, depression, and cognitive problems.[25,27,28,88,89]

1.2.3 Summary: Testicular Cancer and Related Risks

Compared to most other cancer populations, TCS are diagnosed at a younger age and have low cancer-specific mortality. However, as described herein, TCS are at increased risk of direct and indirect treatment-related cardiovascular, psychosocial, and HRQoL deficits. Taken together, these treatment-related risks have more time to manifest and pose a serious threat to their overall survival[41,42] and quality of life.[28,30] Given the pleiotropic nature of their treatment-related deficits, intervention strategies capable of simultaneously augmenting a wide range of outcomes are needed. Aerobic exercise training may be one of the few candidate therapies available to TCS that is capable of concurrently treating multiple interrelated pathways of cardiovascular, psychosocial, and HRQoL dysfunction.

1.3 Exercise Benefits in Healthy and Other Clinical Populations

The capacity of aerobic exercise training to prevent and control the normal age-related development of pro-atherosclerotic, -thrombotic, -arrhythmic and -inflammatory disease states/conditions is firmly established.[90-93] In fact, 50% of established modifiable CVD risk factors (i.e., hypertension, high cholesterol, obesity, and diabetes) can be prevented or controlled with aerobic exercise training.[94] Moreover, aerobic exercise training has also demonstrated psychosocial, HRQoL, and cognitive benefits across a broad range of healthy and clinical populations[95] including healthy adolescents[96] and aging adults,[97] individuals with mood disorders (e.g., anxiety and depression),[98,99] and chronic health conditions often associated with TC treatments (e.g., atrial fibrillation, myocardial infarction, obesity, and heart failure).[95,100-102] The overall etiology of treatment-related risks and injuries in TCS is complex and likely involves multiple interrelated physical and psychosocial factors. To efficiently and effectively manage these risks, intervention strategies capable of simultaneously influencing multiple pathways of physical and psychosocial dysfunction are needed. With well-documented multi-system benefits, aerobic exercise training is a strong candidate-therapy to prevent or control treatment-related cardiovascular, psychosocial, and HRQoL impairments in TCS. The following sections provide a brief review of the effects of aerobic exercise training in oncology and TCS.

1.4 Exercise Benefits and Testicular Cancer Survivorship

1.4.1 Exercise Benefits: Cardiovascular

To date, only two studies have examined the relationships between of physical activity or exercise training and physical health outcomes in TCS. In a cross-sectional survey of 952 TCS

treated with cisplatin, Fung et al.[85] reported that only vigorous physical activity was associated with increased protection from adverse health outcomes (e.g., coronary artery disease, hypertension, peripheral vascular disease, diabetes, obesity, peripheral neuropathies, and psychosocial deficits). In a series of publications from the only randomized trial to date, Christensen and colleagues reported the effects of 9 weeks of resistance exercise training on muscle function[103] and inflammatory markers[104] in 30 TC patients actively receiving chemotherapy. Compared to healthy controls, the authors reported that resistance exercise training was ineffective at controlling the treatment-related declines in muscle function[103] and normalizing plasma levels of inflammatory cytokines.[104] Unfortunately, no studies have directly assessed the impact of aerobic exercise training on cardiovascular health outcomes in TCS.

Despite the lack of evidence in TCS, meta-analyses and systematic reviews from other cancer patient and survivor groups (reviewed elsewhere[105]) provide considerable evidence supporting the effects of aerobic exercise training on adverse cardiovascular health outcomes also experienced by TCS (e.g., poor aerobic fitness, blood-lipid profiles, body composition, glucose metabolism, and inflammatory profiles). Moreover, interventions in hematological, colorectal, and breast cancer patients/survivors provide preliminary evidence that aerobic exercise training can effect further pathways of CVD risk in TCS including endothelial function and vascular structure,[106] oxidative stress,[107] and in the prevention of treatment-related cardiac dysfunction.[108] Recently, drawing from the available evidence in other cancer survivors groups, aerobic exercise training was proposed as a possible countermeasure for late-onset treatment-related CVD in TCS.[32] Notably, the study of aerobic exercise training effects on CVD outcomes in survivors of early stage breast cancer may offer important insight into the potential benefits in TCS. More specifically, TCS and early-stage breast cancer survivors share several unique traits (i.e., comparatively younger age at diagnosis, high survival rates, and high-risk of treatment-related

CVD) which makes the largely positive findings of aerobic exercise trials on cardiovascular outcomes in breast cancer survivors more relevant. In fact, several recent reviews of exercise in early stage breast cancer have highlighted exercise-related improvements in multiple pathways of CVD risk common to both breast cancer survivors and TCS including hormone deprivation, hypertension, metabolic dysregulation, autonomic dysfunction, inflammation, and oxidative stress.[109,110] Overall, this evidence provides an intriguing biological signal suggesting that aerobic exercise training may similarly improve CVD risks and outcomes in TCS. Please see **Appendix E** for an expansion of this review on the role of aerobic exercise training in TC survivorship which includes details of aerobic exercise training-related benefits for cardiorespiratory, vascular, and parasympathetic nervous system health in general, clinical, and cancer survivor populations.

1.4.2 Exercise Benefits: Psychosocial & HRQoL

Literature describing the relationships between regular physical activity or exercise training and psychosocial and HRQoL outcomes in TCS is similarly scant. In the first study of physical activity in TCS, Thorsen et al.[111] compared the associations between self-report physical activity and the prevalence of psychosocial disorders (i.e., depression and anxiety) in TCS and the general population. This cross-sectional comparison included data from 1,260 TCS and 20,207 individuals in the general population. Overall, the prevalence of depression was lower in physically active members in both groups compared to those who were inactive (TCS: 9% vs. 17%, $p<0.001$; general population: 8% vs 15%, $p<0.001$, respectively). Similar associations were observed for anxiety in both groups, but they failed to reach significance in TCS ($p=0.07$). More recently, Sprauten et al.[28] reported an inverse association between increasing amounts of physical activity and the prevalence of CRF in TCS [i.e., moderately physically active (odds ratio=0.47;

95% CI, 0.25 to 0.87; p=0.02) vs. highly physically active (odds ratio=0.31; 95% CI, 0.17 to 0.60; p≤0.001)]. In the same RCT cited previously, Christensen et al.[104] reported that 9 weeks of resistance exercise training had no effect on mitigating treatment-related declines in global quality of life, physical functioning, social functioning, and fatigue. Although this preliminary evidence suggests a positive association between physical activity and PROs, the effects of aerobic exercise on psychosocial function and HRQoL in TCS have yet to be confirmed.

Again, despite the lack of evidence in TCS, substantial evidence supporting the beneficial effects of aerobic exercise on psychosocial function (e.g., CRF and depression)[112-115] and HRQoL[116,117] does exist in other cancer survivor groups. Tian et al.[113] reviewed the effects of exercise on CRF. Data from 26 randomized controlled trials (RCTs) involving 2,830 cancer patients and survivors was included in the meta-analysis. Overall, exercise had a small-to-moderate effect on CRF (standardized mean difference=-0.22; 95% CI, -0.39 to -0.04; p=0.01). In a more recent meta-analysis, Mustian et al.[112] compared the respective benefits of pharmaceutical, psychological, and exercise-based interventions on CRF. The review included data from 113 unique studies involving 11,525 cancer patients and survivors and reported that exercise interventions caused the significant improvements in CRF (weighted effect size=0.30; 95% CI, 0.25 to 0.36; p<0.001) whereas pharmaceutical interventions had no effect. Craft et al.[115] conducted a systematic review and meta-analysis on the effects of exercise on depressive symptoms in cancer survivors. Reporting data on 1,287 cancer survivors, the overall effects for the 15 RCTs included in the review were such that exercise caused modest improvements in depressive symptoms (effect size=-0.22; 95% CI, -0.43 to -0.09; p=0.04). Mishra et al.[117] assessed the impact of 12-week exercise programs on HRQoL in cancer survivors. Their review included data on 3,694 participants from 30 aerobic exercise and 10 mixed exercise (e.g., resistance exercise or yoga) RCTs and non-randomized controlled trials. Overall, exercise was

associated with significant improvements in overall HRQoL, emotional well-being, social functioning, anxiety and fatigue. Notable consistencies across all the analyses were that supervised exercise sessions of moderate to longer durations (i.e., 30-50 minutes) performed at least 3 days a week for longer than 8 weeks elicited the greatest improvements in the outcomes of interest; and, many trials did not list CRF, psychosocial function, or HRQoL as their primary outcome.

1.4.3 Summary: Testicular Cancer and Aerobic Exercise

Although the cardiovascular, psychosocial, and HRQoL benefits of aerobic exercise have been well documented in other cancer survivor groups, very few studies have described the relationships between physical activity or exercise on any outcomes in TC patients or survivors. Importantly, the combination of biomedical (e.g., hypogonadism or chemotherapy exposure) and psychological (e.g., younger age/vulnerable life-stage at diagnosis or reduced feelings of masculinity) traits associated with TC diagnoses and treatments are unique; and, therefore, it is inappropriate to assume the generalized findings from exercise research in other cancer survivor groups can be directly ascribed to TCS.[118] The majority of the current evidence base in TCS comes from cross-sectional studies assessing the associations between aerobic physical activity and adverse physical and psychosocial health outcomes,[28,85,111] and regular vigorous physical activity was associated with the greatest benefits.[85] Given their relative youth and lack of functional impairments, TCS are likely capable of engaging in vigorous exercise. In fact, TCS have been shown to be more likely to engage in regular exercise than age-matched controls.[119] However, a recent study of health behavior in TCS reported that 'competing *time-based* demands' is one of the greatest barriers to their exercise engagement.[120] Taken together, this

evidence suggests that TCS may benefit most greatly from vigorous intensity exercise which, compared to MCT, may be a highly protective and time-efficient (i.e., decreasing barriers) exercise strategy to reduce their risks of multiple, overlapping physical, psychosocial, and HRQoL deficits. Please see **Appendix F** for a supplemental literature review on additional exercise prescription considerations for TCS.

1.5 Overview of the Dissertation

The purpose of this dissertation was to evaluate the effects of a 12-week high-intensity aerobic interval training (HIIT) program on traditional and novel CVD risk factors, surrogate markers of cardiovascular and overall mortality, psychosocial function, and HRQoL in a population-based sample of TCS. This dissertation is comprised of 5 Chapters and 16 Appendices.

Chapter 1 of this dissertation provides an overview of TC and its treatments (***Subsection 1.1***), ii) treatment-related cardiovascular, psychosocial, and HRQoL risks in TCS (***Subsection 1.2***), and iii) the effects of aerobic exercise training on cardiovascular, psychosocial, and HRQoL outcomes in TCS (***Subsection 1.3***). Supplemental information and literature reviews related to the contents of each subsection have been provided in the appendices including i) TC diagnostic and prognostic information, ii) methods of cardiovascular health assessment, iii) methods of psychosocial and HRQoL health assessment, iv) CVD risk screening & treatment-related CVD risks in TCS, v) the role of aerobic exercise training in TC survivorship, and vii) exercise prescription considerations for TCS (**Appendices A-F**, respectively).

The body of the dissertation is comprised of two manuscripts based on the HIITTS trial, a phase II randomized controlled trial examining the effects of 12 weeks of HIIT exercise on CVD

risk, psychosocial function, and HRQoL in a population-based sample of 63 TCS. Manuscript 1 (**Chapters 2** & **3**) examines the impact of HIIT on traditional and novel CVD risk factors and surrogate markers of cardiovascular and overall mortality at postintervention. This manuscript is in press at *Cancer*. Manuscript 2 (**Chapter 4**) examines the impact of HIIT on CRF, psychosocial function, and HRQoL at postintervention and 3-month follow-up. This manuscript has been submitted for publication. **Chapter 5** contains a general discussion of the overall findings, directions for future research, practical implications, and conclusions for the overall dissertation.

1.6 References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics (2014): **Canadian cancer statistics 2014**, in Society CC (ed). Toronto, ON., pp 132.

2. La Vecchia C, Bosetti C, Lucchini F*, et al.* (2010): **Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975**. *Ann Oncol* 21:1323-60.

3. Siegel R, Naishadham D, Jemal A (2013): **Cancer statistics 2013**. *CA Cancer J Clin* 63:11-30.

4. Nigam M, Aschebrook-Kilfoy B, Shikanov S*, et al.* (2015): **Increasing incidence of testicular cancer in the United States and Europe between 1992 and 2009**. *World J Urol* 33:623-31.

5. Le Cornet C, Lortet-Tieulent J, Forman D*, et al.* (2014): **Testicular cancer incidence to rise by 25% by 2025 in Europe? Model-based predictions in 40 countries using population-based registry data**. *Eur J Cancer* 50:831-9.

6. McGlynn KA, Cook MB (2009): **Etiologic factors in testicular germ-cell tumors**. *Future Oncol* 5:1389-402.

7. Skakkebaek NE, Rajpert-De Meyts E, Main KM (2001): **Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects**. *Hum Reprod* 16:972-8.

8. Verhoeven RH, Karim-Kos HE, Coebergh JW*, et al.* (2014): **Markedly increased incidence and improved survival of testicular cancer in the Netherlands**. *Acta Oncol* 53:342-50.

9. Eble JN (2004): **WHO histological classification of testis tumours**, Pathology and genetics of tumours of the urinary system and male genital organs, *International Agency for Research on Cancer*, pp 359.

10. Albers P, Albrecht W, Algaba F*, et al.* (2011): **EAU guidelines on testicular cancer: 2011 update**. *Eur Urol* 60:304-19.

11. Fossa SD, Aass N, Winderen M*, et al.* (2002): **Long-term renal function after treatment for malignant germ-cell tumours**. *Ann Oncol* 13:222-8.

12. Cancer Care Ontario (2017): **Cisplatin**, Drug formulary.

13. Altena R, Hummel YM, Nuver J*, et al.* (2011): **Longitudinal changes in cardiac function after cisplatin-based chemotherapy for testicular cancer**. *Ann Oncol* 22:2286-93.

14. Haugnes HS, Wethal T, Aass N*, et al.* (2010): **Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study**. *J Clin Oncol* 28:4649-57.

15. Meinardi MT, Gietema JA, van der Graaf WT*, et al.* (2000): **Cardiovascular morbidity in long-term survivors of metastatic testicular cancer**. *J Clin Oncol* 18:1725-32.

16. Nuver J, De Haas EC, Van Zweeden M*, et al.* (2010): **Vascular damage in testicular cancer patients: a study on endothelial activation by bleomycin and cisplatin in vitro**. *Oncol Rep* 23:247-53.

17. Nuver J, Smit AJ, Sleijfer DT*, et al.* (2004): **Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer**. *Eur J Cancer* 40:701-6.

18. Soultati A, Mountzios G, Avgerinou C*, et al.* (2012): **Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications**. *Cancer Treat Rev* 38:473-83.

19. van den Belt-Dusebout AW, Nuver J, de Wit R*, et al.* (2006): **Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer**. *J Clin Oncol* 24:467-75.

20. Vaughn DJ, Palmer SC, Carver JR*, et al.* (2008): **Cardiovascular risk in long-term survivors of testicular cancer**. *Cancer* 112:1949-53.

21. Willemse PM, Burggraaf J, Hamdy NA*, et al.* (2013): **Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors**. *Br J Cancer* 109:60-7.

22. Haugnes HS, Oldenburg J, Bremnes RM (2015): **Pulmonary and cardiovascular toxicity in long-term testicular cancer survivors**, Urol Oncol Semin Ori, *Elsevier*, pp 399-406.

23. Fung C, Fossa SD, Williams A*, et al.* (2015): **Long-term morbidity of testicular cancer treatment**. *Urol Clin North Am* 42:393-408.

24. Nuver J, Smit AJ, Wolffenbuttel BH*, et al.* (2005): **The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer**. *J Clin Oncol* 23:3718-25.

25. Fossa SD, Dahl AA, Loge JH (2003): **Fatigue, anxiety, and depression in long-term survivors of testicular cancer**. *J Clin Oncol* 21:1249-54.

26. Oechsle K, Hartmann M, Mehnert A*, et al.* (2016): **Symptom burden in long-term germ cell tumor survivors**. *Support Care Cancer* 24:2243-50.

27. Orre IJ, Fossa SD, Murison R*, et al.* (2008): **Chronic cancer-related fatigue in long-term survivors of testicular cancer**. *J Psychosom Res* 64:363-71.

28. Sprauten M, Haugnes HS, Brydøy M*, et al.* (2015): **Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: increasing prevalence and risk factors**. *Ann Oncol* 26:2133-2140.

29. Dahl AA, Haaland CF, Mykletun A*, et al.* (2005): **Study of anxiety disorder and depression in long-term survivors of testicular cancer**. *J Clin Oncol* 23:2389-95.

30. Smith AB, Butow P, Olver I*, et al.* (2016): **The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study**. *J Cancer Surviv* 10:223-33.

31. Feldman DR, Bosl GJ, Sheinfeld J*, et al.* (2008): **Medical treatment of advanced testicular cancer**. *JAMA* 299:672-84.

32. Christensen JF, Bandak M, Campbell A*, et al.* (2015): **Treatment-related cardiovascular late effects and exercise training countermeasures in testicular germ cell cancer survivorship**. *Acta Oncol* 54:592-9.

33. Robinson D, Moller H, Horwich A (2007): **Mortality and incidence of second cancers following treatment for testicular cancer**. *Br J Cancer* 96:529-33.

34. Travis LB, Fossa SD, Schonfeld SJ*, et al.* (2005): **Second cancers among 40,576 testicular cancer patients: focus on long-term survivors**. *J Natl Cancer Inst* 97:1354-65.

35. Huyghe E, Matsuda T, Daudin M*, et al.* (2004): **Fertility after testicular cancer treatments: results of a large multicenter study**. *Cancer* 100:732-7.

36. Wiechno P, Demkow T, Kubiak K*, et al.* (2007): **The quality of life and hormonal disturbances in testicular cancer survivors in the cisplatin era**. *Eur Urol* 52:1448-54.

37. Boogerd W, ten Bokkel Huinink WW, Dalesio O*, et al.* (1990): **Cisplatin induced neuropathy: central, peripheral and autonomic nerve involvement**. *J Neurooncol* 9:255-63.

38. Hartmann JT, Kollmannsberger C, Kanz L*, et al.* (1999): **Platinum organ toxicity and possible prevention in patients with testicular cancer**. *Int J Cancer* 83:866-9.

39. Sprauten M, Darrah TH, Peterson DR*, et al.* (2012): **Impact of long-term serum platinum concentrations on neuro- and ototoxicity in cisplatin-treated survivors of testicular cancer**. *J Clin Oncol* 30:300-7.

40. Kero AE, Jarvela LS, Arola M*, et al.* (2014): **Cardiovascular morbidity in long-term survivors of early-onset cancer: a population-based study**. *Int J Cancer* 134:664-73.

41. Fossa SD, Gilbert E, Dores GM*, et al.* (2007): **Noncancer causes of death in survivors of testicular cancer**. *J Natl Cancer Inst* 99:533-44.

42. Zagars GK, Ballo MT, Lee AK*, et al.* (2004): **Mortality after cure of testicular seminoma**. *J Clin Oncol* 22:640-7.

43. Altena R, Perik PJ, van Veldhuisen DJ*, et al.* (2009): **Cardiovascular toxicity caused by cancer treatment: strategies for early detection**. *Lancet Oncol* 10:391-9.

44. Ewer MS, Lenihan DJ (2008): **Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground?** *J Clin Oncol* 26:1201-3.

45. Brennemann W, Stoffel-Wagner B, Helmers A*, et al.* (1997): **Gonadal function of patients treated with cisplatin based chemotherapy for germ cell cancer**. *J Urol* 158:844-50.

46. Huddart RA, Norman A, Moynihan C*, et al.* (2005): **Fertility, gonadal and sexual function in survivors of testicular cancer**. *Br J Cancer* 93:200-7.

47. Petersen PM, Skakkebæk NE, Vistisen K*, et al.* (1999): **Semen quality and reproductive hormones before orchiectomy in men with testicular cancer**. *J Clin Oncol* 17:941.

48. Nord C, Bjoro T, Ellingsen D*, et al.* (2003): **Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer**. *Eur Urol* 44:322-8.

49. Yeap BB (2009): **Testosterone and ill-health in aging men**. *Nat Clin Pract Endocrinol Metab* 5:113-121.

50. Corn BW, Trock BJ, Goodman RL (1990): **Irradiation-related ischemic heart disease**. *J Clin Oncol* 8:741-50.

51. Lederman GS, Sheldon TA, Chaffey JT*, et al.* (1987): **Cardiac disease after mediastinal irradiation for seminoma**. *Cancer* 60:772-6.

52. Mousavi N, Nohria A (2013): **Radiation-induced cardiovascular disease**. *Curr Treat Options Cardiovasc Med* 15:507-17.

53. Patterson H, Norman AR, Mitra SS*, et al.* (2001): **Combination carboplatin and radiotherapy in the management of stage II testicular seminoma: comparison with radiotherapy treatment alone**. *Radiother Oncol* 59:5-11.

54. Quarmby S, Kumar P, Kumar S (1999): **Radiation-induced normal tissue injury: role of adhesion molecules in leukocyte-endothelial cell interactions**. *Int J Cancer* 82:385-95.

55. Cassady JR (1995): **Clinical radiation nephropathy**. *Int J Radiat Oncol Biol Phys* 31:1249-56.

56. Dewit L, Anninga JK, Hoefnagel CA*, et al.* (1990): **Radiation injury in the human kidney: a prospective analysis using specific scintigraphic and biochemical endpoints**. *Int J Radiat Oncol Biol Phys* 19:977-983.

57. Kim TH, Somerville PJ, Freeman CR (1984): **Unilateral radiation nephropathy--the long-term significance**. *Int J Radiat Oncol Biol Phys* 10:2053-9.

58. Verheij M, Dewit LG, Valdes Olmos RA*, et al.* (1994): **Evidence for a renovascular component in hypertensive patients with late radiation nephropathy**. *Int J Radiat Oncol Biol Phys* 30:677-83.

59. Dorr RT (1992): **Bleomycin pharmacology: mechanism of action and resistance, and clinical pharmacokinetics**, Semin Oncol, pp 3-8.

60. Hecht SM (2000): **Bleomycin: new perspectives on the mechanism of action**. *J Nat Prod* 63:158-68.

61. Mabeta P, Pepper MS (2009): **A comparative study on the anti-angiogenic effects of DNA-damaging and cytoskeletal-disrupting agents**. *Angiogenesis* 12:81-90.

62. Adamson IY (1976): **Pulmonary toxicity of bleomycin**. *Environ Health Perspect* 16:119-26.

63. Meinardi MT, Gietema JA, van Veldhuisen DJ*, et al.* (2000): **Long-term chemotherapy-related cardiovascular morbidity**. *Cancer Treat Rev* 26:429-47.

64. Vogelzang NJ, Bosl GJ, Johnson K*, et al.* (1981): **Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer**. *Ann Intern Med* 95:288-92.

65. Berger CC, Bokemeyer C, Schneider M*, et al.* (1995): **Secondary Raynaud's phenomenon and other late vascular complications following chemotherapy for testicular cancer**. *Eur J Cancer* 31A:2229-38.

66. Toumbis-Ioannou E, Cohen PR (1994): **Chemotherapy-induced Raynaud's phenomenon**. *Cleve Clin J Med* 61:195-9.

67. Senkus E, Jassem J (2011): **Cardiovascular effects of systemic cancer treatment**. *Cancer Treat Rev* 37:300-11.

68. Fuertes MA, Castilla J, Alonso C*, et al.* (2003): **Cisplatin biochemical mechanism of action: from cytotoxicity to induction of cell death through interconnections between apoptotic and necrotic pathways**. *Curr Med Chem* 10:257-266.

69. Einhorn LH, Donohue J (1977): **Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer**. *Ann Intern Med* 87:293-8.

70. Boer H, Proost JH, Nuver J*, et al.* (2015): **Long-term exposure to circulating platinum is associated with late effects of treatment in testicular cancer survivors**. *Ann Oncol* 26:2305-10.

71. Gietema JA, Meinardi MT, Messerschmidt J*, et al.* (2000): **Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer**. *The Lancet* 355:1075-1076.

72. Hjelle LV, Gundersen PO, Oldenburg J*, et al.* (2015): **Long-term platinum retention after platinum-based chemotherapy in testicular cancer survivors: a 20-year follow-up study**. *Anticancer Res* 35:1619-25.

73. Hansen SW (1990): **Autonomic neuropathy after treatment with cisplatin, vinblastine, and bleomycin for germ cell cancer**. *BMJ* 300:511-2.

74. Dahl CF, Haugnes HS, Bremnes R*, et al.* (2010): **A controlled study of risk factors for disease and current problems in long-term testicular cancer survivors**. *J Cancer Surviv* 4:256-65.

75. Kim C, McGlynn KA, McCorkle R*, et al.* (2011): **Quality of life among testicular cancer survivors: a case-control study in the United States**. *Qual Life Res* 20:1629-37.

76. Vidrine DJ, Hoekstra-Weebers JE, Hoekstra HJ*, et al.* (2010): **The effects of testicular cancer treatment on health-related quality of life**. *Urology* 75:636-41.

77. Pedersen AF, Rossen P, Olesen F*, et al.* (2012): **Fear of recurrence and causal attributions in long-term survivors of testicular cancer**. *Psychooncology* 21:1222-8.

78. Skaali T, Fossa SD, Bremnes R*, et al.* (2009): **Fear of recurrence in long-term testicular cancer survivors**. *Psychooncology* 18:580-8.

79. Fossa SD, Dahl AA, Haaland CF (1999): **Health-related quality of life in patients treated for testicular cancer**. *Curr Opin Urol* 9:425-9.

80. Joly F, Heron JF, Kalusinski L*, et al.* (2002): **Quality of life in long-term survivors of testicular cancer: a population-based case-control study**. *J Clin Oncol* 20:73-80.

81. Rossen PB, Pedersen AF, Zachariae R*, et al.* (2009): **Health-related quality of life in long-term survivors of testicular cancer**. *J Clin Oncol* 27:5993-9.

82. Mykletun A, Dahl AA, Haaland CF*, et al.* (2005): **Side effects and cancer-related stress determine quality of life in long-term survivors of testicular cancer**. *J Clin Oncol* 23:3061-8.

83. Takamochi K, Nagai K, Yoshida J*, et al.* (2000): **The role of computed tomographic scanning in diagnosing mediastinal node involvement in non-small cell lung cancer**. *J Thorac Cardiovasc Surg* 119:1135-40.

84. van Basten JP, Jonker-Pool G, van Driel MF*, et al.* (1996): **Fantasies and facts of the testes**. *Br J Urol* 78:756-62.

85. Fung C, Sesso HD, Williams AM*, et al.* (2017): **Multi-institutional assessment of adverse health outcomes among north american testicular cancer survivors after modern cisplatin-based chemotherapy**. *J Clin Oncol* 35:1211-1222.

86. Mock V, Atkinson A, Barsevick A*, et al.* (2000): **NCCN practice guidelines for cancer-related fatigue**. *Oncology* 14:151-61.

87. Orre IJ, Murison R, Dahl AA*, et al.* (2009): **Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue**. *Brain Behav Immun* 23:868-74.

88. Haugnes HS, Bosl GJ, Boer H*, et al.* (2012): **Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up**. *J Clin Oncol* 30:3752-63.

89. Skaali T, Fossa SD, Andersson S*, et al.* (2011): **Self-reported cognitive problems in testicular cancer patients: relation to neuropsychological performance, fatigue, and psychological distress**. *J Psychosom Res* 70:403-10.

90. Billman GE (2002): **Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention**. *J Appl Physiol* 92:446-54.

91. Green DJ (2009): **Exercise training as vascular medicine: direct impacts on the vasculature in humans**. *Exerc Sport Sci Rev* 37:196-202.

92. Kadoglou NP, Moustardas P, Kapelouzou A*, et al.* (2013): **The anti-inflammatory effects of exercise training promote atherosclerotic plaque stabilization in apolipoprotein E knockout mice with diabetic atherosclerosis**. *Eur J Histochem* 57:e3.

93. Wienbergen H, Hambrecht R (2013): **Physical exercise and its effects on coronary artery disease**. *Curr Opin Pharmacol* 13:218-25.

94. Thompson PD, Buchner D, Pina IL*, et al.* (2003): **Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)**. *Circulation* 107:3109-16.

95. Penedo FJ, Dahn JR (2005): **Exercise and well-being: a review of mental and physical health benefits associated with physical activity**. *Curr Opin Psychiatry* 18:189-93.

96. Motl RW, Birnbaum AS, Kubik MY*, et al.* (2004): **Naturally occurring changes in physical activity are inversely related to depressive symptoms during early adolescence**. *Psychosom Med* 66:336-42.

97. Weuve J, Kang JH, Manson JE*, et al.* (2004): **Physical activity, including walking, and cognitive function in older women**. *JAMA* 292:1454-61.

98. Ross CE, Hayes D (1988): **Exercise and psychologic well-being in the community**. *Am J Epidemiol* 127:762-71.

99. Babyak M, Blumenthal JA, Herman S*, et al.* (2000): **Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months**. *Psychosom Med* 62:633-638.

100. Hegbom F, Stavem K, Sire S*, et al.* (2007): **Effects of short-term exercise training on symptoms and quality of life in patients with chronic atrial fibrillation**. *Int J Cardiol* 116:86-92.

101. Izawa K, Hirano Y, Yamada S*, et al.* (2004): **Improvement in physiological outcomes and health-related quality of life following cardiac rehabilitation in patients with acute myocardial infarction**. *Circ J* 68:315-20.

102. van Tol BA, Huijsmans RJ, Kroon DW*, et al.* (2006): **Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis**. *Eur J Heart Fail* 8:841-50.

103. Christensen JF, Jones LW, Tolver A*, et al.* (2014): **Safety and efficacy of resistance training in germ cell cancer patients undergoing chemotherapy: a randomized controlled trial**. *Br J Cancer* 111:8-16.

104. Christensen JF, Tolver A, Andersen JL*, et al.* (2014): **Resistance training does not protect against increases in plasma cytokine levels among germ cell cancer patients during and after chemotherapy**. *J Clin Endocrinol Metab* 99:2967-76.

105. Courneya KS, Crawford JJ, Adams SC (2015): **Physical activity and exercise interventions in cancer survivors.**, in Holland JC, Breitbart WS, Jacobsen PB, et al (eds): Psychooncology (ed 3rd). New York, , *Oxford University Press.*

106. Jarvela LS, Niinikoski H, Heinonen OJ*, et al.* (2013): **Endothelial function in long-term survivors of childhood acute lymphoblastic leukemia: effects of a home-based exercise program**. *Pediatr Blood Cancer* 60:1546-51.

107. Allgayer H, Owen RW, Nair J*, et al.* (2008): **Short-term moderate exercise programs reduce oxidative DNA damage as determined by high-performance liquid chromatography-electrospray ionization-mass spectrometry in patients with colorectal carcinoma following primary treatment**. *Scand J Gastroenterol* 43:971-8.

108. Scott JM, Khakoo A, Mackey JR*, et al.* (2011): **Modulation of Anthracycline-Induced Cardiotoxicity by Aerobic Exercise in Breast Cancer: Current Evidence and Underlying Mechanisms**. *Circulation* 124:642-650.

109. Scott JM, Koelwyn GJ, Hornsby WE*, et al.* (2013): **Exercise therapy as treatment for cardiovascular and oncologic disease after a diagnosis of early-stage cancer**. *Semin Oncol* 40:218-28.

110. Scott JM, Adams SC, Koelwyn GJ*, et al.* (2016): **Cardiovascular late effects and exercise treatment in breast cancer: current evidence and future directions**. *Can J Cardiol* 32:881-90.

111. Thorsen L, Nystad W, Stigum H*, et al.* (2005): **The association between self-reported physical activity and prevalence of depression and anxiety disorder in long-term survivors of testicular cancer and men in a general population sample**. *Support Care Cancer* 13:637-46.

112. Mustian KM, Alfano CM, Heckler C*, et al.* (2017): **Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis**. *JAMA Oncol*.

113. Tian L, Lu HJ, Lin L*, et al.* (2016): **Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials**. *Support Care Cancer* 24:969-83.

114. Brown JC, Huedo-Medina TB, Pescatello LS*, et al.* (2012): **The efficacy of exercise in reducing depressive symptoms among cancer survivors: a meta-analysis**. *PLoS One* 7:e30955.

115. Craft LL, Vaniterson EH, Helenowski IB*, et al.* (2012): **Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis**. *Cancer Epidemiol Biomarkers Prev* 21:3-19.

116. Gerritsen JK, Vincent AJ (2016): **Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials**. *Br J Sports Med* 50:796-803.

117. Mishra SI, Scherer RW, Snyder C*, et al.* (2014): **Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis**. *Oncol Nurs Forum* 41:E326-42.

118. Courneya KS (2014): **Physical activity and cancer survivorship: a simple framework for a complex field**. *Exerc Sport Sci Rev* 42:102-9.

119. Shinn EH, Swartz RJ, Thornton BB*, et al.* (2010): **Testis cancer survivors' health behaviors: comparison with age-matched relative and demographically matched population controls**. *J Clin Oncol* 28:2274-9.

120. Reilley MJ, Jacobs LA, Vaughn DJ*, et al.* (2014): **Health behaviors among testicular cancer survivors**. *J Community Support Oncol* 12:121-8.

Chapter II – Primary Manuscript

Running Head: Exercise & CVD risk in testicular cancer

Original Article (unsolicited)

Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: a phase II randomized controlled trial

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Precis: Overall survival from testicular cancer may be reduced by the development of treatment-related cardiovascular disease. We report the first phase II randomized controlled trial to demonstrate that high-intensity aerobic interval training positively influences drivers of atherosclerotic cardiovascular disease and surrogate markers of cardiovascular- and overall-mortality in testicular cancer survivors.

Key Words: testicular neoplasms; cardiovascular diseases; risk factors; atherosclerosis; biomarkers; exercise therapy; high-intensity interval training

2.1 Abstract

Background

Testicular cancer survivors (TCS) have an increased risk of treatment-related cardiovascular disease (CVD) which may limit their overall survival. We evaluated the effects of high-intensity aerobic interval training (HIIT) on traditional and novel CVD risk factors and surrogate markers of mortality in a population-based sample of TCS.

Methods

This phase II trial (Edmonton, AB; Registration #NCT02459132) randomly assigned 63 TCS to usual care (UC) or 12 weeks of supervised HIIT (i.e., alternating periods of vigorous- and light-intensity aerobic exercise). Our primary outcome was peak aerobic fitness (VO_{2peak}) assessed via a treadmill-based maximal cardiorespiratory exercise test. Secondary endpoints included CVD risk (e.g., Framingham Risk Score), arterial health, parasympathetic nervous system function, and blood-based biomarkers.

Results

Postintervention VO_{2peak} data were obtained for 61 (97%) participants. HIIT participants attended 99% of exercise sessions and achieved 98% of target exercise intensity. ANCOVA revealed HIIT was superior to UC for improving VO_{2peak} (adjusted between-group mean difference=3.7 ml O_2/kg/min; 95% confidence interval (CI) 2.4-5.1; $p<0.001$) and multiple secondary outcomes including CVD risk ($p=0.011$), arterial-thickness ($p<0.001$), arterial-stiffness ($p<0.001$), post-exercise parasympathetic reactivation ($p=0.001$), inflammation ($p=0.045$), and low-density lipoprotein ($p=0.014$). Overall, HIIT reduced the prevalence of modifiable CVD risk factors by 20% compared to UC.

Conclusions

This randomized trial provides the first evidence that HIIT improves cardiorespiratory fitness, multiple pathways of CVD risk, and surrogate markers of mortality in TCS. These findings have important implications for the management of TCS. Further research on the long-term effects of HIIT on CVD morbidity and mortality in TCS is warranted.

2.2 Introduction

Testicular cancer (TC) is the most commonly diagnosed malignancy in men aged 15-35 years[1] and the incidence has been rising for more than two decades.[2] Although germ-cell disease is highly curable (5-year relative survival rates approaching 97%),[3] each of the conventional therapies used to treat TC contribute to an increased risk of subclinical and overt cardiovascular disease (CVD) in TC survivors (TCS).[4] As reviewed elsewhere,[4] orchiectomy-related subclinical/overt hypogonadism, chemotherapy-related vascular injury (extending beyond two decades posttreatment[5]), and metabolic disturbances (associated with all TC treatment modalities) all likely contribute to increased CVD risk in TCS.[4] Together, if untreated, these long-term disturbances present a chronic stimulus for atherosclerotic disease development[4,6] and may impact the overall survival of TCS. Strategies to mitigate the effects of these therapies on CVD risk in TCS are urgently needed.

Aerobic exercise training improves CVD risk factors and surrogate markers of mortality in numerous populations,[7,8] including some cancer survivor groups,[9,10] and has been proposed as a potential countermeasure to mitigate CVD risks in TCS.[4] The mechanisms underlying increased CVD risk, however, are fundamentally different in TCS (i.e., treatment-related vs. lifestyle-related factors), making it difficult to extrapolate the same degree of benefit from other populations to TCS. Moreover, compared to other modalities of aerobic exercise, high-intensity aerobic interval training (HIIT) involves alternating periods of vigorous- and light-intensity work and has been shown to elicit the greatest magnitudes of improvement across traditional and novel CVD risk factors.[8] Chief among these effects is an improvement in aerobic fitness (VO_{2peak}) which is among the most robust surrogate markers of human health, longevity, and CVD risk.[7,11]

Given the multiple competing drivers of CVD risk (e.g., vascular injury, metabolic syndrome, hypogonadism), VO_{2peak} may be the best single measure of global cardiovascular health in TCS.

Recent observational evidence in cisplatin-treated TCS[12] suggests that vigorous physical activity is protective against adverse health outcomes including CVD; however, no randomized evidence exists demonstrating the causal effects of aerobic exercise training on reducing CVD risks in TCS. The purpose of the High-Intensity Interval Training in Testicular cancer Survivors (HIITTS) trial was to evaluate the impact of HIIT on the established pathways of treatment-related CVD risk in TCS. We hypothesized that 12 weeks of HIIT would be superior to usual care (UC) for improving VO_{2peak}. We also hypothesized that, compared to UC, HIIT would elicit significant improvements in novel CVD risk factors and markers of atherogenesis including arterial wall thickness, central and peripheral arterial stiffness, parasympathetic nervous system function, and blood-based markers of inflammation and endothelial health.

2.3 Methods

Full details of the HIITTS trial methods are provided in an online supplement.

Participants

Participants were recruited via mail (using the Alberta Cancer Registry) and from the surveillance clinic at the Cross Cancer Institute (Edmonton, AB). Men 18-80 years of age with a confirmed history of TC and no evidence of pre-cancer CVD were eligible. Men were excluded if they were unable to complete the first two stages of the exercise test, had any psychiatric condition impairing their ability to perform the exercise, had any uncontrolled cardiovascular condition, or already performed regular vigorous aerobic exercise. The HIITTS trial received

ethical approval from the Health Research Ethics Board of Alberta – Cancer Committee (Trial ID# 14-0183) and the University of Alberta (Clinical Trial Registration #NCT02459132).

Study design and Randomization

The HIITTS trial was a prospective two-armed, phase II, randomized controlled trial. Consenting participants were stratified by age (<50 vs. ≥50 years) and treatment exposure (surgery-only vs. radiotherapy/chemotherapy/both) and randomized to HIIT or UC using a 1:1 ratio and a variable 4-6 permuted block design. The allocation sequence was produced via computer-generated random numbers and concealed from staff involved in recruitment and baseline testing.

Exercise Training and Usual Care Conditions

Participants randomly assigned to HIIT were asked to attend thrice-weekly supervised exercise sessions consisting of uphill treadmill walking/running and to maintain other low-to-moderate intensity exercise they were performing at baseline. HIIT sessions began with a 5-minute warm-up (performed at +/-5% of ventilatory threshold calculated from a maximal exercise test), transitioned to the work-period, and ended with a 5-minute cool-down (total of 35 minutes). During the work-period, participants completed four, 4-minute, high-intensity intervals, which progressed from 75-95% of VO_{2peak} over the intervention period. High-intensity intervals were separated by 3-minute active-recovery intervals (performed 5-10% below ventilatory threshold). Exercise intensity was monitored using heart rate (HR) monitors, and programs were augmented to maintain target HRs. Participants randomly assigned to the UC group were asked not to initiate HIIT and to maintain their baseline exercise levels. Using a wait-list control design, UC participants were offered a 6-week supervised HIIT program after the 12-week observation period and 3-month follow-up assessment.

Assessment Protocol

Within the 48-hour period prior to testing, participants had their blood drawn in a fasted-state (≥12 hours) after avoiding exercise (≥8 hours), vasoactive medications (≥5 half-lives), and the consumption of caffeine, vitamin C, alcohol and tobacco (≥8 hours).[13] On test days, participants arrived in the same fasted-state. Participants first completed the resting portion of the testing protocol (≈2 hours), were fed while they completed their baseline questionnaire (≈45 minutes), and finished with a maximal exercise test (≈1 hour).

Assessment of Primary and Secondary Endpoints

Exercise Assessments

Our primary outcome, aerobic fitness (relative VO_{2peak}), was assessed via a treadmill-based maximal cardiorespiratory exercise test (Woodway - 4Front, Waukesha, WI) with a constant individualized belt speed and an incline increasing by 2% every two minutes until exhaustion. During the test, oxygen uptake (ParvoMedics - TrueOne 2400, Murray, UT) and HR (12-lead ECG; Nasiff - CardioCard, Central Square, NY) were measured continuously. VO_{2peak} was defined as the highest oxygen-uptake value recorded during the test. Data are presented as relative (primary outcome) and absolute VO_{2peak}. Ventilatory threshold was used to prescribe exercise intensities. HR was measured for an additional 6 minutes of recovery (1st minute standing plus 5 minutes of active recovery). One-minute HR recovery (HRR; an index of post-exercise parasympathetic reactivation[14]) was calculated as the HR-difference between peak exercise and following one minute of quiet treadmill-standing immediately post-test.

Resting Hemodynamic, Vascular, and Nervous System Assessments

Participants were tested under the same conditions (e.g., ≥12-hour fast) as when their blood specimen was collected.[13] Participants began resting in a quiet, darkened room for 30 minutes. During the rest period, carotid plaque burden was assessed via bilateral ultrasound scans

of the near and far walls of the common carotid, carotid bifurcation, and internal carotid arteries, per the Mannheim Consensus Guidelines.[15] Immediately following the rest-period, bilateral carotid artery intima-media thickness (i.e., arterial wall thickness) was measured via ultrasound.[15] Carotid distensibility, an index of local arterial stiffness, was calculated as the average difference between maximum (systolic) and minimum (diastolic) arterial cross-sectional areas (assessed via ultrasound), normalized to brachial pulse pressure.[16] Left brachial artery structure, endothelial function, and microvascular function were assessed via flow-mediated dilation (FMD), per best practice guidelines.[13] FMD was calculated as the percent increase in arterial diameter from baseline to peak[13] and was then normalized for the total shear rate stimulus.[13,17] Two markers of microvascular function, and independent predictors of CVD risk (i.e., velocity time integral (VTI) and shear stress during reactive hyperemia),[18] were calculated using blood velocity data collected during the FMD protocol. Respiratory sinus arrhythmia (RSA; an index of parasympathetic function) was assessed by measuring the magnitude of heart-period variability during a paced deep breathing challenge.[19] Central arterial stiffness (i.e., carotid-femoral pulse wave velocity (PWV)) and peripheral arterial stiffness (i.e., femoral-toe PWV) were assessed via applanation tonometry (Millar Instruments SPT-301, Houston, TX), per best practice guidelines.[20] Using the foot-to-foot method,[20] the velocity of each pulse wave was calculated as the time difference between the arrival of the blood pressure waveform at each site of the central and peripheral arterial segments.

Blood-based Biomarker Assessments

Blood specimen collection took place at various DynaLife laboratories between Edmonton and Red Deer (AB). Each specimen was immediately stored, shipped, and analyzed at a central processing facility. Anonymized results were emailed directly to the study coordinator within 48 hours of collection and interpreted per national standards.[21]

Cardiovascular Disease Risk Assessments

Framingham 10-year CVD risk score (FRS) and vascular age were used to estimate CVD risk and were calculated using the general cardiovascular risk profile criteria for the Framingham Heart Study.[22] The modifiable CVD risk factor score (MRFS) was used as an index of total CVD risk and incorporated 24 novel and traditional surrogate markers of cardiovascular morbidity and mortality risk.

Statistical Analyses and Sample Size Calculation

Data cleaning, processing, and analyses were either conducted or verified by a research assistant blinded to group allocation. With 33 participants per group (total N=66), and using an ANCOVA to adjust for baseline values and relevant covariates, we had 80% power to detect a 3.5 ml O_2/kg/min between-group difference in VO_{2peak} based on a standard deviation of 5.8 ml O_2/kg/min. We report unadjusted baseline data and adjusted post-intervention data, mean between-group difference, 95% confidence interval (CI) and p-value for all hypothesized comparisons. Data were analyzed using an intention-to-treat approach (SPSS version 24). No missing data strategy was employed given the minimal amount of missing data.

2.4 Results

Participant Flow

Participants were recruited from June 2015 to March 2016. Of the 948 potentially eligible participants contacted, 108 (11%) were screened for eligibility, and 63 (7%) were randomized (see **Figure 1** for full details). We obtained postintervention VO_{2peak} data on 61 (97%) participants.

Baseline Characteristics and Participant Adherence

Participant demographic, medical, and behavioural profiles are described in **Table 1**. The groups were balanced on baseline descriptive variables. Exercise adherence data are described in **Table 2**. Participants completed 99% of all exercise sessions and achieved 98% and 103% of their target HRs during the work and active recovery periods, respectively. No exercise-related adverse events were reported or observed. No changes in self-directed exercise from baseline were reported in either group.

Primary and Secondary Endpoints

Table 3 reports the changes in exercise capacity and resting measures of cardiovascular function. VO_{2peak} increased by 0.6 ml O_2/kg/min in the UC group compared to 4.2 ml O_2/kg/min in the HIIT group (adjusted between-group mean difference=3.7 ml O_2/kg/min; 95% CI 2.4-5.1; $p<0.001$). Compared to UC, HIIT increased absolute VO_{2peak} ($p<0.001$), HRR ($p=0.001$), and RSA ($p=0.033$), and decreased resting HR ($p=0.012$) and diastolic blood pressure ($p=0.013$).

Table 4 reports the changes in vascular structure and function. Compared to UC, HIIT significantly reduced carotid intima-media thickness (average, $p<0.001$; maximum, $p<0.001$), increased carotid distensibility ($p=0.049$), decreased arterial stiffness (carotid-femoral PWV, $p<0.001$; femoral-toe PWV, $p=0.001$), increased brachial artery diameter ($p=0.009$), and improved microvascular reactivity (VTI; $p=0.039$). **Table 5** reports the changes in blood-based biomarkers. HIIT significantly decreased high-sensitivity C-reactive protein ($p=0.045$) and low-density lipoprotein ($p=0.014$) compared to UC. **Table 6** reports the changes in CVD risk. HIIT caused a significant reduction in the FRS ($p=0.011$), vascular age ($p=0.011$), and the MRFS ($p=0.002$).

2.5 Discussion

To our knowledge, HIITTS is the first randomized trial to demonstrate significant and potentially clinically meaningful improvements in CVD risk factors and surrogate markers of mortality in TCS. As hypothesized, HIIT significantly improved VO_{2peak} by 3.7 ml/kg/min compared to UC. This magnitude of improvement is greater than that typically reported in exercise oncology trials that have tested mostly moderate intensity continuous exercise protocols.[23] Moreover, this magnitude of improvement is likely clinically significant as each 3.5 ml O_2/kg/min improvement in VO_{2peak} is associated with a 10-25% relative risk reduction in overall mortality.[24] Furthermore, in healthy men, VO_{2peak} declines an average of 10% per decade.[25] The relative HIIT-related VO_{2peak} improvement achieved in our trial of approximately 10%, therefore, represents the reversal of nearly a decade-worth of cardiorespiratory aging.

HIIT also caused significant and pathophysiologically-relevant improvements in multiple CVD risk factors accounting for a 20% reduction from baseline in the MRFS. Specifically, HIIT caused concurrent improvements in pathways of atherosclerotic CVD development including arterial stiffness, arterial thickness, microvascular reactivity, parasympathetic function, inflammation, and dyslipidemia. Notably, the consistent HIIT-related improvement across indices of parasympathetic tone/reactivity[14] may have important pathophysiological implications as decreased parasympathetic activity predisposes affected individuals to exaggerated pro-inflammatory responses and endothelial dysfunction (two principle drivers of atherogenesis).[26,27] Not only are markers of parasympathetic function strong predictors of mortality,[14,27] preliminary evidence indicates a survival advantage for those who improved markers of parasympathetic function with 12 weeks of aerobic exercise-based cardiac rehabilitation.[28]

Overall, the pattern of HIIT-related benefit was consistent with most of the major mechanisms of increased CVD morbidity and mortality risks in TCS.[4] Importantly, comparable

improvements in these outcomes within other clinical populations are associated with relative risk reductions of 10-30% for CVD-related and overall mortality.[24,28,29] Although HIIT did not improve all CVD risk factors [e.g., FMD: potentially owing to arterial remodelling or follow-up assessment timing (training adaptations may peak at 3-4 weeks)[30]], our findings provide strong preliminary support that HIIT may mitigate cancer-related cardiovascular morbidity and mortality in TCS.

The HIITTS trial has several notable strengths and limitations. HIITTS is the first randomized aerobic exercise trial in TCS and provides the most comprehensive cardiovascular risk assessment in exercise oncology research to date. The near-perfect participant adherence rates and absence of adverse events suggest that HIIT is safe and feasible for TCS. Despite the self-selection sampling bias inherent to exercise research, our unselected population-based sampling approach (i.e., inclusion of participants with varied treatment exposures) may portend even larger effects in more targeted high-CVD-risk subgroups of TCS. Moreover, the inclusion of traditional and novel CVD risk factors facilitated a more comprehensive characterization of CVD risk in TCS and helps justify expanding CVD risk screening parameters in TCS. Limitations of HIITTS included the lack of postintervention outcome assessor blinding, the 11% response rate, the short follow-up period, variable time since diagnosis, and the use of surrogate markers instead of clinical cardiovascular events/mortality rates.

In summary, the HIITTS trial provides robust phase II evidence that 12 weeks of HIIT causes significant improvements in important CVD risk factors and surrogate markers of mortality in TCS. That HIIT caused concurrent improvements across multiple pathways of CVD risk suggests that it may be an effective therapeutic intervention for mitigating long-term CVD risks in TCS and has important implications for the management of TCS. Further investigation of

the potential for long-term HIIT to reduce cardiovascular morbidity and mortality in TCS is warranted.

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2.6 References

1. Curado M-P, Edwards B, Shin HR*, et al.* (2007): **Cancer incidence in five continents**, *International Agency for Research on Cancer*, pp. 896.

2. Le Cornet C, Lortet-Tieulent J, Forman D*, et al.* (2014): **Testicular cancer incidence to rise by 25% by 2025 in Europe? Model-based predictions in 40 countries using population-based registry data**. *Eur J Cancer* 50:831-9.

3. Canadian Cancer Society's Advisory Committee on Cancer Statistics (2014): **Canadian cancer statistics 2014**, in Society CC (ed). Toronto, ON., pp 132.

4. Christensen JF, Bandak M, Campbell A*, et al.* (2015): **Treatment-related cardiovascular late effects and exercise training countermeasures in testicular germ cell cancer survivorship**. *Acta Oncol* 54:592-9.

5. Hjelle LV, Gundersen PO, Oldenburg J*, et al.* (2015): **Long-term platinum retention after platinum-based chemotherapy in testicular cancer survivors: a 20-year follow-up study**. *Anticancer Res* 35:1619-25.

6. Haugnes HS, Wethal T, Aass N*, et al.* (2010): **Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study**. *J Clin Oncol* 28:4649-57.

7. Thompson PD, Buchner D, Pina IL*, et al.* (2003): **Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)**. *Circulation* 107:3109-16.

8. Weston KS, Wisloff U, Coombes JS (2014): **High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis**. *Br J Sports Med* 48:1227-34.

9. Scott JM, Adams SC, Koelwyn GJ*, et al.* (2016): **Cardiovascular late effects and exercise treatment in breast cancer: current evidence and future directions**. *Can J Cardiol* 32:881-90.

10. Scott JM, Koelwyn GJ, Hornsby WE*, et al.* (2013): **Exercise therapy as treatment for cardiovascular and oncologic disease after a diagnosis of early-stage cancer**. *Semin Oncol* 40:218-28.

11. Myers J, Prakash M, Froelicher V*, et al.* (2002): **Exercise capacity and mortality among men referred for exercise testing**. *N Engl J Med* 346:793-801.

12. Fung C, Sesso HD, Williams AM*, et al.* (2017): **Multi-institutional assessment of adverse health outcomes among north american testicular cancer survivors after modern cisplatin-based chemotherapy**. *J Clin Oncol* 35:1211-1222.

13. Thijssen DH, Black MA, Pyke KE*, et al.* (2011): **Assessment of flow-mediated dilation in humans: a methodological and physiological guideline**. *Am J Physiol Heart Circ Physiol* 300:H2-12.

14. Pecanha T, Silva-Junior ND, Forjaz CL (2014): **Heart rate recovery: autonomic determinants, methods of assessment and association with mortality and cardiovascular diseases**. *Clin Physiol Funct Imaging* 34:327-39.

15. Touboul PJ, Hennerici MG, Meairs S*, et al.* (2012): **Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and**

20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis* 34:290-6.

16. Engelen L, Bossuyt J, Ferreira I*, et al.* (2015): **Reference values for local arterial stiffness. Part A: carotid artery**. *J Hypertens* 33:1981-96.

17. Pyke KE, Tschakovsky ME (2007): **Peak vs. total reactive hyperemia: which determines the magnitude of flow-mediated dilation?** *J Appl Physiol* 102:1510-1519.

18. Anderson TJ, Charbonneau F, Title LM*, et al.* (2011): **Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study**. *Circulation* 123:163-9.

19. Freeman RL (2008): **Noninvasive evaluation of heart rate: time and frequency domains.**, in Low PA, Benarroch EE (eds): Clinical Autonomic Disorders. (ed 3rd). Philadelphia, *Lippincott Williams & Wilkins*, pp 185-197.

20. Van Bortel LM, Laurent S, Boutouyrie P*, et al.* (2012): **Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity**. *J Hypertens* 30:445-448.

21. Genest J, McPherson R, Frohlich J*, et al.* (2009): **2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations**. *Can J Cardiol* 25:567-79.

22. D'Agostino RB, Sr., Vasan RS, Pencina MJ*, et al.* (2008): **General cardiovascular risk profile for use in primary care: the Framingham Heart Study**. *Circulation* 117:743-53.

23. Jones LW, Liang Y, Pituskin EN*, et al.* (2011): **Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis**. *Oncologist* 16:112-20.

24. Kaminsky LA, Arena R, Beckie TM*, et al.* (2013): **The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association**. *Circulation* 127:652-62.

25. Hawkins S, Wiswell R (2003): **Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training**. *Sports Med* 33:877-88.

26. Libby P (2012): **Inflammation in atherosclerosis**. *Arterioscler Thromb Vasc Biol* 32:2045-51.

27. Thayer JF, Lane RD (2007): **The role of vagal function in the risk for cardiovascular disease and mortality**. *Biol Psychol* 74:224-42.

28. Hodis HN, Mack WJ, LaBree L*, et al.* (1998): **The role of carotid arterial intima-media thickness in predicting clinical coronary events**. *Ann Intern Med* 128:262-9.

29. Vlachopoulos C, Aznaouridis K, Stefanadis C (2010): **Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis**. *J Am Coll Cardiol* 55:1318-27.

30. Tinken TM, Thijssen DH, Black MA*, et al.* (2008): **Time course of change in vasodilator function and capacity in response to exercise training in humans**. *J Physiol* 586:5003-12.

Figure Caption:

Figure 1: Flow of Participants through the HIITTS Trial.

Legend: Dx: diagnosis; CVD: cardiovascular disease; ECG: electrocardiogram; Avg: average.

Note: Discrepancies between *Postintervention Assessment* sample sizes and *Results Table* sample sizes are the result of unanalyzable data (e.g., poor signal quality, anatomical variability, or non-trial-related injury).

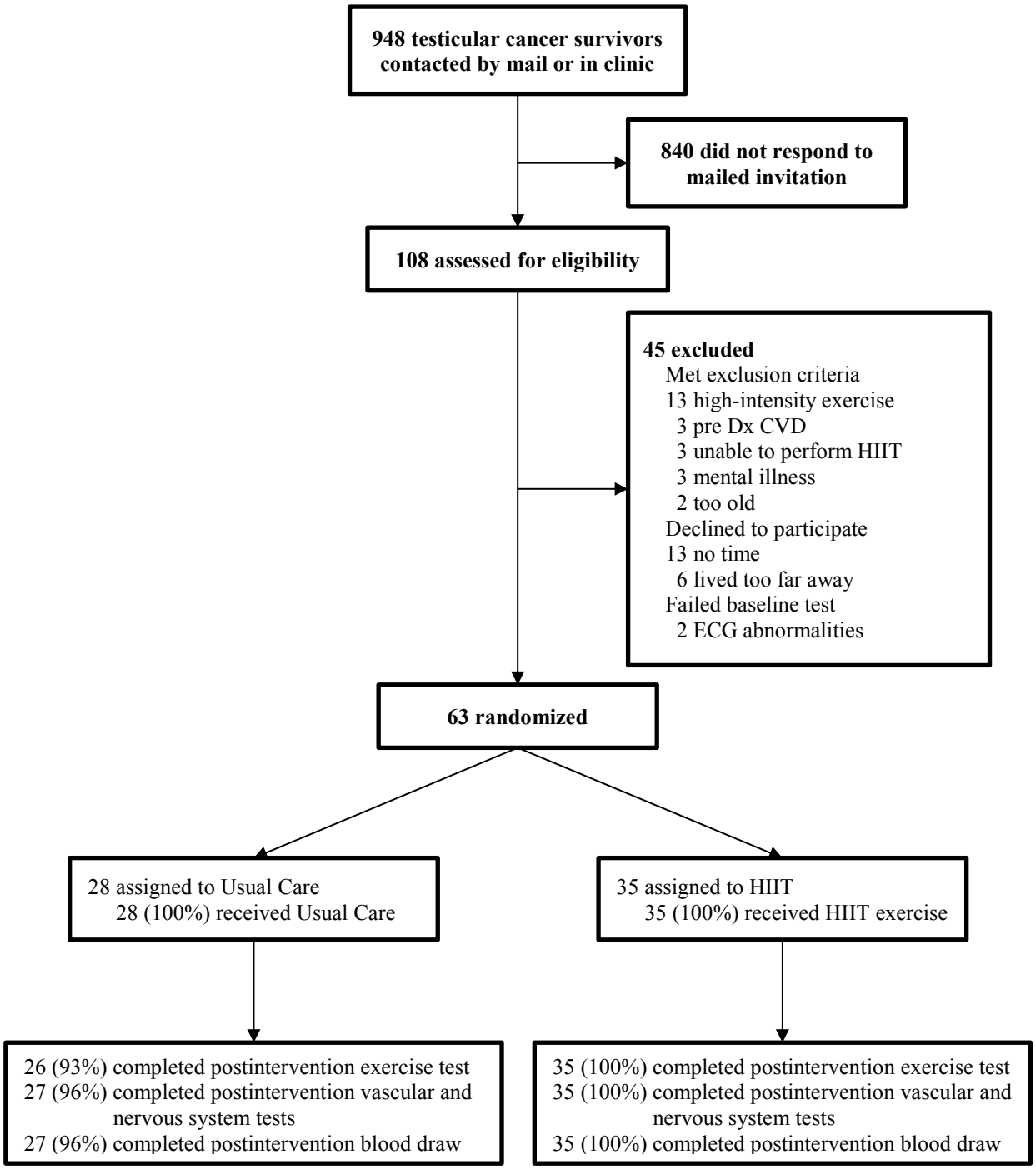

948 testicular cancer survivors contacted by mail or in clinic
840 did not respond to mailed invitation
108 assessed for eligibility
45 excluded
Met exclusion criteria
13 high-intensity exercise
3 pre Dx CVD
3 unable to perform HIIT
3 mental illness
2 too old
Declined to participate
13 no time
6 lived too far away
Failed baseline test
2 ECG abnormalities
63 randomized
28 assigned to Usual Care
28 (100%) received Usual Care
35 assigned to HIIT
35 (100%) received HIIT exercise
26 (93%) completed postintervention exercise test
27 (96%) completed postintervention vascular and nervous system tests
27 (96%) completed postintervention blood draw
35 (100%) completed postintervention exercise test
35 (100%) completed postintervention vascular and nervous system tests
35 (100%) completed postintervention blood draw

Table 1: Baseline demographic, medical, and behavioral profile of HIITTS trial participants, overall and by group assignment

	Overall (n = 63)		Usual Care (n = 28)		HIIT (n = 35)	
	No. of Patients	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**
Demographic Profile						
Age, years						
Mean (SD)	43.7 (10.8)		43.3 (9.9)		44.0 (11.6)	
Range	21-61		22-61		21-60	
Married	43	68.3	18	64.3	25	71.4
Completed university	42	66.7	19	67.9	23	65.7
Income > $100,000/year	41	65.1	19	67.9	22	62.9
Full-time employment	54	85.7	27	96.4	27	77.1
Medical Profile						
Weight, kg						
Mean (SD)	88.9 (18.3)		89.7 (16.3)		88.3 (19.8)	
BMI, kg/m^2						
Mean (SD)	27.5 (4.7)		27.9 (4.2)		27.2 (5.0)	
Obese	13	20.6	3	10.7	10	28.6
Pre-hypertensive	12	19.0	3	10.7	9	25.7
Hypogonadic	9	14.3	4	14.3	5	14.3
Metabolic Syndrome	12	19.0	4	14.3	8	22.9
Carotid plaque burden						
Mild	36	57.1	19	67.9	17	48.6
Moderate-Severe	15	23.8	4	14.3	11	31.5
Time since diagnosis, years						
Mean (SD)	8.0 (5.5)		7.5 (5.5)		8.5 (5.5)	
Range	1-20		1-20		1-20	
Disease history						
Localized	41	65.1	20	71.4	21	60.0
Surgical protocol						
Single orchidectomy	58	92.1	27	96.4	31	88.6
Received radiotherapy	11	17.5	5	17.9	6	17.1
Received chemotherapy	23	36.5	8	28.6	15	42.9
Behavioral Profile						
Current aerobic exercisers	23	36.5	7	25.0	16	45.7
Current resistance exercisers	17	27.0	10	35.7	7	20
Current smoker	5	7.9	2	7.1	3	8.6

Notes: HIIT: high-intensity interval training; No.: number; SD: standard deviation; kg: kilograms; BMI: body mass index; m: meter

Table 2: HIIT exercise prescription and delivery details per phase of intervention

Intervention Phase	Week(s)	W:R Ratio (*mins:mins*)	# of Work Intervals	Work Period Intensity				Session Attendance	
				Target		Achieved		Target	Achieved
				Intensity (% of VO_{2peak})	Heart Rate (beats/minute)	Heart Rate (beats/minute)	% of Target Heart Rate	# /phase	mean (%)
1a	1	4:3	4	75	135	144	107	3	3 (100)
1b	2	4:3	4	80	143	147	103	3	3 (100)
1c	3-4	4:3	4	85	152	151	100	6	6 (100)
2	5-8	4:3	4	90	160	154	96	12	12 (99.8)
3	9-12	4:3	4	95	168	157	94	12	11.5 (95.7)

Notes: W: work period; R: rest period (active recovery); mins: minutes; HR: heart rate; bpm: beats per minute

***** Target/Achieved HRs reflect group averages during each phase. Recovery intensity set at 10% less than estimated ventilatory threshold.

Table 3: Effects of 12 weeks of HIIT on exercise capacity and resting cardiovascular function in TCS

			Baseline		Follow-up		Between-group difference			
Measure	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	***p***
Exercise										
Relative VO_{2peak} (mL $O_2 \cdot kg^{-1} \cdot minute^{-1}$)	Control	26	37.0	7.2	37.6	0.5	3.7	0.7	2.4 to 5.1	<0.001
	Exercise	35	37.1	5.7	41.3	0.4				
Absolute VO_{2peak} ($L \cdot minute^{-1}$)	Control	26	3.22	0.46	3.27	0.03	0.27	0.04	0.18 to 0.35	<0.001
	Exercise	35	3.23	0.61	3.53	0.03				
One-minute heart rate recovery (beats·$minute^{-1}$)	Control	26	25.2	11.3	23.4	1.5	5.9	2.0	2.0 to 9.9	0.001
	Exercise	35	20.6	8.9	29.4	1.3				
Resting										
Heart rate (beats·$minute^{-1}$)	Control	27	58.4	8.8	56.0	1.0	-3.4	1.3	-6.0 to -0.8	0.012
	Exercise	35	57.2	8.8	52.6	0.9				
Systolic blood pressure (mmHg)	Control	27	114.3	10.3	114.3	1.2	-0.7	1.6	-3.8 to 2.5	0.67
	Exercise	35	115.8	11.5	113.6	1.0				
Diastolic blood pressure (mmHg)	Control	27	70.1	7.4	71.6	1.1	-3.8	1.5	-6.7 to -0.8	0.013
	Exercise	35	73.3	8.7	67.8	1.0				
Respiratory sinus arrhythmia [a] (beats·$minute^{-1}$)	Control	27	18.4	6.8	17.3	1.0	2.9	1.3	0.2 to 5.5	0.033
	Exercise	35	19.0	7.7	20.2	0.8				

Notes: Adj.: adjusted; SE: standard error; CI: confidence interval; VO_{2peak}: maximal aerobic fitness; mL: milliliters; O_2: oxygen; L: liters; mmHg: millimeters of mercury

***** all follow-up and between-group difference values were adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

[a] also adjusted for change in BMI

Table 4: Effects of 12 weeks of HIIT on vascular structure and function in TCS

			Baseline		Follow-up		Between-group difference			
Measure	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	**p**
Carotid intima-media thickness [a, b]										
Average (mm)	Control	27	0.58	0.07	0.62	0.01	-0.06	0.01	-0.08 to -0.03	<0.001
	Exercise	35	0.62	0.14	0.56	0.01				
Maximum (mm)	Control	27	0.67	0.09	0.71	0.01	-0.08	0.01	-0.10 to -0.05	<0.001
	Exercise	35	0.72	0.17	0.63	0.01				
Carotid distensibility [a, c] (10^{-3}/kPa)	Control	27	13.97	4.75	13.59	0.44	1.54	0.70	0.13 to 2.95	0.049
	Exercise	34	13.02	4.71	15.13	0.43				
Carotid diameter (mm)	Control	27	7.00	0.43	6.91	0.04	-0.07	0.06	-0.18 to 0.05	0.23
	Exercise	35	7.00	0.60	6.85	0.04				
Brachial flow-mediated dilation [a, b, d] (%)	Control	23	3.71	2.16	4.18	0.31	0.29	0.43	-0.57 to 1.14	0.50
	Exercise	30	3.96	2.45	4.47	0.26				
Brachial flow-mediated dilation$_{normalized}$ [e]	Control	23	6.0	3.0	8.0	1.0	1.0	1.0	-2.0 to 3.0	0.34
	Exercise	30	8.0	6.0	9.0	1.0				
Brachial diameter [a] (mm)	Control	23	4.43	0.59	4.56	0.06	0.14	0.08	0.01 to 0.29	0.009
	Exercise	30	4.47	0.66	4.70	0.05				
Velocity time integral (cm)	Control	23	66.4	15.3	71.4	3.8	10.9	5.2	0.54 to 21.3	0.039
	Exercise	30	61.6	18	82.4	3.3				
Shear stress during reactive hyperemia (dynes/cm^2)	Control	23	41.07	9.91	42.24	2.16	2.38	2.91	-3.48 to 8.24	0.42
	Exercise	30	37.68	12.53	44.62	1.88				
Carotid-femoral PWV [a, f] (m/s)	Control	26	7.68	1.5	7.94	0.15	-2.02	0.2	-2.42 to -1.62	<0.001
	Exercise	33	8.69	2.0	5.92	0.13				
Femoral-toe PWV [a, f] (m/s)	Control	25	9.4	0.93	9.51	0.14	-0.74	0.2	-1.14 to -0.35	0.001
	Exercise	32	10.49	1.32	8.77	0.12				

Notes: mm: millimeters; kPa: kilopascals; cm: centimeters; s: second; PWV: pulse wave velocity

***** follow-up and between-group difference values adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

[a] also adjusted for change in mean arterial pressure

[b] also adjusted for change in arterial diameter

[c] also adjusted for change in intima-media thickness

[d] also adjusted for change in shear rate

[e] unadjusted and adjusted group means, SDs, SEs, and CIs multiplied by a factor of 1000 for display purposes

[f] also adjusted for change in HR

Table 5: Effects of 12 weeks of HIIT on blood-based biomarkers in TCS

			Baseline		Follow-up		Between-group difference			
Measures	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	**p**
Endothelial and inflammatory markers										
Fibrinogen (g/L)	Control	27	2.90	0.57	2.78	0.07	-0.02	0.09	-0.20 to 0.16	0.82
	Exercise	34	3.03	0.61	2.76	0.06				
hsCRP (mg/L)	Control	26	1.66	1.50	1.61	0.24	-0.6	0.32	-1.24 to -0.03	0.045
	Exercise	35	1.65	2.35	1.01	0.21				
Blood lipids										
Total cholesterol (mmol/L)	Control	27	5.11	0.81	5.09	0.11	-0.18	0.14	-0.47 to 0.10	0.20
	Exercise	35	5.12	0.80	4.90	0.09				
High-density lipoprotein (mmol/L)	Control	26	1.29	0.35	1.40	0.05	0.02	0.07	-0.12 to 0.15	0.20
	Exercise	35	1.44	0.41	1.40	0.04				
Low-density lipoprotein (mmol/L)	Control	25	3.05	0.68	3.06	0.08	-0.26	0.10	-0.46 to -0.05	0.014
	Exercise	35	3.09	0.71	2.80	0.07				
Total cholesterol : High-density lipoprotein ratio	Control	26	4.14	1.02	3.91	0.10	-0.24	0.14	-0.52 to 0.04	0.09
	Exercise	35	3.75	0.93	3.67	0.09				
Triglycerides (mmol/L)	Control	27	1.67	0.78	1.45	0.10	0.03	0.14	-0.25 to 0.31	0.82
	Exercise	35	1.30	0.54	1.48	0.09				
Metabolic and gonadal function										
Fasting glucose (mmol/L)	Control	27	5.06	0.50	5.17	0.08	-0.09	0.11	-0.31 to 0.13	0.39
	Exercise	35	5.15	0.44	5.07	0.07				
Testosterone (nmol/L)	Control	27	14.6	4.8	14.2	0.9	0.6	1.2	-1.8 to 3.0	0.24
	Exercise	35	15.1	6.1	14.8	0.8				

Notes: g: grams; hsCRP: high sensitivity c-reactive protein; mg: milligrams; mmol: millimoles; nmol: nanomole
* all follow-up and between-group difference values were adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

Table 6: Effects of 12 weeks of HIIT on CVD risk factors in TCS

			Baseline		Follow-up		Between-group Difference			
Measures	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	**p**
Framingham Risk Score (%)	Control	27	5.8	5.4	6.3	0.2	-0.6	0.2	-1.0 to -0.1	0.011
	Exercise	35	6.9	6.1	5.7	0.2				
Vascular Age (years)	Control	27	42.7	12.1	43.0	0.4	-1.3	0.5	-2.3 to -0.3	0.011
	Exercise	35	43.7	15.7	41.6	0.3				
Modifiable CVD Risk Factor Score (# /max 24)	Control	27	6.3	3.0	6.1	0.3	-1.4	0.4	-2.2 to -0.5	0.002
	Exercise	35	7.0	3.6	4.7	0.3				

* all follow-up and between-group difference values were adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

Chapter III – Online Supplement for the Primary Manuscript

Methods Supplement

3.1 Participants

Participants were recruited via mail (using the Alberta Cancer Registry) and from the surveillance clinic at the Cross Cancer Institute (Edmonton, AB). Men 18-80 years of age with a confirmed history of TC and no evidence of pre-cancer CVD were eligible. Men were excluded if they were unable to complete the first two stages of the exercise test (potentially resulting in insufficient data to generate exercise prescriptions and unreliable VO_{2peak} measures; and, indicating a greater functional/mobility deficit which would preclude participation in HIIT), had any psychiatric condition impairing their ability to perform the exercise, had any uncontrolled cardiovascular condition, or already performed regular vigorous aerobic exercise. The HIITTS trial received ethical approval from the Health Research Ethics Board of Alberta – Cancer Committee (Trial ID# 14-0183) and the University of Alberta (Clinical Trial Registration #NCT02459132).

3.2 Randomization and Blinding

The allocation sequence was generated by a computer-generated random numbers list by a research assistant not otherwise involved in the study. Participant allocation was only revealed to the research coordinator following the completion of the entire baseline assessment. It was not possible to blind participants or intervention supervisors to group allocation. Outcome assessors for the primary outcome of VO_{2max} and secondary vascular and nervous system outcomes were

also not blinded to group assignment but were trained in the importance of following a standardized protocol. Data cleaning, processing, and analyses were either conducted or verified by a research assistant blinded to group allocation.

3.3 Exercise Training and Usual Care Conditions

During the work period, participants completed four, 4-minute, high-intensity intervals at a speed and grade that would elicit a progressively increasing VO_{2peak} target over the intervention period (i.e. week 1, 75% VO_{2peak}; week 2, 80% VO_{2peak}; weeks 3-4, 85% VO_{2peak}; weeks 5-8, 90% VO_{2peak}; weeks 9-12, 95% VO_{2peak}). Exercise intensity, although prescribed using %VO_{2peak}, was monitored via heart rate (HR) monitors, and programs were augmented to maintain target HRs [i.e., training intensity was augmented by the least possible increment (i.e., 0.5 mph or 0.5% incline) when HRs dropped below 15% of target during the final work interval for 3 consecutive sessions]. A 4×3 HIIT exercise protocol was selected for our intervention based on the evidence that the frequency and magnitude of positive cardiovascular adaptations in persons at risk of, and living with, lifestyle induced CVD[1,2] are generally greatest with HIIT compared to moderate-intensity continuous training or sprint interval training. Moreover, we believed that the specific combination of greater exercise intensity and time efficiency provided by this 4×3 HIIT prescription was well-aligned with the abilities and needs of TCS, given that TCS are typically younger (i.e., more able-bodied) and their greatest barrier to exercise engagement is 'competing *time-based* demands'[3]. Ultimately, we decided that this 4×3 HIIT prescription showed the greatest promise to improve the greatest number of cardiovascular outcomes, to the greatest

extent, in the specific context of TCS. Using a wait-list control design, UC group participants were informed that they would be offered a 6-week supervised HIIT exercise program after the 12-week observation period and 3-month follow-up assessment (only patient-reported outcome data was collected at the 3-month follow-up assessment).

3.4 Assessment of Primary and Secondary Endpoints

3.4.1 Exercise Assessments

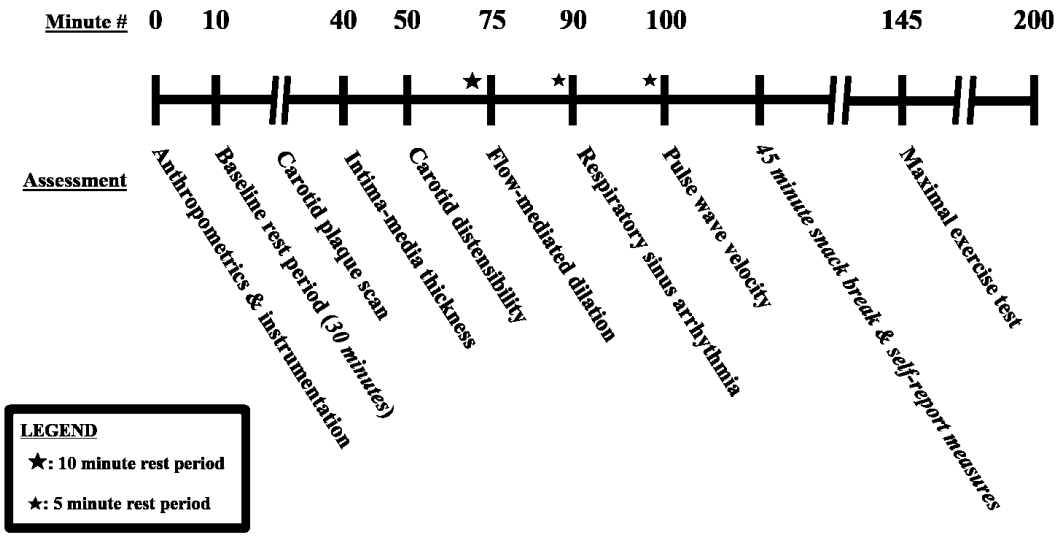
True VO_{2max} measures are sometimes difficult to obtain, especially in clinical populations.[4] As this was the first aerobic exercise training study in TCS, we were unsure how reliably our participants could achieve VO_{2max}. Accordingly, we selected peak aerobic fitness (VO_{2peak}) as our primary outcome and principle marker of systemic cardiovascular health. Prior to the test, participants performed a 5-minute warm-up at 0% incline and a belt speed sufficient to elicit 60% of their age-predicted maximal HR (this belt speed used for the test). VO_{2peak} was assessed via a treadmill-based maximal cardiorespiratory exercise test (Woodway - 4Front, Waukesha, WI) with a constant individualized belt speed and an incline increasing by 2% every two minutes until exhaustion. During the test, oxygen consumption (ParvoMedics - TrueOne 2400, Murray, UT) and HR (12-lead ECG; Nasiff - CardioCard, Central Square, NY) were measured continuously. HR was measured for an additional 6 minutes of recovery (1st minute standing plus 5 minutes of active recovery). Blood pressure, rate of perceived exertion and arterial oxygen saturation were recorded every two minutes – during the final minute of each 2-minute stage.

VO_{2peak} was defined as the highest 15-second average value of oxygen uptake recorded over the test. Data are presented as relative (primary outcome) and absolute values. Maximal participant effort was confirmed by meeting at least two of the following three criteria i) a leveling off of oxygen uptake despite an increased workload, ii) achievement of a respiratory exchange ratio >1.1, or iii) a rate of perceived exertion ≥9/10.[4] Ventilatory threshold was used to prescribe the intensity of the warm-up and active recovery intervals.[5] Ventilatory threshold was estimated using the V-slope method and according to the following criteria: i) an exaggerated response in the volume of carbon-dioxide (i.e., VCO_2) relative to the volume of oxygen (i.e., VO_2), and ii) the first identifiable break-point in in the minute ventilation (i.e., VE/VO_2 vs work rate relationship).[5] Based on these criteria, we identified the work rate (i.e., VO_2) and HR which corresponded to the attainment of each individual's ventilatory threshold. We then used this VO_2 value to prescribe the intensity of the warm-up and active recovery periods. Throughout the intervention, however, we used the HR values corresponding to these estimated ventilatory thresholds to monitor the intensity of the warm-up and active recovery periods. One-minute HR recovery (HRR; an index of post-exercise parasympathetic reactivation[6,7]) was calculated as the HR-difference between peak exercise and following one minute of quiet standing on the treadmill immediately post test.

3.4.2 Resting Hemodynamic, Vascular, and Nervous System Assessments

Upon arrival at the laboratory, participants completed informed consent and medical screening questionnaire (baseline test only). Once complete, participant anthropometric data was recorded and used to calibrate the testing equipment. Participants were then instrumented and

began 30 minutes of supine rest in a darkened, quiet, temperature controlled (21°C to 23°C) room. Please see **eFigure 1** for an overview of the order of the resting assessments.



eFigure 1: Order of resting tests.

Participants were tested under the same conditions (e.g., having fasted (≥12 hours)) as when their blood specimen was collected.[8] Resting HR was continuously measured using a standard single lead ECG. Beat-to-beat blood pressure changes were continuously recorded via photoplethysmography from the right middle finger (Finapres Medical Systems - Finometer, Enschede, NL). Manual sphygmomanometry at the brachial artery and an automated return-to-flow procedure were used to calibrate the Finometer data at baseline and prior to each individual test. Carotid and brachial vascular structure, brachial vascular reactivity, forearm microvascular reactivity, and brachial blood velocity measures were captured using high-resolution B-mode ultrasonography (8L MHz; G.E. Vivid-i, Waukesha, WI) and stored for off-line analysis. All

resting HR, blood pressure, blood velocity, and applanation tonometry (Millar Instruments SPT-301, Houston, TX) data were simultaneously captured using LabChart 7.0 (AD Instruments, Colorado Springs, CO). Offline vascular ultrasound analyses were completed using Vascular Tools (Medical Imaging Applications LLC, Carotid/Brachial Analyzer for Research, Corafille, IA).

3.4.3 Carotid Plaque

During the 30-minute rest period (baseline only), carotid plaque burden was assessed, via bilateral ultrasound scans (8L MHz; G.E. Vivid-i, Waukesha, WI) of the near and far walls of the common carotid, carotid bifurcation, and internal carotid arteries, as per the Mannheim Consensus Guidelines.[9,10] Plaque was defined as focal structures encroaching at least 0.5 mm or 50% of the adjacent intima-media thickness value, or ii) with an intima-media thickness of >1.5 mm).[9] The total number of plaque-present sites were recorded and used to generate a total plaque score, based on a total of 12 possible affected locations (i.e., 6 measurement sites per side). The severity of arterial plaque development was categorized according to no plaque (0 sites), mild plaque (1-4 sites), moderate plaque (5-8 sites) and severe plaque (9-12 sites).[10]

3.4.4 Carotid Intima-Media Thickness

Following the 30-minute rest period, ultrasound-based measures of carotid artery intima-media thickness (i.e., arterial wall thickness) were taken. Bilateral carotid artery intima-media thickness was measured via ultrasound (8L MHz; G.E. Vivid-i, Waukesha, WI). Rotating around

the long-axis of the vessel, the mean and maximal carotid intima-media thickness values were recorded as the average of three serial measurements of the far wall, bilaterally.[9] The measurements were made during diastole within 10 mm, plaque-free regions, of the far wall of the common carotid arteries and at least 5 mm below the origin of the internal carotid artery.[9]

3.4.5 Carotid Distensibility

Carotid distensibility was used as an index of local arterial stiffness.[11] ECG-gated maximum (i.e., systolic) and minimum (i.e., diastolic) carotid artery diameters were recorded continuously via carotid artery ultrasound (8L MHz; G.E. Vivid-i, Waukesha, WI) for 15 cardiac cycles seconds, twice. The recorded arterial diameters were used to calculate the relative maximum and minimum cross-sectional areas. Beat-to-beat blood pressure was simultaneously recorded and used to calculate the pulse pressure for each cardiac cycle. Carotid distensibility was then calculated per the following equation[11]:

$$Carotid\ distensibility\ (10^{-3}/kPa) = (CSA_{SYS} - CSA_{DIA})/\left(CSA_{DIA} \times (P_{SYS} - P_{DIA})\right), (1)$$

where CSA is the arterial cross-sectional area and P is the arterial pressure during systole (SYS) and diastole (DIA). Carotid distensibility was recorded as the largest of the 2 values obtained at baseline and follow-up.

3.4.6 Flow-Mediated Dilation and Microvascular Function

Left brachial artery structure, endothelial function, and microvascular function were assessed via flow-mediated dilation (FMD), according to best practice guidelines.[8,12-15] Resting brachial artery diameter (measured in millimeters) and blood velocity (measured in centimeters per second) were recorded, via ultrasound (8L MHz; G.E. Vivid-i, Waukesha, WI), at a site 3 cm proximal to the antecubital fossa for five minutes. After this rest period, brachial artery blood flow was occluded using a rapid-inflation blood pressure cuff (placed immediately distal to the elbow), at an average pressure of 220 mmHg (≥50 mmHg above systolic blood pressure), for an additional five minutes. The reactive hyperemic response to the rapid deflation of the blood pressure cuff was then recorded for an additional four minutes. Diastolic brachial artery diameters were extracted and averaged every 2 seconds throughout baseline and following cuff-release until peak diameter was reached. FMD was calculated as the percent increase in arterial diameter from baseline to peak using the following equation[16]:

$$FMD_{\%} = \left((D_P - D_B)/D_B\right)\times 100, \text{ (2)}$$

where D_P is the peak arterial diameter recorded post cuff release and D_B is the average arterial diameter recorded at baseline. FMD was also normalized to the total shear rate per the following equation[17,18]:

$$FMD_{normalized} = FMD_{\%}/AUC_{SR}, \text{ (3)}$$

where AUC_{SR} is the total area under the curve for shear rate from cuff release to peak brachial artery dilation.

Data collected during the FMD protocol was used to calculate indices of microvascular function in the resistance vessels of the distal arm. Velocity time integral (VTI) and shear stress during reactive hyperemia have been shown to independently predict CVD risk.[12,19-21] Measured (probe frequency of 13 MHz) as the total velocity envelope from the first waveform post cuff release, VTI of the brachial artery was used to calculate blood velocity during reactive hyperemia (VRH) according to the following equation[21]:

$$VRH\ (cm/s) = VTI \times (HR/60), (4)$$

where HR is heart rate and 60 is a constant used to convert from ml/sec to ml/min. Finally, using VRH, shear stress during reactive hyperemia was calculated per the following equation[21]:

$$Shear\ stress\ during\ reactive\ hyperemia\ (dynes/cm^2) = 8 \times \mu \times (VRH/D_B/10), (5)$$

where μ was the viscosity of blood (assumed to be 0.035 dyne·sec/cm^2).[20]

3.4.7 Respiratory Sinus Arrhythmia

Respiratory sinus arrhythmia (RSA) is an index of parasympathetic nervous system/cardio-vagal function. RSA was assessed by measuring the magnitude of heart period

variability during a paced deep breathing challenge. Prior to beginning the test, participants performed a maximal inspiration maneuver. During this maneuver (and throughout the test), the expansion of the thorax was tracked using a piezo-electric respiration transducer (Pneumotrace II, UFI, Morro Bay, CA); and, the maximum and minimum thorax expansion values were used to ensure maximal patient breathing effort throughout the remainder of the test. Participants then rested quietly for 3 minutes prior to beginning the test. Following the rest period, participants were asked to maintain a 10-second respiratory cycle (i.e., maximal inspiration - held up to 5 seconds; followed by maximal expiration - held up to 5 seconds) for 90 seconds.[22] RSA was calculated by taking the average difference between the maximum and minimum HRs from the largest 6 successive HR oscillations.[22]

3.4.8 Pulse Wave Velocity

Central arterial stiffness (i.e., carotid-femoral pulse wave velocity (PWV)) and peripheral arterial stiffness (femoral-toe PWV) were assessed on the left side of the body via applanation tonometry (Millar Instruments SPT-301, Houston, TX) located at the distal common carotid artery, proximal femoral artery, and the distal phalange of the first digit.[23] Using the foot-to-foot method,[23] the velocity of each pulse wave was calculated as the time difference between the arrival of the blood pressure waveform at each site for the central and peripheral arterial segments. Carotid-femoral distance was corrected to 80% of the straight distance between the two sites.[24] Femoral-toe distance was measured from the femoral site, posterior to the medial malleolus, and around to the midpoint of the distal phalange of the first digit. A total of 30 pulse-waveforms were recorded simultaneously (2× 15 pulse-wave segments) across the central and

peripheral sites. To control for the influence of outliers, the recorded PWV for each segment (i.e., central and peripheral) was taken as the median of these measures.[23]

3.4.9 Blood-based Biomarker Assessments

Blood specimen collection took place at various DynaLife laboratory locations within Edmonton and Red Deer (AB). Each specimen was immediately stored, shipped, and analyzed at a central processing facility. Anonymized results were emailed directly to the study coordinator within 48 hours of collection. The blood factors analyzed included markers of inflammation (i.e., high-sensitivity C-reactive protein), endothelial activation (i.e., fibrinogen), glucose metabolism (i.e., fasting glucose), hypogonadism (i.e., testosterone), and a standard blood lipid panel (i.e., total cholesterol, high-density lipoprotein, low-density lipoprotein, total cholesterol : high-density lipoprotein ratio, and triglycerides). Results were interpreted per national standards.[25]

3.4.10 Cardiovascular Disease Risk Assessments

Framingham 10-year CVD risk score (FRS) was used to estimate CVD risk. Vascular age was used as a tool to communicate participants' CVD risk.[26] FRS and vascular age were calculated using the general CVD risk profile criteria for the Framingham Heart Study.[27] The modifiable CVD risk factor score (MRFS) was used as an index of total CVD risk. MRFSs incorporated 24 novel and traditional surrogate markers of cardiovascular morbidity and mortality risk according to **eTable 1**.[7,9,11,22-33] Individual MRFSs were generated for each

participant at baseline and follow-up by comparing participant values to the established risk factor thresholds and adding the number of positive risk factors together.

3.5 Statistical Analyses and Sample Size Calculation

The primary objective of this study was to determine the effects of HIIT on cardiorespiratory fitness (VO_{2peak}), compared to UC. With 33 participants per group (total N = 66), using an ANCOVA to adjust for baseline values and relevant covariates[34] (without adjusting for multiple comparisons), we had 80% power to detect a standardized effect size *d* of approximately 0.60 with a two-tailed alpha = 0.05. A standardized effect size of 0.60 corresponds to a 3.5 ml O_2/kg/min improvement in VO_{2peak}, based on a baseline mean value of 30.25 ml O_2/kg/min and a standard deviation of 5.78 ml O_2/kg/min.[35-38] Due to our unselected recruitment methods, our sample had a high degree of variability in characteristics which may have confounded our results (e.g., time since treatment). In addition to our randomization stratification, we controlled for the influence of other potential confounders (i.e., age, treatment exposure, and time since treatment) by including them as covariates in each of our analyses. We report unadjusted baseline data and adjusted post-intervention data, mean between group difference, 95% confidence interval (CI) and p-value for all hypothesized comparisons. Data were analyzed using an intention-to-treat approach (SPSS version 24). No missing data strategy was employed given the minimal amount of missing data in our study.

3.6 References

1. Kessler HS, Sisson SB, Short KR (2012): **The potential for high-intensity interval training to reduce cardiometabolic disease risk**. *Sports Med* 42:489-509.

2. Weston KS, Wisloff U, Coombes JS (2014): **High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis**. *Br J Sports Med* 48:1227-34.

3. Reilley MJ, Jacobs LA, Vaughn DJ*, et al.* (2014): **Health behaviors among testicular cancer survivors**. *J Community Support Oncol* 12:121-8.

4. Stickland MK, Butcher SJ, Marciniuk DD*, et al.* (2012): **Assessing exercise limitation using cardiopulmonary exercise testing**. *Pulmonary medicine* 2012:13.

5. Mezzani A, Hamm LF, Jones AM*, et al.* (2013): **Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation**. *Eur J Prev Cardiol* 20:442-67.

6. Lauer MS (2009): **Autonomic function and prognosis**. *Cleve Clin J Med* 76 Suppl 2:S18-22.

7. Pecanha T, Silva-Junior ND, Forjaz CL (2014): **Heart rate recovery: autonomic determinants, methods of assessment and association with mortality and cardiovascular diseases**. *Clin Physiol Funct Imaging* 34:327-39.

8. Thijssen DH, Black MA, Pyke KE*, et al.* (2011): **Assessment of flow-mediated dilation in humans: a methodological and physiological guideline**. *Am J Physiol Heart Circ Physiol* 300:H2-12.

9. Touboul PJ, Hennerici MG, Meairs S*, et al.* (2012): **Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011**. *Cerebrovasc Dis* 34:290-6.

10. van Popele NM, Grobbee DE, Bots ML*, et al.* (2001): **Association between arterial stiffness and atherosclerosis: the Rotterdam Study**. *Stroke* 32:454-460.

11. Engelen L, Bossuyt J, Ferreira I*, et al.* (2015): **Reference values for local arterial stiffness. Part A: carotid artery**. *J Hypertens* 33:1981-96.

12. Anderson TJ, Charbonneau F, Title LM*, et al.* (2011): **Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study**. *Circulation* 123:163-9.

13. Corretti MC, Anderson TJ, Benjamin EJ*, et al.* (2002): **Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force**. *J Am Coll Cardiol* 39:257-65.

14. Green DJ (2005): **Point: flow-mediated dilation does reflect nitric oxide-mediated endothelial function**. *J Appl Physiol* 99:1233-8.

15. Pyke KE, Dwyer EM, Tschakovsky ME (2004): **Impact of controlling shear rate on flow-mediated dilation responses in the brachial artery of humans**. *J Appl Physiol* 97:499-508.

16. Nichols W, O'Rourke M, Vlachopoulos C (2011): **McDonald's blood flow in arteries: theoretical, experimental and clinical principles**, *CRC Press.*,

17. Pyke KE, Tschakovsky ME (2005): **The relationship between shear stress and flow-mediated dilatation: implications for the assessment of endothelial function**. *J Physiol* 568:357-69.

18. Pyke KE, Tschakovsky ME (2007): **Peak vs. total reactive hyperemia: which determines the magnitude of flow-mediated dilation?** *J Appl Physiol* 102:1510-1519.

19. Irace C, Cortese C, Fiaschi E*, et al.* (2004): **Wall shear stress is associated with intima-media thickness and carotid atherosclerosis in subjects at low coronary heart disease risk**. *Stroke* 35:464-8.

20. Mitchell GF, Parise H, Vita JA*, et al.* (2004): **Local shear stress and brachial artery flow-mediated dilation: the Framingham Heart Study**. *Hypertension* 44:134-9.

21. Philpott AC, Lonn E, Title LM*, et al.* (2009): **Comparison of new measures of vascular function to flow mediated dilatation as a measure of cardiovascular risk factors**. *Am J Cardiol* 103:1610-5.

22. Freeman RL (2008): **Noninvasive evaluation of heart rate: time and frequency domains.**, in Low PA, Benarroch EE (eds): Clinical Autonomic Disorders. (ed 3rd). Philadelphia, *Lippincott Williams & Wilkins*, pp 185-197.

23. Van Bortel LM, Laurent S, Boutouyrie P*, et al.* (2012): **Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity**. *J Hypertens* 30:445-448.

24. Reference Values for Arterial Stiffness Collaboration (2010): **Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'**. *Eur Heart J* 31:2338-50.

25. Genest J, McPherson R, Frohlich J*, et al.* (2009): **2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations**. *Can J Cardiol* 25:567-79.

26. Anderson TJ, Gregoire J, Pearson GJ*, et al.* (2016): **2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult**. *Can J Cardiol* 32:1263-1282.

27. D'Agostino RB, Sr., Vasan RS, Pencina MJ*, et al.* (2008): **General cardiovascular risk profile for use in primary care: the Framingham Heart Study**. *Circulation* 117:743-53.

28. American College of Sports Medicine (2013): **ACSM's guidelines for exercise testing and prescription** (ed 9), *Lippincott Williams & Wilkins*,

29. Anderson TJ, Gregoire J, Hegele RA*, et al.* (2013): **2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult**. *Can J Cardiol* 29:151-67.

30. Engelen L, Ferreira I, Stehouwer CD*, et al.* (2013): **Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors**. *Eur Heart J* 34:2368-80.

31. Nuver J, Smit AJ, Sleijfer DT*, et al.* (2004): **Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer**. *Eur J Cancer* 40:701-6.

32. Peters SA, den Ruijter HM, Bots ML (2012): **The incremental value of brachial flow-mediated dilation measurements in risk stratification for incident cardiovascular events: a systematic review**. *Ann Med* 44:305-12.

33. Woodward M, Webster R, Murakami Y*, et al.* (2014): **The association between resting heart rate, cardiovascular disease and mortality: evidence from 112,680 men and women in 12 cohorts**. *Eur J Prev Cardiol* 21:719-26.

34. Borm GF, Fransen J, Lemmens WA (2007): **A simple sample size formula for analysis of covariance in randomized clinical trials**. *J Clin Epidemiol* 60:1234-8.

35. Moholdt TT, Amundsen BH, Rustad LA*, et al.* (2009): **Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life**. *Am Heart J* 158:1031-7.

36. Molmen-Hansen HE, Stolen T, Tjonna AE*, et al.* (2012): **Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients**. *Eur J Prev Cardiol* 19:151-60.

37. Schjerve IE, Tyldum GA, Tjonna AE*, et al.* (2008): **Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults**. *Clin Sci* 115:283-93.

38. Tjonna AE, Lee SJ, Rognmo O*, et al.* (2008): **Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study**. *Circulation* 118:346-54.

eTable 1: Traditional and novel modifiable cardiovascular risk factors and cut-offs

Risk Factor	Risk Factor Criteria	Reference
Systemic Cardiovascular Function		
VO_{2peak} (ml O_2/kg/min)	Age-/sex-based norms	American College of Sports Medicine
Vascular Structure, Function and Health		
Carotid intima-media thickness (mm)	Age-/sex-based norms	Engelen et al., 2013
Carotid plaque presence	Yes	Gepner et al., 2015
Carotid distensibility (10^{-3}/kPa)	Age-/sex-based norms	Engelen et al., 2015
Flow-mediated dilation (%)	<4.75	Peters et al., 2012
Carotid-femoral pulse wave velocity (m/s)	Age-/sex-based norms	Reference Values Collaboration, 2010
Vascular age	> chronologic age	Anderson et al., 2016
Parasympathetic Function		
1 minute heart rate recovery (bpm)	<25	Pecanha et al., 2014
Respiratory sinus arrhythmia (bpm)	Age-/sex-based norms	Freeman et al., 2008
Resting heart rate (bpm)	>80	Woodward et al., 2012
Resting Cardiovascular Function		
Systolic BP (mmHg or on treatment)	≥130 or Yes	Canadian CV Society, 2009, 2012, 2016
Diastolic BP (mmHg or on treatment)	≥90 or Yes	Canadian CV Society, 2009, 2012, 2016
Anthropometric		
Waist circumference (cm)	≥102	Canadian CV Society, 2009, 2012, 2016
Waist:Hip ratio	≥1	Canadian CV Society, 2009, 2012, 2016
Obesity (BMI; kg/m^2)	≥30	Canadian CV Society, 2009, 2012, 2016
Blood Markers		
High sensitivity C-reactive protein (mg/L)	≥2	Canadian CV Society, 2009, 2012, 2016
Fibrinogen (g/L)	≥4.0 g/L	Nuver et al., 2004
Glucose (mmol/L)	>5.8	Canadian CV Society, 2009, 2012, 2016
High-density lipoprotein (mmol/L)	<1	Canadian CV Society, 2009, 2012, 2016
Low-density lipoprotein (mmol/L)	≥3.5	Canadian CV Society, 2009, 2012, 2016
Total cholesterol (mmol/L or on treatment)	≥5.2 - ≥6.2	Canadian CV Society, 2009, 2012, 2016
TC:HDL ratio	≥5	Canadian CV Society, 2009, 2012, 2016
Triglyceride (mmol/L or on treatment)	≥2.2	Canadian CV Society, 2009, 2012, 2016
Testosterone (nmol/L or on treatment)	≤8	Canadian CV Society, 2009, 2012, 2016

Notes: ml: milliliter; O_2: oxygen; kg: kilograms; min: minute; mm: millimeter; kPa: kilopascals; m/s: meters per second; bpm: beats per minute; mmHg: millimeters of mercury; cm: centimeters; BMI: body mass index; mg/L: milligrams per liter; g/L: grams per liter; mmol: millimoles; TC:HDL: total cholesterol : high-density lipoprotein ratio; nmol: nanomoles

Chapter IV – Secondary Manuscript

Running Head: Exercise and quality of life in testicular cancer survivors

A randomized controlled trial of the effects of high-intensity aerobic interval training on fatigue, psychosocial function, and health-related quality of life in testicular cancer survivors

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Key words: testicular cancer, high-intensity aerobic interval training, fatigue, psychosocial function, health-related quality of life

4.1 Abstract

Purpose

Testicular cancer survivors (TCS) have an increased risk of cancer-related fatigue (CRF), psychosocial dysfunction, and poor mental health-related quality of life (HRQoL). We previously reported the effects of high-intensity aerobic interval training (HIIT) on CVD risk factors and surrogate markers of cardiovascular and overall mortality in a population-based sample of TCS. Here, we report the effects of HIIT on the patient-reported outcomes (PROs) and explored cardiorespiratory fitness changes as a potential mediator of the intervention effects.

Patients and Methods

TCS (*n*=63) were randomly assigned to 12 weeks of supervised HIIT or usual care (UC). PROs included CRF, depression, anxiety, stress, self-esteem, sleep quality, and HRQoL assessed at baseline, postintervention, and at 3-month follow-up.

Results

PROs were obtained from 62 participants (98%) at postintervention and 52 participants (83%) at 3-month follow-up. HIIT participants attended 99% of supervised exercise sessions and achieved 98% of target exercise intensity. ANCOVA revealed that, compared to UC, HIIT caused significant improvements in postintervention CRF (adjusted between-group mean difference=4.4; 95% confidence interval, 1.5 to 7.3; p=0.003), self-esteem (p=0.029), the mental component score (p=0.034), role-physical (p=0.048), general health (p=0.016), vitality (p=0.001), and social functioning (p=0.011). Effects on CRF (p=0.031) and vitality (p=0.015) persisted at 3-month follow-up. Exploratory analyses provided preliminary evidence that cardiorespiratory fitness may have partially mediated the postintervention improvements in the mental component score, vitality, and mental health; and the 3-month follow-up improvements in CRF and vitality.

Conclusion

This trial provides the first randomized evidence that a 12-week supervised HIIT program causes significant and meaningful improvements in key psychosocial and HRQoL outcomes for TCS. The finding that HIIT caused clinically meaningful and sustained improvements in fatigue-related constructs at 3-month follow-up, which appears to be related to changes in VO_{2peak}, is novel, has important implications for the long-term care of TCS, and merits follow-up.

4.2 Introduction

In North America, testicular cancer (TC) is the most commonly diagnosed malignancy in men 20 to 40 years old.[1,2] Conventional therapies used to treat TC (i.e., orchidectomy, radiotherapy, and chemotherapy) are highly effective at curing germ-cell disease (5-year relative survival rate 97%)[1] even with advanced disease.[3] Unfortunately, TC and its treatments are associated with short- and long-term health effects including cardiovascular disease, peripheral neuropathy, hypogonadism, cancer-related fatigue (CRF), anxiety, poor mental health-related quality of life (HRQoL), and, less commonly, depression.[4-11]

Among patient-reported outcomes (PROs), CRF may be especially burdensome for TCS. The National Comprehensive Cancer Network defines CRF as "a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning".[12] The prevalence of CRF is greater in TCS than the general population (17-30% vs. 10-12%) and increases from 12-19 years posttreatment, independent of treatment exposure.[9,11] CRF is among the most frequent and highly distressing symptoms in TCS[8] and is associated with poor HRQoL,[9] anxiety,[11] depression,[11] and cognitive impairments.[7]

Although CRF is consistently reported by TCS, early cross-sectional studies found that TCS generally do not report HRQoL deficits[13] compared to healthy controls[14] regardless of treatment exposure.[15] Contrarily, more recent cross-sectional and prospective studies have reported mild,[16] moderate,[10] and short-term[17] HRQoL impairments. One reason for these discrepant findings is that the TCS surveyed in these studies may have experienced a response shift[18-20] wherein survivors regain a mainly positive outlook in the years after being cured of a life-threatening disease. Indeed, TCS have been shown to rate their health as good or better than healthy controls despite living with an increased number of adverse health conditions.[21] Unlike

most cancers, which are associated with advanced age, TC is most often diagnosed at an age and life-stage associated with important social-, emotional-, physical-, and cognitive-development.[10] Compared to older cancer survivor groups, TCS are not afflicted by age-related physical or functional impairments; and, as such, it is perhaps not surprising then that TC diagnoses and treatments have recently been shown to be associated with greater mental HRQoL impairments than physical.[10] With the incidence of TC continuing to rise,[22,23] strategies to prevent or mitigate the effects of TC on CRF, psychosocial function, and HRQoL are needed as part of high quality survivorship care.

Aerobic exercise training is a promising intervention for improving CRF,[24,25] depression,[26,27] and HRQoL[28,29] in several cancer survivor groups although very few studies have focused on TCS. Cross-sectional evidence in TCS suggests that physical activity is associated with lower levels of CRF,[11] depression,[30] and adverse health outcomes.[21] To date, however, no randomized controlled trials have examined whether aerobic exercise training can improve PROs that are important to TCS.

The High-Intensity Interval Training in Testicular cancer Survivors (HIITTS) trial was developed to assess the effects of 12 weeks of high-intensity aerobic interval training (HIIT) on cardiovascular disease risk in TCS (reported previously[31]). In the primary paper for the HIITTS trial we reported that HIIT significantly improved the primary trial outcome [i.e., cardiorespiratory fitness (VO_{2peak})] and reduced CVD risk evidenced by favorable changes in traditional and novel risk factors including measures of vascular structure and function, parasympathetic nervous system function, and blood-based biomarkers for cardiovascular disease.[31] Here, we report the effects of HIIT on the PROs at postintervention and 3-month follow-up. Based on previous research in other cancer survivor populations,[24-29] we hypothesized that HIIT would elicit significant postintervention improvements in CRF, psychosocial

functioning, and HRQoL compared to usual care (UC). It was unclear if these improvements would be maintained at 3-month follow-up. Moreover, we explored whether there was evidence of improvements in VO_{2peak} mediating improvements in PROs. Based on previous research in breast cancer and lymphoma patients,[32,33] we hypothesized that there would be evidence of improvements in VO_{2peak} partially mediating improvements in the physical and functional components of HRQoL but not the psychosocial components.

4.3 Methods

Settings and Participants

The detailed methods of our trial have been reported elsewhere.[31] Briefly, HIITTS trial participants were recruited through the Alberta Cancer Registry (*mailed survey*) and the surveillance clinic at the Cross Cancer Institute (Edmonton, AB; *in person*). Men between the ages of 18 and 80 with a confirmed history of TC were eligible. Exclusion criteria included the inability to complete the first two stages of the aerobic exercise test, the presence of any uncontrolled cardiovascular condition, the presence of any psychiatric condition impairing their ability to exercise, or the performance of regular vigorous intensity aerobic exercise. The Health Research Ethics Board of Alberta – Cancer Committee (Trial ID# 14-0183) and the University of Alberta approved this trial (Clinical Trial Registration #NCT02459132).

Design and Procedures

The HIITTS trial was a prospective, two-armed, phase II, randomized controlled trial. Interested participants were initially screened by phone. Eligible participants were brought into the lab to complete a baseline aerobic exercise test, resting vascular and nervous system tests, and a self-report questionnaire.

Randomization and Blinding

Participants were stratified by age (<50 vs. ≥50 years) and treatment exposure (surgery-only vs. radiotherapy, chemotherapy, both) and randomized in a 1 to 1 ratio using a variable 4-6 permuted block design to HIIT or UC. A research assistant not otherwise involved in the study generated the allocation sequence via computer-generated random numbers list. It was not possible to blind the participants or intervention supervisors to the group allocation due to the nature of the intervention. Outcome assessors were not blinded for the PROs or the maximal fitness test.

Exercise Training and Usual Care Conditions

Participants randomly assigned to the HIIT group were asked to attend three supervised exercise sessions per week, consisting of uphill treadmill walking or running and to maintain all other exercise they were performing at baseline.[34] Each supervised HIIT session was a total of 35 minutes in length – started with a 5-minute warm-up [performed within 5% of ventilatory threshold (calculated from the maximal exercise test)[35]], transitioned into the work-period, and ended with a 5-minute cool-down. The work period consisted of four, 4-minute, high-intensity intervals – the intensity of which gradually increased from 75% to 95% of VO_{2peak} over the intervention period. Each 4-minute high-intensity interval was separated by a 3-minute active recovery interval (performed 5% to 10% below ventilatory threshold). Heart rate monitors were used to track exercise intensity during every session, and programs were augmented to maintain target heart rates. Exercise adherence was supported by providing flexible 7-day/week access to the training facility, free parking, and one-on-one exercise session supervision. Participants randomly assigned to the UC group were asked to maintain their baseline exercise levels. Each UC participant was informed that, following the 12-week observation period and 3-month follow-up assessment, they would be offered a free 6-week supervised HIIT program.

Assessment of Participant Characteristics

Participant demographic, medical, behavioral, psychosocial, and HRQoL variables were assessed via self-report. Self-directed exercise was assessed at baseline, postintervention, and at 3-month follow-up using the Godin Leisure Time Exercise Questionnaire.[36] Exercise minutes were calculated as moderate intensity minutes plus two times the vigorous intensity.[37]

Assessment of Patient Reported Outcomes

PROs were assessed at baseline (prior to randomization), immediately postintervention (after 12 weeks), and at 3-month follow-up. In line with the primary objective of the trial, postintervention was the primary time point of interest. CRF was assessed using the Functional Assessment of Cancer Therapy-Fatigue scale (FACT-F) which is a 13-item inventory assessing 1-week CRF severity on a 0-4 scale with higher scores reflecting lower CRF.[38] Depression was evaluated using the Center for Epidemiologic Studies Depression Scale 10-item inventory which assesses 1-week depressive symptom frequency on a 0-3 scale with higher scores reflecting higher depressive symptom frequency.[39] Anxiety was evaluated using the Spielberger State Anxiety Scale 10-item inventory which assesses 1-week anxiety symptom severity on a 1-4 scale with higher scores reflecting increased anxiety symptom severity.[40] Stress was evaluated using the Perceived Stress Scale 14-item inventory which assesses 1-month stress symptom frequency on a 0-4 scale, wherein higher scores reflect greater stress symptom frequency.[41] Self-esteem was assessed using the Rosenberg Self-Esteem Scale 10-item inventory which assesses overall self-esteem on a 1-4 scale, wherein higher scores reflect greater self-esteem.[42] Sleep quality was assessed using the Pittsburgh Sleep Quality Index which assesses 1-month subjective sleep quality with lower scores reflecting better sleep quality.[43]

HRQoL was assessed using the well-validated SF-36®.[44] The SF-36 is a 36-item scale assessing eight health domains including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The scores for each

subscale were then transformed into norm-based scores wherein higher scores reflect better functioning. The mental component score (MCS) and physical component score (PCS) were calculated by adding the prespecified weighted contributions of each of the eight subscale scores.

Assessment of Cardiorespiratory Fitness

As reported previously,[31] cardiorespiratory fitness (relative VO_{2peak}) was assessed at baseline (prior to randomization) and immediately postintervention (after 12 weeks) via treadmill-based maximal cardiorespiratory exercise test (Woodway - 4Front, Waukesha, WI) with a constant belt speed (i.e., individualized to each participant) and an increasing incline (i.e., 2% every two minutes until exhaustion). Oxygen consumption (ParvoMedics - TrueOne 2400, Murray, UT) and heart rate (12-lead ECG; Nasiff - CardioCard, Central Square, NY) were measured continuously throughout the test. We defined VO_{2peak} as the highest 15-second average oxygen-uptake value recorded during the test. Ventilatory threshold, determined using the V-slope method,[35] was used to prescribe exercise intensities.

Statistical Analyses and Sample Size Calculation

The primary objective of the overall trial was to determine the effects of HIIT on VO_{2peak} compared to UC.[31] Based on ANCOVAs adjusting for baseline values and relevant covariates,[45] 62 participants provided 80% power to detect a difference of 3.5 ml O_2/kg/min, with a two-tailed alpha = 0.05. This level of power translates into a standardized effect size *d* of approximately 0.60 which applies to the PROs examined in this paper. We report unadjusted baseline data and adjusted postintervention data, adjusted between-group mean difference, 95% confidence interval (CI) and p-value for all hypothesized comparisons. Our exploratory mediation analyses were conducted using the product of coefficients method[46] wherein a series of linear regressions are used to test for possible mediation. We examined the potential mediating role of VO_{2peak} for any PRO that was statistically or borderline significant ($p<0.055$) at postintervention and 3-month

follow-up. Based on our mediation model (please see ***online supplement***), this approach requires (1) calculating the total effect of group allocation on the PRO (*path c*), (2) calculating the effect of group allocation on VO_{2peak} (*path a*), (3) calculating the association between VO_{2peak} and the PRO (*path b*), and (4) calculating the direct effect of group allocation on the PRO (*path c'*) while controlling for the indirect effect (product of coefficients $a \times b$). The statistical test of mediation is the examination of the bias corrected 95% CIs for the mediation effect ($a \times b$) using a bootstrapping method involving 5000 bootstrap resamples.[47,48] Data were analyzed using an intention-to-treat approach for all participants with postintervention or 3-month follow-up data (SPSS version 24).

4.4 Results

Participant Flow

Participant flow through the study has been reported elsewhere.[31] Briefly, recruitment took place from June 2015 to March 2016 (**Figure 1**). Of 948 potentially eligible participants who were initially contacted, 108 (11%) were screened for eligibility and 63 (7%) were randomized. We obtained postintervention PRO data on 62 of 63 (98%) participants and 3-month follow-up data on 52 of 63 (83%) participants.

Baseline Characteristics, Participant Adherence, and Fitness Changes

Participant baseline demographics, medical, and behavioural profiles were reported previously.[31] Briefly, participants were on average 43.7 years of age, 68.3% were married, 66.7% had completed university, 65.1% earned over $100,000/year, 85.7% were full-time employed, and self-reported an average of 105 exercise minutes/week.[36] The groups were balanced on baseline descriptive variables. Exercise attendance was 99% and participants achieved 98% and 103% of their target heart rates during the work and recovery phases, respectively. During the

intervention, self-directed exercise remained low (123 minutes/week) and was not significantly different between-groups (p=0.37). HIIT improved VO_{2peak} by 3.7 ml O_2/kg/min (p<0.001) compared to UC.[31] At 3-month follow-up, self-reported exercise increased significantly (average 263 minutes; p<0.001) from baseline but was not significantly different between groups (p=0.23).

Postintervention Effects

Table 1 reports the postintervention changes in CRF and psychosocial function. Compared to UC, HIIT significantly improved CRF [adjusted between-group mean difference=4.4; 95% CI, 1.5 to 7.3; *p*=0.003] and self-esteem (*p*=0.029) but not depression, anxiety, stress, or sleep quality. **Table 2** reports the postintervention changes in HRQoL. Compared to UC, HIIT caused significant improvements in MCS (*p*=0.034), vitality (*p*=0.001), social functioning (*p*=0.011), general health (*p*=0.016), and role-physical (*p*=0.048), and a borderline significant improvement in mental health (*p*=0.054). No significant effects were noted for physical functioning, bodily pain, role-emotional, or PCS.

3-month Follow-up Effects

Table 3 reports the 3-month follow-up changes in CRF and psychosocial function. A significant HIIT-related improvement in CRF (*p*=0.031) was observed. **Table 4** reports the HRQoL values at 3-month follow-up. A significant HIIT-related improvement in vitality (*p*=0.015) was observed.

Exploratory Mediation

Table 5 reports the linear regression analyses for change in VO_{2peak} as a potential mediator of changes in PROs. At postintervention, we found evidence that changes in VO_{2peak} may mediate changes in MCS ($a \times b = 2.6$; 95% CI: 0.2 to 5.8; p<0.05), vitality ($a \times b = 2.6$; 95% CI: -0.1 to 5.4; p<0.10), and mental health ($a \times b = 2.7$; 95% CI: 0.7 to 5.6; p<0.05). At 3-month

follow-up, we found evidence that changes in VO_{2peak} may mediate changes in CRF ($a \times b$ = 2.5; 95% CI: -0.4 to 5.4; $p<0.10$) and vitality ($a \times b$ = 3.0; 95% CI: 0.02 to 6.4; $p<0.05$).

4.5 Discussion

The HITTS trial provides the first randomized evidence that HIIT causes significant and clinically meaningful improvements in CRF, psychosocial function, and HRQoL in a population-based sample of TCS. Moreover, we found preliminary evidence of HIIT-related improvements in VO_{2peak} being highly associated with, and potentially mediating, the effects of the intervention on the mental components of HRQoL at postintervention as well as CRF and vitality at 3-month follow-up.

As hypothesized, HIIT caused a significant and clinically meaningful postintervention improvement in CRF. Although no previous exercise studies in TCS exist for comparison purposes, the HIIT-related improvement in CRF of 4.4 points exceeded the 3-point clinically important difference (CID) threshold for the FACT-F[49] and the standardized effect size of d=0.52 exceeded a medium effect size. Although indirectly compared, this effect size is larger than that reported in recent meta-analyses of aerobic exercise in other cancer survivor groups of 0.22-0.30.[24,25] The larger improvement in CRF observed in the HIITTS trial may be related to key HIIT-related changes in physiologic (e.g., increased mitochondrial biogenesis, oxidative capacity, or calcium cycling in the active skeletal muscle[50-53]) and psychosocial (e.g., self-efficacy[54]) variables which may not be as greatly influenced by the moderate-intensity continuous aerobic exercise most often prescribed in other exercise oncology research.[24,25] Although speculative, this explanation is partially supported by the agreement between our findings (i.e., changes in VO_{2peak} may have partially mediated changes in CRF) and others[51] who reported that changes in VO_{2peak} were highly correlated with changes in markers of mitochondrial biogenesis ($r=0.72$; $p<0.01$).

The improved CRF may also be related to the anti-inflammatory effects of HIIT.[55,56] Orre et al. reported that CRF is associated with low grade inflammation in TCS,[57] and it is interesting to speculate that the observed HIIT-related reduction in CRF may be related to the significant decrease in high-sensitivity C-reactive protein we reported previously.[31] Randomized controlled trials are needed to directly compare HIIT exercise to moderate-intensity continuous exercise on CRF in cancer survivors.

HIIT elicited a small-to-moderate improvement in self-esteem (d=0.35). This magnitude of improvement is consistent with the findings of previous exercise oncology research in breast cancer patients (d=0.25-0.55)[32,58] as is the finding that change in VO_{2peak} does not mediate improvements in self-esteem.[32] The lack of evidence of statistical mediation by VO_{2peak} suggests that the observed improvement in self-esteem is more likely related to changes in psychosocial constructs such as self-efficacy, positive feedback from others, or a sense of accomplishment – as has been proposed in prostate cancer survivors.[54]

Contrary to the findings of some exercise trials within other cancer survivor groups,[26,27] HIIT did not improve other psychosocial outcomes, including depression, anxiety, stress, and sleep quality. The lack of HIIT-related improvements in these outcomes may be owing to the relatively normal psychosocial functioning of our participants at baseline. In two previous studies, exercise improved depression in breast cancer patients with elevated baseline depressive symptoms[59] and improved sleep quality in lymphoma patients who were poor sleepers at baseline.[60] However, our participants were already somewhat physically active at baseline, and observational evidence suggests that TCS who are physically active have a reduced risk of psychosocial distress (e.g., depression and anxiety).[21,30] Accordingly, future exercise-psychosocial function research should target subgroups of TCS with baseline psychosocial distress.

As hypothesized, HIIT caused postintervention improvements in multiple HRQoL domains, with moderate effects across mental health-related domains [i.e., MCS (*d*=0.49), vitality (*d*=0.61), social functioning (*d*=0.52), and mental health (*d*=0.41)] and small-to-moderate effects across physical health-related domains [i.e., role-physical (*d*=0.27) and general health (*d*=0.41)]; all of which exceeded the 2-3-point CID threshold for these scales.[61] The magnitude of HIIT-related improvement was comparable to, or slightly greater than, the improvement in *overall* HRQoL reported in other aerobic exercise trials of comparable duration in other survivor groups (SMD = 0.48; 95% CI, 0.16 to 0.81).[28,29] Interestingly, our findings indicated stronger and more consistent effects on *mental* HRQoL whereas previous exercise-oncology research has reported stronger and more consistent effects on *physical* HRQoL domains.[28,29] Moreover, the preliminary evidence that VO_{2peak} may have a role in mediating the improvements in *mental* HRQoL domains was also unexpected given that it is inconsistent with previous reports wherein changes in VO_{2peak} were strongly associated with improvements in *physical* but not *mental* HRQoL domains.[32,33] Several factors may contribute to this unique pattern of findings. First, this pattern of improvement is consistent with the nature of HRQoL deficits reported in TCS (i.e., greater *mental* HRQoL impairment than *physical*[10]). Another possibility may be related to the direct influence of CRF. As previously described, CRF is one of the most frequent and highly distressing symptoms in TCS,[8] and recent evidence suggests that CRF is a key mediator of physical fitness-related improvements in HRQoL in cancer survivors.[62] Furthermore, between 15% to 17% of TCS report feeling less masculine because of their surgery or treatments.[10,20,63] In addition to the pronounced fitness and biological benefits of HIIT, it is possible that by engaging in activities perceived to be physically demanding (i.e., masculine) TCS may achieve improved psychosocial function (e.g., self-esteem or sense of accomplishment) which, in turn, may augment multiple domains of mental HRQoL. Further research is required to assess the relative,

and perhaps synergistic, contributions of key mediators of the observed benefits of HIIT on HRQoL in TCS.

Interestingly, the HIIT-related improvements in CRF and vitality persisted at 3-month follow-up. The protracted and clinically meaningful[49,61] benefits of HIIT on these outcomes [i.e., CRF (d=0.43) and vitality (d=0.48)] is surprising given that exercise-oncology studies have typically shown a return to baseline values with the discontinuation of the intervention.[33,64] One notable difference in our trial is that our exercise crossover in the UC group did not occur until after the 3-month follow-up. Previous comparisons of longer term follow-up in exercise oncology trials have often been confounded by a postintervention crossover.[33,64,65] If replicated in future trials, HIIT may be a powerful intervention with longer term effects on the distressing fatigue-related symptoms in TCS.

Finally, our exploratory mediation analyses provided important context for the interpretation of the reported intervention effects. The HIIT-related improvement in VO_{2peak} (d=0.57) was strongly related to, and may have a mediating role in, the observed changes in half of our significantly-improved outcomes. These findings have direct exercise prescription implications for future intervention research, providing preliminary evidence that improving VO_{2peak} (or related physiological factors) may be important for improving CRF and related HRQoL in TCS.

The overall strengths and limitations of the HIITTS trial have been described elsewhere.[31] Briefly, we conducted the first randomized aerobic exercise trial in TCS with virtually 100% adherence and trivial loss-to-follow-up that produced substantial improvements in VO_{2peak} and CVD risk. Additional strengths in the present report include providing the first randomized data examining the effects of HIIT on PROs in TCS, the use of well-validated measures of PROs, the collection of 3-month follow-up data unconfounded by an exercise crossover, and the

examination of VO_{2peak} as a mediator of changes in PROs. Previously reported limitations of the overall trial include no outcome assessor blinding, the low initial response rate, a limited follow-up period, and lack of clinical CV event endpoints.[31] Additional limitations related to our PRO findings include (1) the smaller sample size and loss-to-follow-up at 3-months, (2) the recruitment of TCS without specific psychosocial or HRQoL deficits, and (3) the lack of an attention control comparison group.

In conclusion, the HIITTS trial provides the first randomized evidence that a 12-week HIIT program causes significant, meaningful, and in some cases persistent improvements in CRF, self-esteem, and multiple domains of mental and physical HRQoL in TCS. HIIT caused larger and more consistent improvements in mental HRQoL than previously achieved with moderate continuous exercise in various cancer survivor groups. Moreover, and notably, the effects on fatigue-related outcomes persisted at 3-month follow-up. Furthermore, improvements in VO_{2peak} were highly related to, and may have partially mediated, many of the improvements in the PROs. Finally, the near-perfect adherence to our HIIT prescription suggests that HIIT is a well-tolerated and time efficient exercise option for TCS. Together, these findings suggest that engagement in regular HIIT exercise is safe, feasible, and effective at improving CRF and HRQoL and that improving VO_{2peak} is an important therapeutic target for improving PROs in TCS.

4.6 References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics (2014): **Canadian cancer statistics 2014**, in Society CC (ed). Toronto, ON., pp 132.

2. Siegel R, Naishadham D, Jemal A (2013): **Cancer statistics 2013**. *CA Cancer J Clin* 63:11-30.

3. Feldman DR, Bosl GJ, Sheinfeld J*, et al.* (2008): **Medical treatment of advanced testicular cancer**. *JAMA* 299:672-84.

4. Abouassaly R, Fossa SD, Giwercman A*, et al.* (2011): **Sequelae of treatment in long-term survivors of testis cancer**. *Eur Urol* 60:516-26.

5. Dahl AA, Haaland CF, Mykletun A*, et al.* (2005): **Study of anxiety disorder and depression in long-term survivors of testicular cancer**. *J Clin Oncol* 23:2389-95.

6. Fossa SD, Dahl AA, Loge JH (2003): **Fatigue, anxiety, and depression in long-term survivors of testicular cancer**. *J Clin Oncol* 21:1249-54.

7. Haugnes HS, Bosl GJ, Boer H*, et al.* (2012): **Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up**. *J Clin Oncol* 30:3752-63.

8. Oechsle K, Hartmann M, Mehnert A*, et al.* (2016): **Symptom burden in long-term germ cell tumor survivors**. *Support Care Cancer* 24:2243-50.

9. Orre IJ, Fossa SD, Murison R*, et al.* (2008): **Chronic cancer-related fatigue in long-term survivors of testicular cancer**. *J Psychosom Res* 64:363-71.

10. Smith AB, Butow P, Olver I*, et al.* (2016): **The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study**. *J Cancer Surviv* 10:223-33.

11. Sprauten M, Haugnes HS, Brydøy M*, et al.* (2015): **Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: increasing prevalence and risk factors**. *Ann Oncol* 26:2133-2140.

12. Mock V, Atkinson A, Barsevick A*, et al.* (2000): **NCCN practice guidelines for cancer-related fatigue**. *Oncology* 14:151-61.

13. Fossa SD, Dahl AA, Haaland CF (1999): **Health-related quality of life in patients treated for testicular cancer**. *Curr Opin Urol* 9:425-9.

14. Joly F, Heron JF, Kalusinski L*, et al.* (2002): **Quality of life in long-term survivors of testicular cancer: a population-based case-control study**. *J Clin Oncol* 20:73-80.

15. Rossen PB, Pedersen AF, Zachariae R*, et al.* (2009): **Health-related quality of life in long-term survivors of testicular cancer**. *J Clin Oncol* 27:5993-9.

16. Kim C, McGlynn KA, McCorkle R*, et al.* (2011): **Quality of life among testicular cancer survivors: a case-control study in the United States**. *Qual Life Res* 20:1629-37.

17. Vidrine DJ, Hoekstra-Weebers JE, Hoekstra HJ*, et al.* (2010): **The effects of testicular cancer treatment on health-related quality of life**. *Urology* 75:636-41.

18. Mykletun A, Dahl AA, Haaland CF*, et al.* (2005): **Side effects and cancer-related stress determine quality of life in long-term survivors of testicular cancer**. *J Clin Oncol* 23:3061-8.

19. Takamochi K, Nagai K, Yoshida J*, et al.* (2000): **The role of computed tomographic scanning in diagnosing mediastinal node involvement in non-small cell lung cancer**. *J Thorac Cardiovasc Surg* 119:1135-40.

20. van Basten JP, Jonker-Pool G, van Driel MF*, et al.* (1996): **Fantasies and facts of the testes**. *Br J Urol* 78:756-62.

21. Fung C, Sesso HD, Williams AM*, et al.* (2017): **Multi-institutional assessment of adverse health outcomes among north american testicular cancer survivors after modern cisplatin-based chemotherapy**. *J Clin Oncol* 35:1211-1222.

22. Nigam M, Aschebrook-Kilfoy B, Shikanov S*, et al.* (2015): **Increasing incidence of testicular cancer in the United States and Europe between 1992 and 2009**. *World J Urol* 33:623-31.

23. Le Cornet C, Lortet-Tieulent J, Forman D*, et al.* (2014): **Testicular cancer incidence to rise by 25% by 2025 in Europe? Model-based predictions in 40 countries using population-based registry data**. *Eur J Cancer* 50:831-9.

24. Mustian KM, Alfano CM, Heckler C*, et al.* (2017): **Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis**. *JAMA Oncol*.

25. Tian L, Lu HJ, Lin L*, et al.* (2016): **Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials**. *Support Care Cancer* 24:969-83.

26. Brown JC, Huedo-Medina TB, Pescatello LS*, et al.* (2012): **The efficacy of exercise in reducing depressive symptoms among cancer survivors: a meta-analysis**. *PLoS One* 7:e30955.

27. Craft LL, Vaniterson EH, Helenowski IB*, et al.* (2012): **Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis**. *Cancer Epidemiol Biomarkers Prev* 21:3-19.

28. Gerritsen JK, Vincent AJ (2016): **Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials**. *Br J Sports Med* 50:796-803.

29. Mishra SI, Scherer RW, Snyder C*, et al.* (2014): **Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis**. *Oncol Nurs Forum* 41:E326-42.

30. Thorsen L, Nystad W, Stigum H*, et al.* (2005): **The association between self-reported physical activity and prevalence of depression and anxiety disorder in long-term survivors of testicular cancer and men in a general population sample**. *Support Care Cancer* 13:637-46.

31. Adams SC, DeLorey DS, Davenport MH*, et al.* (2017): **Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: a phase II randomized controlled trial**. *Cancer* in press.

32. Courneya KS, Mackey JR, Bell GJ*, et al.* (2003): **Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes**. *J Clin Oncol* 21:1660-8.

33. Courneya KS, Sellar CM, Stevinson C*, et al.* (2009): **Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients**. *J Clin Oncol* 27:4605-12.

34. Rognmo O, Hetland E, Helgerud J*, et al.* (2004): **High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease**. *Eur J Cardiovasc Prev Rehabil* 11:216-222.

35. Mezzani A, Hamm LF, Jones AM*, et al.* (2013): **Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation**. *Eur J Prev Cardiol* 20:442-67.

36. Godin G, Shephard RJ (1985): **A simple method to assess exercise behavior in the community**. *Can J Appl Sport Sci* 10:141-6.

37. Schmitz KH, Courneya KS, Matthews C*, et al.* (2010): **American College of Sports Medicine roundtable on exercise guidelines for cancer survivors**. *Med Sci Sports Exerc* 42:1409-26.

38. Yellen SB, Cella DF, Webster K*, et al.* (1997): **Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system**. *J Pain Symptom Manage* 13:63-74.

39. Kohout FJ, Berkman LF, Evans DA*, et al.* (1993): **Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index**. *J Aging Health* 5:179-93.

40. Spielberger CD, Gorsuch RL, Lushene R*, et al.* (1983): **Manual for the state-trait anxiety inventory**. Palo Alto, CA, *Consulting Psychologists Press.*,

41. Cohen S, Kamarck T, Mermelstein R (1983): **A global measure of perceived stress**. *J Health Soc Behav* 24:385-96.

42. Rosenberg M (1965): **Society and the adolescent self-image**. NJ, *Princeton university press Princeton*,

43. Beck SL, Schwartz AL, Towsley G*, et al.* (2004): **Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients**. *J Pain Symptom Manage* 27:140-8.

44. Ware JE, Kosinski M, Bjorner JB*, et al.* (2008): **User's manual for the SF-36v2 Health Survey**, *Quality Metric.*,

45. Borm GF, Fransen J, Lemmens WA (2007): **A simple sample size formula for analysis of covariance in randomized clinical trials**. *J Clin Epidemiol* 60:1234-8.

46. MacKinnon DP (2008): **Introduction to statistical mediation analysis**. New York, *Routledge.*, pp. 477.

47. Hayes AF (2013): **Introduction to mediation, moderation, and conditional process analysis: a regression-based approach**, *Guilford Press.*,

48. Preacher KJ, Hayes AF (2004): **SPSS and SAS procedures for estimating indirect effects in simple mediation models**. *Behav Res Methods Instrum Comput* 36:717-31.

49. Cella D, Eton DT, Lai JS*, et al.* (2002): **Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales**. *J Pain Symptom Manage* 24:547-61.

50. Tjonna AE, Lee SJ, Rognmo O*, et al.* (2008): **Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study**. *Circulation* 118:346-54.

51. Wisloff U, Stoylen A, Loennechen JP*, et al.* (2007): **Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study**. *Circulation* 115:3086-94.

52. Daussin FN, Zoll J, Dufour SP*, et al.* (2008): **Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects**. *Am J Physiol Regul Integr Comp Physiol* 295:R264-72.

53. Fu TC, Wang CH, Lin PS*, et al.* (2013): **Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure**. *Int J Cardiol* 167:41-50.

54. Cormie P, Galvao DA, Spry N*, et al.* (2015): **Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial**. *BJU Int* 115:256-66.

55. Bower JE (2007): **Cancer-related fatigue: links with inflammation in cancer patients and survivors**. *Brain Behav Immun* 21:863-71.

56. Bower JE, Lamkin DM (2013): **Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications**. *Brain Behav Immun* 30 Suppl:S48-57.

57. Orre IJ, Murison R, Dahl AA*, et al.* (2009): **Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue**. *Brain Behav Immun* 23:868-74.

58. Courneya KS, Segal RJ, Mackey JR*, et al.* (2007): **Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial**. *J Clin Oncol* 25:4396-404.

59. Courneya KS, McKenzie DC, Gelmon K*, et al.* (2014): **A multicenter randomized trial of the effects of exercise dose and type on psychosocial distress in breast cancer patients undergoing chemotherapy**. *Cancer Epidemiol Biomarkers Prev* 23:857-64.

60. Courneya KS, Sellar CM, Trinh L*, et al.* (2012): **A randomized trial of aerobic exercise and sleep quality in lymphoma patients receiving chemotherapy or no treatments**. *Cancer Epidemiol Biomarkers Prev*.

61. Maruish ME (2011): **User's manual for the SF-36v2 Health Survey**, *Quality Metric Incorporated.*,

62. Buffart LM, De Backer IC, Schep G*, et al.* (2013): **Fatigue mediates the relationship between physical fitness and quality of life in cancer survivors**. *J Sci Med Sport* 16:99-104.

63. Rossen P, Pedersen AF, Zachariae R*, et al.* (2012): **Sexuality and body image in long-term survivors of testicular cancer**. *Eur J Cancer* 48:571-8.

64. Courneya KS, Segal RJ, Gelmon K*, et al.* (2007): **Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy**. *Cancer Epidemiol Biomarkers Prev* 16:2572-8.

65. Rogers LQ, Hopkins-Price P, Vicari S*, et al.* (2009): **Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects**. *Cancer Epidemiol Biomarkers Prev* 18:1410-8.

Figure Caption:

Figure 1: Participant flow through the HIITTS trial.

Legend: Dx: diagnosis; CVD: cardiovascular disease; ECG: electrocardiogram; Avg: average; PRO: patient-reported outcome.

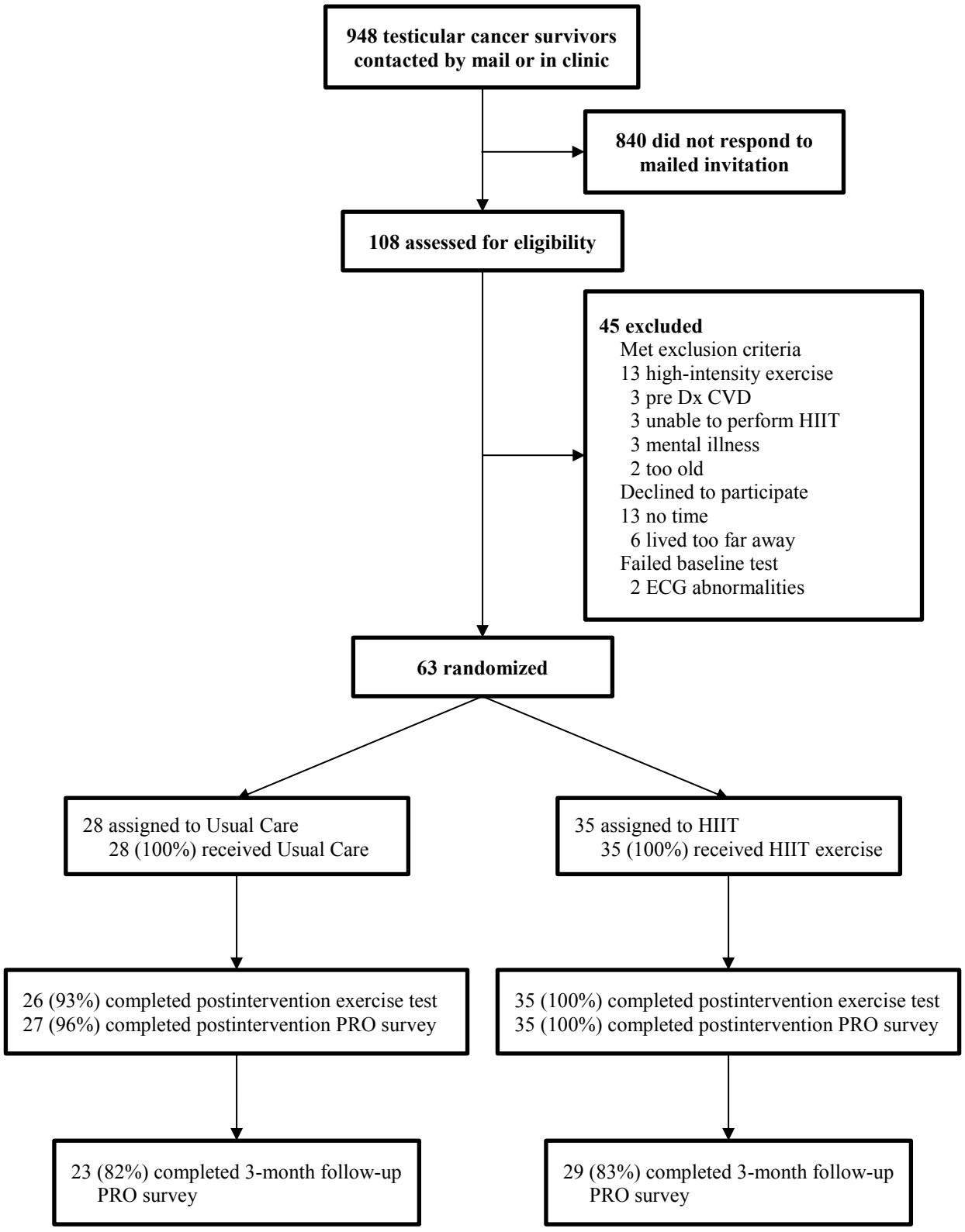

948 testicular cancer survivors contacted by mail or in clinic
840 did not respond to mailed invitation
108 assessed for eligibility
45 excluded
Met exclusion criteria
13 high-intensity exercise
3 pre Dx CVD
3 unable to perform HIIT
3 mental illness
2 too old
Declined to participate
13 no time
6 lived too far away
Failed baseline test
2 ECG abnormalities
63 randomized
28 assigned to Usual Care
28 (100%) received Usual Care
35 assigned to HIIT
35 (100%) received HIIT exercise
26 (93%) completed postintervention exercise test
27 (96%) completed postintervention PRO survey
35 (100%) completed postintervention exercise test
35 (100%) completed postintervention PRO survey
23 (82%) completed 3-month follow-up PRO survey
29 (83%) completed 3-month follow-up PRO survey

Table 1: Effects of 12 weeks of HIIT on CRF and psychosocial functioning at postintervention in TCS

			Baseline		Follow-up		Between-group difference			
Measure	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	***p***
CRF	Control	27	42.8	8.4	40.6	1.1	4.4	1.4	1.5 to 7.3	0.003
	Exercise	35	40.0	8.7	45.0	0.9				
Depression	Control	27	4.5	4.4	4.2	0.5	-0.2	0.7	-1.6 to 1.3	0.81
	Exercise	35	5.3	4.7	4.0	0.5				
Anxiety	Control	27	16.2	4.7	18.0	0.9	-1.6	1.2	-3.9 to 0.8	0.19
	Exercise	35	18.6	5.5	16.4	0.8				
Stress	Control	27	16.3	9.1	18.1	1.0	-1.7	1.3	-4.4 to 1.0	0.22
	Exercise	35	19.7	8.5	16.4	0.9				
Self-esteem	Control	27	36.0	4.8	33.7	0.6	1.8	0.8	0.2 to 3.4	0.029
	Exercise	35	32.5	5.5	35.5	0.5				
Sleep quality	Control	27	3.2	2.5	3.6	0.3	-0.6	0.4	-1.4 to 0.2	0.15
	Exercise	35	3.9	2.0	3.0	0.3				

Notes: SD: standard deviation; Adj.: adjusted; SE: standard error; CI: confidence interval; CRF: cancer-related fatigue

* all follow-up and between-group difference values were adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

Table 2: Effects of 12 weeks of HIIT on HRQoL at postintervention in TCS

			Baseline		Follow-up		Between-group difference			
Measure	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	***p***
Mental component score	Control	27	50.0	6.7	46.9	1.4	3.9	1.8	0.3 to 7.5	0.034
	Exercise	35	48.0	9.4	50.8	1.2				
Physical component score	Control	27	53.4	5.9	53.2	0.9	1.1	1.2	-1.2 to 3.5	0.34
	Exercise	35	51.0	7.3	54.3	0.8				
Physical functioning	Control	27	54.1	4.1	54.4	0.7	0.3	0.9	-1.5 to 2.1	0.77
	Exercise	35	52.6	6.9	54.7	0.6				
Role-physical	Control	27	53.9	5.3	52.3	0.8	2.2	1.1	0.02 to 4.3	0.048
	Exercise	35	50.0	10.9	54.5	0.7				
Bodily pain	Control	27	53.5	8.4	51.9	1.1	1.3	1.5	-1.8 to 4.3	0.41
	Exercise	35	50.7	7.0	53.2	1.0				
General health	Control	27	51.0	8.1	49.8	1.0	3.2	1.3	0.6 to 5.8	0.016
	Exercise	35	48.5	7.5	53.0	0.8				
Vitality	Control	27	52.9	9.6	50.2	1.2	5.4	1.6	2.2 to 8.5	0.001
	Exercise	35	51.2	8.1	55.5	1.0				
Social functioning	Control	27	44.2	5.0	42.1	0.9	3.3	1.3	0.8 to 5.8	0.011
	Exercise	35	43.0	7.6	45.4	0.8				
Role-emotional	Control	27	52.0	6.7	50.5	1.2	1.5	1.6	-1.7 to 4.7	0.36
	Exercise	35	49.5	9.0	52.0	1.0				
Mental health	Control	27	53.7	6.4	50.5	1.2	3.2	1.6	-0.1 to 6.5	0.054
	Exercise	35	50.9	9.1	53.7	1.1				

Notes: SD: standard deviation; Adj.: adjusted; SE: standard error; CI: confidence interval

* all follow-up and between-group difference values were adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

Table 3: Effects of 12 weeks of HIIT on CRF and psychosocial functioning at 3-month follow-up in TCS

			Baseline		Follow-up		Between-group difference			
Measure	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	***p***
CRF	Control	23	42.8	8.4	40.4	1.2	3.7	1.7	0.4 to 7.1	0.031
	Exercise	29	40.0	8.7	44.1	1.1				
Depression	Control	23	4.6	4.7	5.7	0.6	-1.2	0.9	-2.9 to 0.5	0.17
	Exercise	29	4.8	4.1	4.5	0.6				
Anxiety	Control	23	16.5	4.9	19.1	0.8	-1.3	1.1	-3.5 to 0.9	0.25
	Exercise	29	17.9	4.4	17.8	0.7				
Stress	Control	23	16.5	9.3	18.7	1.1	-2.4	1.5	-5.4 to 0.7	0.12
	Exercise	29	18.8	7.5	16.3	1.0				
Self-esteem	Control	23	35.7	5.0	33.7	0.6	1.0	0.8	-0.5 to 2.6	0.19
	Exercise	29	33.2	4.5	34.8	0.5				
Sleep	Control	23	3.4	2.6	3.6	0.4	-0.7	0.5	-1.8 to 0.4	0.19
	Exercise	29	3.9	2.1	2.8	0.4				

Notes: SD: standard deviation; Adj.: adjusted; SE: standard error; CI: confidence interval; CRF: cancer-related fatigue

* all follow-up and between-group difference values were adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

Table 4: Effects of 12 weeks of HIIT on HRQoL at 3-month follow-up in TCS

			Baseline		Follow-up		Between-group difference			
Measure	**Group**	**N**	**Mean**	**SD**	**Adj. Mean***	**SE**	**Adj. Mean***	**SE**	**95% CI**	***p***
Mental component score	Control	23	49.5	6.9	47.8	1.4	1.3	1.9	-2.5 to 5.0	0.51
	Exercise	29	49.3	7.5	49.1	1.2				
Physical component score	Control	23	53.2	6.1	52.2	1.1	2.2	1.5	-0.8 to 5.2	0.14
	Exercise	29	50.7	7.8	54.4	1.0				
Physical functioning	Control	23	53.7	4.3	53.2	1.0	0.8	1.3	-1.9 to 3.5	0.56
	Exercise	29	52.6	7.3	54.0	0.9				
Role-physical	Control	23	53.6	5.6	52.1	1.1	1.7	1.6	-1.4 to 4.8	0.28
	Exercise	29	50.2	11.1	53.7	1.0				
Bodily pain	Control	23	53.1	8.9	51.2	1.4	3.0	1.9	-0.8 to 6.7	0.12
	Exercise	29	50.5	6.8	54.1	1.2				
General health	Control	23	51.3	8.5	50.0	1.2	2.5	1.6	-0.7 to 5.6	0.12
	Exercise	29	49.4	7.6	52.1	1.0				
Vitality	Control	23	52.0	10.0	50.4	1.3	4.5	1.8	0.9 to 8.0	0.015
	Exercise	29	51.7	8.6	54.9	1.2				
Social functioning	Control	23	44.1	5.2	43.1	1.1	0.9	1.4	-1.9 to 3.8	0.51
	Exercise	29	43.8	6.8	44.0	0.9				
Role-emotional	Control	23	51.7	7.1	49.6	1.7	0.4	2.3	-4.1 to 5.0	0.85
	Exercise	29	50.4	7.8	50.0	1.5				
Mental health	Control	23	53.1	6.7	51.6	1.2	1.3	1.7	-2.0 to 4.6	0.44
	Exercise	29	52.2	7.0	52.9	1.1				

Notes: SD: standard deviation; Adj.: adjusted; SE: standard error; CI: confidence interval

* all follow-up and between-group difference values were adjusted for baseline value of the outcome, age, treatment exposure, and time since treatment.

Table 5: Statistical test of change in VO_{2peak} as a mediator of the effects of 12 weeks of HIIT on change in PROs in TCS

Outcome [c]	Total Effect[a]: Group → Δ Outcome (path c) Estimate (95% CI)	Direct Effect[a,b]: Group → Δ Outcome (path c') Estimate (95% CI)	Indirect Effect[a]: Group → Δ VO_{2peak} (path a) Estimate (95% CI)	Indirect Effect[a]: Δ VO_{2peak} → Outcome (path b) Estimate (95% CI)	Mediation Effect[a]: (a x b) Estimate (95% CI)
Postintervention					
CRF change	4.1 (1.2; 7.1) **	2.5 (-1.1; 6.1)	4.0 (2.5; 5.5) **	0.4 (-0.1;0.9)	1.6 (-0.7; 3.9)
Self-Esteem change	1.3 (-0.3; 3.0)	0.5 (-1.5; 2.5)	4.2 (2.6; 5.8) **	0.2 (-0.1; 0.5)	0.8 (-0.4; 2.1)
MCS change	3.7 (-0.04; 7.4) *	1.1 (-3.4; 5.6)	3.9 (2.5; 5.4) **	0.7 (-0.003; 1.3) *	**2.6 (0.2; 5.8)** **
Role-Physical change	1.5 (-0.4; 3.5)	1.2 (-1.2; 3.7)	4.0 (2.5; 5.6) **	0.1 (-0.3; 0.4)	0.3 (-1.0; 1.8)
General Health change	3.1 (0.4; 5.8) **	2.5 (-1.0; 5.9)	4.3 (2.8; 5.8) **	0.2 (-0.4; 0.7)	0.7 (-1.2; 2.8)
Vitality change	4.9 (1.7; 8.2) **	2.4 (-1.5; 6.2)	4.0 (2.5; 5.5) **	0.6 (0.1; 1.2) **	**2.6 (-0.1; 5.4)** *
Social Function change	2.7 (0.3; 5.2) **	1.5 (-1.5; 4.5)	4.0 (2.5; 5.5) **	0.3 (-0.1; 0.8)	1.2 (-0.6; 3.4)
Mental Health change	2.4 (-0.8; 5.5)	-0.4 (-4.1; 3.4)	4.0 (2.5; 5.5) **	0.7 (0.1; 1.2) **	**2.7 (0.7; 5.8)** **
3-month Follow-up					
CRF change	3.0 (-0.3; 6.3) *	0.5 (-3.5; 4.5)	4.4 (2.7; 6.1) **	0.6 (0.01; 1.1) **	**2.5 (-0.4; 5.4)** *
Vitality change	4.1 (0.5; 7.8) **	1.1 (-3.3; 5.6)	4.4 (2.7; 6.1) **	0.7 (0.1; 1.3) **	**3.0 (0.02; 6.4)** **

Notes: Δ: change; VO_{2peak}: peak cardiorespiratory fitness; CRF: cancer-related fatigue; MCS: mental component score

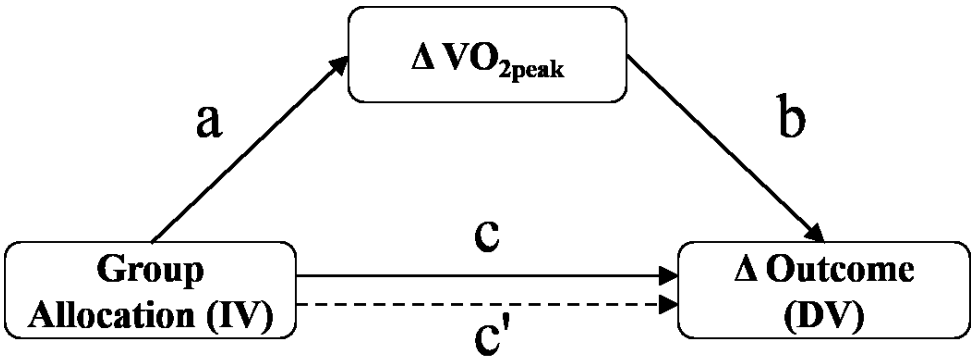
* $p \leq .10$; ** $p < 0.05$. Mediation effects with $p < 0.10$ are bolded.

[a] Beta-weights are adjusted for baseline value of the outcome, baseline value of the mediator (VO_{2peak}), age, treatment exposure, and time since treatment.

[b] Adjusted for the mediator (change in VO_{2peak}).

[c] Total effect in mediation analyses is slightly different than the ANCOVA analyses because 1 participant was eliminated from the mediation analyses due to missing VO_{2peak} at postintervention.

4.7 Online Supplement



Legend

Total effect (c) = a × b + c'

Mediated effect = a × b

Direct effect (c') = c – (a × b)

Figure 4.2: Basic mediation model

Chapter V - Discussion

5.1 Overview

The purpose of this dissertation was to examine the effects of HIIT on treatment-related risks (i.e., traditional and novel CVD risk factors, surrogate markers of cardiovascular and overall mortality, psychosocial dysfunction, and HRQoL impairment) in TCS. Previous exercise oncology research has established that aerobic exercise training is a safe, well-tolerated, and effective means to improve cardiovascular, psychosocial, and HRQoL outcomes in some cancer survivor groups; however, prior to this trial, only cross-sectional evidence existed supporting the association between aerobic physical activity and improved physical and mental health in TCS. The HIITTS trial is the first randomized controlled trial to demonstrate the causal effects of HIIT on improving cardiovascular health, CRF, and multiple aspects of HRQoL in TCS.

5.2 Summary of Findings

The major findings of the HIITTS trial have been discussed in Chapters 2 and 4. Briefly, 12 weeks of HIIT caused significant and potentially clinically meaningful improvements in traditional and novel CVD risk factors (**Chapter 2**), surrogate markers of cardiovascular and overall mortality (**Chapter 2**), CRF (**Chapter 4**), and both mental and physical aspects of HRQoL (**Chapter 4**). The key findings from Chapters 2 and 4 are briefly expanded upon below.

According to traditional CVD risk prediction metrics (e.g., blood pressure or lipid profile), there was evidence of increased CVD risk in 14% to 21% of our sample at baseline. However, analysis of novel CVD risk factors revealed evidence of increased CVD risk in over 80% of participants. This lack of traditional CVD risk factor sensitivity is consistent with previous cardio-oncology research (**Appendix D**), whereas the novel CVD factors we assessed

revealed the presence of a variety of subclinical cardiovascular injuries and pathologic states which may predispose the affected TCS to developing overt CVD and related events (e.g., myocardial infarction). Overall, these findings support the inclusion of novel CVD risk factors in the screening and long-term follow-up of TCS.

The concurrent improvements in established mechanisms and factors involved in atherogenesis (e.g., vascular wall stiffness and thickness, parasympathetic function, inflammation, and low-density lipoprotein) suggests that HIIT may be an effective therapeutic exposure capable of mitigating the risk of atherosclerotic disease development in TCS. Moreover, the magnitude of improvement in these outcomes often exceeded previously reported improvements in other cancer survivor groups (**Appendix E**) which may be suggestive of greater protective benefits associated with HIIT. The moderate-to-large HIIT-related improvements in VO_{2peak}, vascular structure and function (i.e., carotid intima-media thickness and central/ peripheral PWV), parasympathetic function (i.e., respiratory sinus arrhythmia and HRR), and blood-markers of inflammation and dyslipidemia were likely due to multiple factors including, but not limited to, the greater degree of physiologic stress imposed by our exercise prescription (i.e., HIIT vs. MCT)[1] and the specific nature of TCS's treatment-related deficits.[2-4]

Overall, HIIT caused a 20% reduction in the prevalence of total modifiable CVD risk factors reported at baseline. Moreover, the HIIT-related improvements across the surrogate markers of overall mortality (e.g., VO_{2peak}, intima-media thickness, and carotid-femoral PWV) were associated with relative risk reductions ranging from 10% to 30%. Previous evidence suggests that at least 40% of the mortality risk reduction associated with exercise is not accounted for by changes in traditional CVD risk prediction metrics;[5] and, the significant improvement in FRS achieved with just 12 weeks of HIIT is surprising because this composite score is based on traditional CVD risk factors which are known to be less sensitive to short-term

exercise training interventions.[6] Notably, the overall pattern of HIIT-related benefit was consistent with most of the major mechanisms of increased CVD development risks in TCS.[2,4,7-9] Together, these findings are important because they provide preliminary evidence that even short-term exposure to HIIT can positively influence multiple established pathways of CVD development and are suggestive that the adoption of regular HIIT-based exercise may be capable of reducing cardiovascular morbidity and mortality risks in TCS over the long-term.

Similarly, the pattern of HIIT-related improvements in psychosocial function and HRQoL was directly aligned with the nature of the specific deficits reported in TCS. More specifically, HIIT caused moderate-to-large improvements in PROs including CRF, self-esteem, and multiple HRQoL domains. Previous exercise oncology trials typically report small-to-moderate effects of exercise on PROs,[10-15] sometimes only in select subgroups of participants with poorer functioning at baseline,[16,17] and often describe greater *physical* than *mental* health related effects.[12,13] Although HIIT did improve *physical* aspects of HRQoL to a similar extent as reported in previous research, HIIT caused even greater improvements in *mental* HRQoL in TCS. Moreover, the persistent HIIT-related improvements in fatigue-related outcomes (i.e., CRF and vitality) at 3-month follow-up is rare in exercise oncology research;[18,19] and, if reproducible in TCS or other cancer survivor groups, these findings would provide strong support for the inclusion of HIIT exercise as critical adjuvant treatment strategy for at-risk or affected cancer patients and survivors.

We also found preliminary evidence that changes in VO_{2peak} (or physiological and psychosocial factors closely related to it) may be important mediators of psychosocial and mental HRQoL outcomes in TCS. Overall, there was statistical evidence that changes in VO_{2peak} partially mediated three of the eight PROs which significantly improved at postintervention and accounted for between 53% and 100% of the variance in their improvements. There was further statistical

evidence that changes in VO_{2peak} partially mediated changes in both significantly improved fatigue-related outcomes at 3-month follow-up, accounting for between 73% and 83% of the variance in the improvements. These findings are somewhat inconsistent with previous exercise oncology research. An RCT of aerobic exercise training in 53 postmenopausal breast cancer survivors found evidence that changes in VO_{2peak} mediated changes in global quality of life and physical function-related quality of life but not self-esteem.[20] Similarly, in an RCT involving 122 lymphoma patients randomized to aerobic exercise training and usual care, Courneya et al.[18] reported that changes in VO_{2peak} mediated changes in physical function but had little-to-no mediation effect on other aspects of psychosocial function (e.g., fatigue and happiness). Interestingly, recent findings from an uncontrolled trial of combined high-intensity resistance and aerobic interval exercise training in a group of 119 mixed cancer survivors identified CRF as an important mediator of physical fitness-related improvements in HRQoL in cancer survivors.[21] However, they also reported that the physical facets of CRF more strongly mediated changes in HRQoL than mental facets.[21] These findings were partially reproduced in another RCT of combined resistance and aerobic exercise training vs. usual care in 57 prostate cancer patients undergoing androgen deprivation therapy – finding that both fatigue and walking speed mediated the intervention effects on general health of study participants.[22] More recently, an RCT involving 100 long-term prostate cancer survivors compared the effects of a 12 month intervention (i.e., 6 months of combined resistance and aerobic exercise training plus 6 months of home-based exercise training) vs. control (i.e., physical activity literature-only), finding that changes in lower body functional performance mediated the intervention effects on global quality of life, physical function and social function.[23] However, contrary to our findings and that of the two trials described previously, they reported no mediation effects for changes in aerobic fitness or fatigue on changes in HRQoL.[23] Several factors may account for these discrepant findings.

First, the factors which cause HRQoL deficits in cancer survivors are likely population-specific (e.g., functional limitations vs. anxiety) and differ according treatment-status (e.g., active treatment vs. post treatment). Second, these trials tested drastically different exercise interventions (e.g., HIIT or MCT or combined high-intensity resistance exercise and HIIT). These discrepancies notwithstanding, our findings have direct exercise prescription implications for future research, providing preliminary evidence that increasing VO_{2peak}, or closely related physiological/psychological factors, may be important intervention targets for improving CRF and related HRQoL deficits in TCS.

Overall these findings suggest that HIIT causes meaningful improvements in the specific psychosocial and HRQoL domains affected by TC and its treatments. Notably, these results were achieved against a background of reasonably normal psychosocial function and HRQoL. It is, therefore, possible that HIIT may elicit even greater benefits in more affected subgroups of TCS. Taken together, the capacity of HIIT to cause concurrent improvements in the major pathways of CVD risk (i.e., markers of atherosclerosis, arteriosclerosis, inflammation, and endothelial dysfunction), CRF, and HRQoL deficits strongly supports HIITS potential to improve long-term morbidity and mortality outcomes in TCS.

5.3 Future Research Directions

One important future research direction would involve assessing the impact of HIIT in more homogeneous subgroups of TCS. The HIIT protocol tested in this trial positively influenced many of the treatment-related deficits often experienced by TCS (i.e., CVD, CRF, and poor mental HRQoL). However, the mechanisms underpinning the effect of aerobic exercise training – in this case HIIT – on the unique symptom cluster or symptom profile of TCS are likely complex

and may be best characterized according to an emerging research paradigm in the field of exercise oncology called 'precision exercise therapy'.[24] The precision medicine approach to patient treatment requires the identification of distinct groupings of symptoms or phenotypic traits (i.e., phenogroups) that are predictive of outcomes (e.g., treatment-related risks or responsiveness to interventions).[24] Recently, several exercise oncology research groups have proposed the adoption of a 'precision medicine' or a 'precision exercise therapy' approach.[24-26] In line with this framework, future HIIT research in TCS should target subgroups of patients or survivors at high-risk of, or living with, any of the aforementioned population-specific deficits (e.g., CVD, CRF, or poor mental HRQoL). Furthermore, TCS share a number of traits with other cancer survivor groups such as increased atherosclerotic CVD risk (e.g., breast cancer survivors), mental HRQoL impairments (e.g., young adult cancer survivors), cisplatin exposure (e.g., genitourinary and gynecologic cancer survivors), and CRF (e.g., hematologic cancer survivors) which may make them similarly responsive to HIIT. Accordingly, it would also be reasonable to extend this line of HIIT-related research into other cancer patient and survivor groups with common risk- or symptom-profiles.

Building off our findings, another line of research would involve refining and improving upon our specific HIIT prescription. According to Saltin et al.,[27] HIIT exercise prescriptions can be modulated in four primary domains including intensity (i.e., average power output), interval ratio (i.e., the proportion of time spent at high vs. low exercise intensities), amplitude (i.e., the ratio of the work-rest intensity difference and the average intensity), and duration (i.e., the length of the interval periods). Additional HIIT protocol adjustments that may improve outcomes include extending the intervention period (e.g., 6 to 12 months), periodizing the prescription to include different HIIT permutations at different time points (e.g., Month 1 - 4:3 work-to-rest ratio; Month 2 - 1:2 work-to-rest ratio), and combining HIIT with other modalities of exercise

(e.g., HIIT + moderate-intensity continuous aerobic exercise or HIIT + resistance exercise training). However daunting, given the variable nature of the treatment-related deficits in TCS and other cancer survivor groups, it is theoretically possible that this type of superiority trial testing would need to be repeated in distinct patient/survivor subgroups to precisely match the exercise prescription to the population-specific deficits.

To date, the acceptance and uptake of exercise throughout the medical oncology community has been somewhat limited by the fact that the overwhelming majority of previous research in cancer survivors typically report small-to-moderate improvements in important survivor outcomes like CRF and HRQoL. As suggested in a recent editorial,[28] these modest exercise findings are likely an artifact of suboptimal exercise prescriptions – namely the over use of the 'traditional' aerobic exercise prescriptions (i.e., 12-15 weeks of MCT performed 2-3 days per week). Unlike the findings of studies based on traditional exercise prescription methods, HIIT caused moderate-to-large (and in some cases lasting) improvements in multiple cardiovascular, psychosocial, and HRQoL outcomes. However, as this was the first aerobic exercise intervention ever tested in TCS and one of the few tested in oncology, it would be prudent to take a 'step back' and conduct another form of superiority trial to determine if the specific HIIT protocol we tested is indeed more protective than other more established (i.e., MCT) or experimental (e.g., sprint interval training, non-linear aerobic exercise, and combination aerobic + resistance training) models of exercise training. This body of superiority trial-based research will be critically important to the field of exercise oncology in order to assess if the previously reported modest MCT-related benefits can be improved upon with a better quality of 'targeted' exercise prescriptions (i.e., phenogrouping-based precision exercise therapy).

The natural extension of the research streams outlined above involves assessing the effects of HIIT on 'targeted' treatment-specific or patient subgroup-specific outcomes. Drawing

from our findings, an example of this would be to assess the anti-antherogenic properties of HIIT across diverse groups of at-risk cancer patients and survivors. The effectiveness of aerobic exercise and physical activity to prevent and treat atherosclerotic CVD has long been recongnized.[29] With steadily increasing cancer survival rates, more cancer survivors are living long enough for delayed and late treatment effects (particularly CVD) to manifest and compete as the leading causes of death in these populations (e.g., breast cancer).[30] These long-term CVD risks are serious enough that a new subdiscipline of medical research called 'cardio-oncology' has emerged. Most of the cardio-oncology literature to date has focused on the potential effects of pharmacological interventions to decrease long-term cardiovascular morbidity and mortality risks in cancer survivors.[31,32] However, no pharmacologic intervention to date has demonstrated a similar breadth of cardioprotective benefits as we have in the HIITTS trial. As described throughout this dissertation, the simultaneous improvement in markers of atherosclerosis, arteriosclerosis, autonomic nervous system function, inflammation, and dyslipidemia suggests that HIIT may have potent anti-atherogenic properties and its capacity to mitigate CVD risks in cancer survivors merits further investigation.

Based on our data, another intriguing 'targeted' outcome for future HIIT-related research is the persistent VO_{2peak}-mediated improvement in CRF. Exercise studies in non-cancer and cancer populations typically do not report intervention-related improvements persisting once the formal intervention has been discontinued.[18,19] In fact, this 'reversibility' is one of the basic tenets of exercise prescription and predictably occurs with most exercise training-related adaptations.[33] In exercise oncology research, another important confounder of postintervention follow-up data is the use of cross-over designs wherein control group participants are given the opportunity to experience some form of the intervention immediately following the postintervention assessment.[18,19,34] Overall, the combined influence of natural detraining (i.e., reversibility) and

cross-over control group contamination make it less likely that the affected trials will be able to detect significant, persistent between-group differences. In the HIITTS trial, the persistent improvement in CRF may be partially explained by the combination of no control group cross-over and an increase in self-reported physical activity between postintervention and 3-month follow-up (which did not differ between groups). Other potential contributors to the persistent HIIT-related improvements in fatigue-related outcomes are described below.

First, CRF is a multifactorial phenomenon driven by physical, cognitive, and emotional deficits.[35] The modest and short-term exercise-related improvements in CRF reported previously may be due to a discordance between the population-specific nature of CRF's development (i.e., differences in the causes of CRF and how the contributing factors to CRF interact) and the nature of the intervention-specific benefits (i.e., smaller and primarily physical HRQoL-based caused by MCT).[12,13] In the case of TCS, specific interactions between their treatment-induced cardiovascular impairments, psychosocial distress, and mental HRQoL deficits likely all contribute to the CRF they experience. In our study, HIIT caused moderate-to-large and clinically relevant improvements in VO_{2peak}, self-esteem, and mental HRQoL. Individually, any of these factors may partially account for the improvement in CRF. Improvements in VO_{2peak} reflect a systemic improvement in the O_2 diffusion cascade which is typically attributed to improved cardiac output.[36] However, in clinical populations with specific cardiovascular deficits, VO_{2peak} improvements may also be related to increased pulmonary gas exchange, red blood cell content, and skeletal muscle cell adaptations (e.g., mitochondrial biogenesis).[33] In fact, our exploratory mediation analysis suggested that VO_{2peak} may be a key mediator of the persistent improvement in CRF at 3-month follow-up (explaining between 73% and 83% of the variance in CRF). It is interesting to speculate that this association may partially be explained by improvements in submaximal exercise capacity (e.g., increased ventilatory threshold – potentially related to HIIT-

related increases in muscle mitochondrial content or enhanced substrate utilization and turn over).[36] The residual 17% to 27% variance in 3-month CRF may partially be explained by the HIIT-mediated improvements in psychosocial function and mental HRQoL. Indeed, as discussed in **Chapter 4**, evidence suggests that TCS may bolster their psychosocial health (e.g., sense of accomplishment or self-esteem) by engaging in physically demanding activities they perceive to be more masculine (a known deficit in TCS);[37-39] and, the resulting improvements in psychosocial function may in turn drive improvements in mental HRQoL. Further research is required to unravel the specific combination of factors that cause CRF and explain the HIIT-related improvements in TCS and other cancer survivor groups. Importantly, given the complexity of this research, future exercise-CRF research efforts would likely benefit from the adoption of a phenogrouping-precision exercise therapy approach.

Finally, the HIITTS trial generated robust phase II data upon which a phase III investigation of the effects of HIIT on cardiovascular morbidity and mortality outcomes may be developed. Incorporating many of the themes developed throughout this section, the following paragraph provides an outline a proposed phase III extension of the HIITTS trial (i.e., HIITTS 2.0). The HIITTS 2.0 trial will be a two-armed, multi-centre, RCT assessing the impact of HIIT on cardiovascular morbidity and mortality outcomes in TCS. ***Population Selection***: HIITTS 2.0 will target radiotherapy- and chemotherapy-treated TCS at high-risk of CVD. ***Eligibility Criteria***: Men between the ages of 18 and 50 who recently completed (<6 months) adjuvant therapy for a histologically confirmed diagnosis of TC will be eligible. ***Exclusion Criteria***: Individuals will be excluded if they meet any of the following criteria: i) a confirmed pre-cancer diagnosis of CVD (e.g., hypertension or metabolic syndrome – or history of medication use), ii) any psychiatric condition impairing their ability to perform HIIT, iii) regular participation in high-intensity aerobic exercise (>1 session per week), and iv) inability to complete the first two stages of a

maximal cardiopulmonary exercise test. ***Intervention/Control Supervision & Follow-up Periods***: To ensure adequate time to reduce the risks and track the incidence of long-term cardiovascular morbidity (e.g., myocardial infarction) and mortality events, the duration of intervention/control group engagement and follow-up periods will be extended. The best available model for such a trial can be found in the Colon Health and Life-Long Exercise Change Trial (CO.21).[40] In line with this model, the exercise intervention and control groups' participation will begin fully supervised and be progressively scaled down over a 3 year period (i.e., 6 months of full supervision, 6 months of partial supervision, and 2 years of supported home- or facility-based exercise). Participant assessments will also be progressively scaled down, but more gradually, over a 15-year follow-up period (i.e., full fitness, cardiovascular, and psychosocial screening at baseline, 6 months, 12 months, 24 months, and 36 months – beyond 36 months, only medical record screening for cardiovascular morbidity and mortality events will be tracked). ***Intervention & Control Conditions***: HIITTS 2.0 will test the same HIIT protocol as was used in the HIITTS trial. In addition to supervised exercise, the intervention group will also receive structured behavioural support and physical activity education information. To provide an adequate attention-control condition, HIITTS 2.0 control group participants will receive supplemental physical activity education information and be asked to perform a structured low-intensity stretching program (i.e., 3 days/week and 35 minutes per session). ***Outcome Selection***: Ideally, the co-primary outcomes would include incidence of cardiovascular morbidity and overall mortality. Cardiovascular morbidity events will include any medically diagnosed cardiopulmonary condition (e.g., hypertension, metabolic syndrome, Raynaud's phenomenon, or myocardial infarction). Moreover, the predictive value of surrogate markers will be assessed and used to establish specific risk factor thresholds for increased risks of the co-primary outcomes. In addition to the surrogate markers used in HIITTS trial, coronary artery calcium score, body

composition (i.e., lean body mass and fat mass), and additional markers of renal impairment (e.g., Glomerular filtration rate, 24 hour albumin excretion), endothelial activation (e.g., von Willebrand factor, plasminogen activator inhibitor type 1 antigen, and tissue-type plasminogen activator antigen), and inflammation/atherosclerosis (e.g., oxidized LDL, TNF-α, leucocyte count) will also be included. Finally, 3D ultrasonography will be used to quantify and track changes in carotid plaque volume over time. ***Outcomes & Impact***: Demonstrating that HIIT significantly reduces the risk of cardiovascular morbidity and mortality in TCS would directly inform clinical and surveillance practices within this vulnerable and high-risk cancer survivor population. Moreover, these findings would help substantiate the development cost-effective community-/clinic-based interventions to treat these preventable forms of cancer-related CVD. If successful, these survivorship programs would help reduce the financial burden of these diseases on the Canadian health care system. The practical implications and challenges of translating these findings into practice are described below.

5.4 Practical Implications

Despite this being the first aerobic exercise RCT to assess CVD risks and PROs in this population, our findings are directly aligned with previous research which found greater levels of aerobic physical activity (i.e., vigorous-intensity and high-volume) to be protective against a broad range of adverse physical and psychosocial health outcomes in TCS.[41-43] Together, these findings provide provocative biological/mental/emotional signals (i.e., regular HIIT may simultaneously improve CVD risk and psychosocial/HRQoL outcomes in TCS) to guide future research and serve as a starting point for the development of aerobic exercise training guidelines for TCS. If these findings are confirmed, the eventual translation of this knowledge into practice has several advantages and challenges which merit further discussion.

The overarching goal of exercise oncology research is to protect patients living with and after a cancer diagnosis. This protection encompasses all aspects of primary (e.g., improving cancer-specific survival) and secondary (e.g., preventing late effects of treatment) outcomes. In the context of TCS, there is little room to improve upon the current cancer survival rates (≈97%). Although exercise may play a role in controlling acute treatment-related injuries,[44] the more promising opportunity for intervention in TCS likely occurs in the posttreatment setting.[45] One of the obvious practical challenges associated with implementing any behavioural intervention, especially a physically demanding one, is poor intervention compliance and adherence. However, compared to the *active-treatment* setting, *posttreatment* is the optimal intervention setting in TCS because: i) intervention participation will be less confounded by treatment-related symptoms (e.g., nausea and CRF); ii) having just confronted their mortality, TCS may be more inclined to prioritize and engage in protective health behaviours; and, iii) the need for rigorous risk management and complete exercise supervision is reduced.

Notably, cancer survivorship programs (e.g., LIVESTRONG at the YMCA)[46,47] are being developed in communities across North America and provide free or inexpensive assess to facilities and specialized training equipment (e.g., treadmills and heart rate monitors) not otherwise available to TCS – especially for those who were disadvantaged financially during their extended treatment-related absences from work. Moreover, many of these survivorship services are supervised by cancer-experienced exercise professionals who can assist TCS with tasks that exercise-naïve TCS may not be able to manage on their own (e.g., setting up and adapting HIIT exercise prescriptions). However, despite the perceived benefits of these community-based services, developing effective programs and services that attract and retain male cancer survivors (e.g., TCS) remains a major challenge in translating these findings into practice. Indeed, preliminary evidence suggests that the users of these community-based exercise

support services are primarily female (70% to 82%) and over half are breast cancer survivors (52% to 56%).[46,47] To date, only one randomized comparison of LIVESTRONG at the YMCA users vs. non-users has been generated and included data on a mixed group of 186 cancer patients and survivors.[46] The exercise intervention consisted of 2x 90-minute exercise sessions per week of combined aerobic and resistance exercise (following the 'traditional' ACSM guidelines) for 12 weeks. Predictably, the results from this trial are consistent with the null-to-modest effects reported by most other exercise oncology research including improvements in self-reported physical activity ($p<0.001$), 6-minute walk distance ($p=0.004$), and general quality of life ($p=0.039$).[46] Unfortunately, the lack of exercise-related improvements in fatigue, body composition (i.e., body mass index, lean body mass, percent body fat, and bone mineral density), insulin, or CRP levels[46] reinforces the general misconception that exercise in incapable of causing meaningful improvements in important patient and survivor outcomes.

Overcoming these challenges will require the coordinated efforts of practitioners across all tiers of patient care and follow-up (i.e., primary care professionals to tertiary care program leaders and exercise specialists within the community). It is imperative that patient engagement begin within the primary care setting[48] and continue throughout patients' transition back into the community. To achieve this, the first step will require ensuring that the compelling findings from rigorous research trials, like the HIITTS trial, be appropriately disseminated across echelons of patient care and survivorship services. With the right information, primary care professionals could more confidently educate their patients on the therapeutic benefits of exercise and encourage their participation in it; after-care professionals in outpatient surveillance clinics would be better positioned to make informed recommendations to their patients about the specific types of support services they should seek out; and, community-based non-profit support providers and exercise professionals could develop more effective and engaging exercise prescriptions to

address the specific risks and deficits of distinct groups of cancer survivors (e.g., TCS or males). Once this infrastructure has been developed, collaborative partnerships between patient advocacy groups and these non-profit support services will be required to effectively promote these specialized support services to their intended audience. Long-term, if these results are confirmed and community-based programs are properly implemented, HIIT-related reductions in cardiovascular morbidity and mortality risk, psychosocial dysfunction, and HRQoL impairment in TCS (and other survivor groups) may help control or reduce the rising costs associated with treating potentially preventable forms of cancer-related CVD and psychological distress.

5.5 Strengths and Limitations

The major strengths and limitations for the HIITTS trial have been described briefly in Chapters 2 and 4. Overall, the HIITTS trial tested the first-ever aerobic exercise intervention in a novel and understudied cancer survivor population, incorporated rigorous participant assessment and exercise prescription methods, had nearly perfect participant compliance, and had virtually no loss to follow-up at our primary postintervention timepoint.

One of the greatest strengths of the HIITTS trial was its novelty. Beginning with our target population, there are approximately 9,000 new TC diagnoses in North America annually.[49,50] Given their ≈97% survival rate, conservative estimates (using a 51-year life expectancy, a disability weight of 0.09, and not accounting for the confounding effects of CVD development) suggest that TC-related morbidity and mortality accounts for 40,071 years of life affected and 13,770 years of life lost annually.[51] Extrapolated over the limited average 'time since diagnosis' in the HIITTS trial participants (i.e., 8 years) these numbers increase to 320,568 years of life affected and 110,160 years of life lost. The HIITTS trial provided the first

compelling data that HIIT may be effective in reducing the long-term disease-/treatment-burden experienced by TCS and, therein, the overall burden of TC on society.

Another novel feature of the HIITTS trial was our study design. Compared to the associations explored in previous cross-sectional and prospective study designs, our use of a RCT design provides the most rigorous evidence to date of a causal relationship between exercise and important outcomes of interest in TCS. A third novel feature of the HIITTS trial was our intervention. In many populations (including TCS), one of the greatest barriers to exercise participation is a lack of time. Most other aerobic exercise trials in oncology have tested the effects of a 'traditional' or 'standard' dose of aerobic exercise (i.e., ≥150 minutes of MCT for 12 to 24 weeks) resulting in - *at best* - modest improvements in cardiovascular, psychosocial, and HRQoL outcomes. However, our HIIT intervention required just 2/3^{rds} of the total training time and resulted in greater improvements. Moreover, the specific HIIT protocol we used (i.e., 4:3 work-to-rest intervals) has demonstrated efficacy in improving patient outcomes in other clinical CVD populations (e.g., heart failure),[6,52] and our findings contribute to a growing body of evidence supporting the overall effectiveness of this specific modality of aerobic exercise.

Another major strength of the HIITTS trial is the rigor of our assessment methods. To our knowledge, the HIITTS trial represents the most comprehensive assessment of CVD risk in any cancer survivor group to date. The inclusion of both traditional and novel surrogate markers of CVD risk can inform the expansion of current CVD risk screening practices in TCS. Moreover, our exercise and resting test protocols adhered to best practice guidelines[53-62] and, whenever possible, included gold-standard measurement techniques (e.g., maximal cardiorespiratory exercise tests, carotid intima-media thickness and plaque scan, and central PWV) and well-validated PRO inventories (e.g., SF-36 and FACT-F).

A further strength of the HIITTS trial is the care taken to ensure our intervention was delivered with limited contamination and with the intended dose. Throughout the intervention/ observation period, we limited the likelihood of behavioural contamination by verifying and tracking participant compliance with non-protocol diet and exercise behaviours. Furthermore, each participant's progress through the HIIT intervention was documented carefully at every session, and the exercise prescriptions were regularly adjusted to ensure the proper dose of exercise was being delivered. We also maintained flexible 7 day/week access to the training facility and provided an off-site training option to help accommodate the fluctuating scheduling and travel needs of our participants. More specifically, four participants living over 60 minutes away from the training facility were allowed a maximum of 1 external exercise session per week. Off-site sessions were only counted if participants returned continuous HR data for the session which was recorded using the specialized HR monitors we provided. Notably, our near perfect intervention attendance and achievement of target training intensities provide direct evidence of our success in supervising and supporting our participants.

Other notable strengths of the HIITTS trial include the lack contamination in our 3-month follow-up data (typically confounded by control group crossover) and the insight gained into the nature of the HIIT-related improvements in our PROs through our exploratory mediation analyses (i.e., likely related to changes VO_{2peak}).

Despite the strengths of the HIITS trial, several limiting factors should be carefully considered when interpreting the findings. First, there is an inherent self-selection bias associated with volunteering for exercise-based research. This bias usually results in the recruitment of a more select group of motivated participants into exercise trials, and our 11% participant response rate may be evidence of this bias. This recruitment bias can limit the generalizability of research

findings in that the feasibility of/adherence to the intervention and the results achieved may not be representative of the entire population (e.g., less motivated TCS).

Another limitation of the HIITTS trial was the lack of outcome assessor blinding. Although this is not an uncommon limitation in single centre exercise trials with limited financial resources, it can impact the findings of a trial. More specifically, despite efforts to properly train outcome assessors to strictly adhere to testing protocols, it is possible that the awareness of group allocation can lead to subtle subconscious biases in how the outcome assessor interacts with and evaluates the participant. In the HIITTS trial, the randomization was not revealed to the outcome assessors until after the participant had completed baseline testing. However, the post-intervention testing and PRO data collection (postintervention and 3-month follow-up) was conducted by the same staff, and may have inadvertently introduced some degree of unintended bias in the evaluation process.

A related limitation was the lack of participant blinding. This is another common limitation in *efficacy*-based exercise research because, unlike pharmaceutical trials which use placebo-based control group deception techniques, it is impossible to blind participants of their group allocation (i.e., whether they are exercising or not). Notably, this is less of an issue for *superiority* trials wherein two or more intervention arms are being compared. Although the lack of participant blinding was less likely to confound our cardiovascular measures, it is possible that how the participants felt (e.g., disappointment) about their group allocation influenced their responses to the questions in the PRO inventories. One strategy to help overcome this issue is to include an attention control group (e.g., supervised stretching). The purpose of this attention control group is to ensure that the participants feel more included and cared for in the hopes that they will still perceive some degree of potential benefit from their participation and be less influenced by the fact that they are not in the intervention group. Another strategy, which we

employed in the HIITTS trial, is the use of a wait-list control design. This strategy involves disclosing to the participant that they will not receive the intervention during the actual observation period, but that they will be invited to complete some or all of the tested intervention once they have completed their postintervention assessments.

Unfortunately, given the smaller initial sample size, our 17% loss to follow-up at 3 months postintervention likely resulted in our being underpowered to detect significant between-group differences in our PROs at this timepoint. Moreover, compared to targeting TCS with specific CVD or emotional deficits, our unselected population-based sampling methods likely limited our capacity to detect meaningful intervention effects. One last major limitation of the HIITTS trial was our reliance on surrogate markers of cardiovascular morbidity and mortality instead hard clinical cardiovascular endpoints. Despite their inherent practical value and prognostic utility, surrogate markers are viewed with skepticism clinical oncology research – therein limiting the acceptance and uptake of our findings by clinicians.

5.6 Conclusions

Advances in anti-cancer therapies have led to dramatic improvements in cancer survival rates, and the specific advances in the treatment of TC are widely considered a modern medical-oncology success story. However, the improvement in overall mortality in TCS is limited by the emergence late-onset treatment-related CVD; and, the quality of TCS' survivorship is further compromised by treatment-related psychosocial and HRQoL deficits. This dissertation was developed to assess the impact of HIIT on mitigating the treatment-related cardiovascular, psychosocial, and HRQoL deficits experienced by TCS. Overall, this dissertation provides preliminary evidence that participation in regular HIIT exercise is effective at improving CVD

risk factors, surrogate markers of cardiovascular and overall mortality, psychosocial function, and HRQoL outcomes in TCS. Importantly, the remarkable consistency and greater magnitudes of improvement caused by HIIT across multiple outcomes suggests that HIIT exercise is well-aligned with the specific deficits experienced by TCS and merits further investigation in this and other cancer survivor groups. A phase III extension of the HIITTS trial is now required to confirm our findings and to generate the rigorous evidence required to facilitate the translation of this knowledge into practice.

5.7 References

1. Jones LW, Liang Y, Pituskin EN*, et al.* (2011): **Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis**. *Oncologist* 16:112-20.

2. Fung C, Fossa SD, Williams A*, et al.* (2015): **Long-term morbidity of testicular cancer treatment**. *Urol Clin North Am* 42:393-408.

3. Haugnes HS, Wethal T, Aass N*, et al.* (2010): **Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study**. *J Clin Oncol* 28:4649-57.

4. Nuver J, Smit AJ, Sleijfer DT*, et al.* (2004): **Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer**. *Eur J Cancer* 40:701-6.

5. Green DJ, O'Driscoll G, Joyner MJ*, et al.* (2008): **Exercise and cardiovascular risk reduction: time to update the rationale for exercise?** *J Appl Physiol* 105:766-8.

6. Kessler HS, Sisson SB, Short KR (2012): **The potential for high-intensity interval training to reduce cardiometabolic disease risk**. *Sports Med* 42:489-509.

7. Gandaglia G, Becker A, Trinh QD*, et al.* (2014): **Long-term survival in patients with germ cell testicular cancer: a population-based competing-risks regression analysis**. *Eur J Surg Oncol* 40:103-12.

8. Haugnes HS, Oldenburg J, Bremnes RM (2015): **Pulmonary and cardiovascular toxicity in long-term testicular cancer survivors**, Urol Oncol Semin Ori, *Elsevier*, pp 399-406.

9. Nuver J, Smit AJ, Wolffenbuttel BH*, et al.* (2005): **The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer**. *J Clin Oncol* 23:3718-25.

10. Brown JC, Huedo-Medina TB, Pescatello LS*, et al.* (2012): **The efficacy of exercise in reducing depressive symptoms among cancer survivors: a meta-analysis**. *PLoS One* 7:e30955.

11. Craft LL, Vaniterson EH, Helenowski IB*, et al.* (2012): **Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis**. *Cancer Epidemiol Biomarkers Prev* 21:3-19.

12. Gerritsen JK, Vincent AJ (2016): **Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials**. *Br J Sports Med* 50:796-803.

13. Mishra SI, Scherer RW, Snyder C*, et al.* (2014): **Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis**. *Oncol Nurs Forum* 41:E326-42.

14. Mustian KM, Alfano CM, Heckler C*, et al.* (2017): **Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis**. *JAMA Oncol*.

15. Tian L, Lu HJ, Lin L*, et al.* (2016): **Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials**. *Support Care Cancer* 24:969-83.

16. Courneya KS, McKenzie DC, Gelmon K*, et al.* (2014): **A multicenter randomized trial of the effects of exercise dose and type on psychosocial distress in breast cancer patients undergoing chemotherapy**. *Cancer Epidemiol Biomarkers Prev* 23:857-64.

17. Courneya KS, Sellar CM, Trinh L*, et al.* (2012): **A randomized trial of aerobic exercise and sleep quality in lymphoma patients receiving chemotherapy or no treatments**. *Cancer Epidemiol Biomarkers Prev*.

18. Courneya KS, Sellar CM, Stevinson C*, et al.* (2009): **Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients**. *J Clin Oncol* 27:4605-12.

19. Courneya KS, Segal RJ, Gelmon K*, et al.* (2007): **Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy**. *Cancer Epidemiol Biomarkers Prev* 16:2572-8.

20. Courneya KS, Mackey JR, Bell GJ*, et al.* (2003): **Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes**. *J Clin Oncol* 21:1660-8.

21. Buffart LM, De Backer IC, Schep G*, et al.* (2013): **Fatigue mediates the relationship between physical fitness and quality of life in cancer survivors**. *J Sci Med Sport* 16:99-104.

22. Buffart LM, Galvao DA, Chinapaw MJ*, et al.* (2014): **Mediators of the resistance and aerobic exercise intervention effect on physical and general health in men undergoing androgen deprivation therapy for prostate cancer**. *Cancer* 120:294-301.

23. Buffart LM, Newton RU, Chinapaw MJ*, et al.* (2015): **The effect, moderators, and mediators of resistance and aerobic exercise on health-related quality of life in older long-term survivors of prostate cancer**. *Cancer* 121:2821-30.

24. Scott JM, Adams SC, Koelwyn GJ*, et al.* (2016): **Cardiovascular late effects and exercise treatment in breast cancer: current evidence and future directions**. *Can J Cardiol* 32:881-90.

25. Friedenreich CM, Neilson HK, Farris MS*, et al.* (2016): **Physical activity and cancer outcomes: a precision medicine approach**. *Clin Cancer Res* 22:4766-4775.

26. Jones LW (2015): **A precision oncology framework for investigation of exercise as treatment for cancer**. *J Clin Oncol* 33:4134-4137.

27. Saltin B, Essén B, Pedersen PK (1976): **Intermittent exercise: its physiology and some practical applications**, *Karger Publishers.*,

28. Sasso JP, Eves ND, Christensen JF*, et al.* (2015): **A framework for prescription in exercise-oncology research**. *J Cachexia Sarcopenia Muscle* 6:115-24.

29. Thompson PD, Buchner D, Pina IL*, et al.* (2003): **Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)**. *Circulation* 107:3109-16.

30. Armenian SH, Lacchetti C, Barac A*, et al.* (2017): **Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline**. *J Clin Oncol* 35:893-911.

31. Lenneman CG, Sawyer DB (2016): **Cardio-oncology: an update on cardiotoxicity of cancer-related treatment**. *Circ Res* 118:1008-20.

32. Minotti G (2013): **Pharmacology at work for cardio-oncology: ranolazine to treat early cardiotoxicity induced by antitumor drugs**. *J Pharmacol Exp Ther* 346:343-9.

33. Hoffman J (2014): **Physiological aspects of sport training and performance** (ed 2), *Human Kinetics*,

34. Rogers LQ, Hopkins-Price P, Vicari S*, et al.* (2009): **Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects**. *Cancer Epidemiol Biomarkers Prev* 18:1410-8.

35. Bower JE (2014): **Cancer-related fatigue--mechanisms, risk factors, and treatments**. *Nat Rev Clin Oncol* 11:597-609.

36. Smith DL, Fernhall B (2011): **Advanced cardiovascular exercise physiology**, *Human Kinetics.*,

37. Rossen P, Pedersen AF, Zachariae R*, et al.* (2012): **Sexuality and body image in long-term survivors of testicular cancer**. *Eur J Cancer* 48:571-8.

38. Smith AB, Butow P, Olver I*, et al.* (2016): **The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study**. *J Cancer Surviv* 10:223-33.

39. van Basten JP, Jonker-Pool G, van Driel MF*, et al.* (1996): **Fantasies and facts of the testes**. *Br J Urol* 78:756-62.

40. Courneya KS, Booth CM, Gill S*, et al.* (2008): **The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group**. *Curr Oncol* 15:279-85.

41. Fung C, Sesso HD, Williams AM*, et al.* (2017): **Multi-institutional assessment of adverse health outcomes among north american testicular cancer survivors after modern cisplatin-based chemotherapy**. *J Clin Oncol* 35:1211-1222.

42. Sprauten M, Haugnes HS, Brydøy M*, et al.* (2015): **Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: increasing prevalence and risk factors**. *Ann Oncol* 26:2133-2140.

43. Thorsen L, Nystad W, Stigum H*, et al.* (2005): **The association between self-reported physical activity and prevalence of depression and anxiety disorder in long-term survivors of testicular cancer and men in a general population sample**. *Support Care Cancer* 13:637-46.

44. Christensen JF, Jones LW, Tolver A*, et al.* (2014): **Safety and efficacy of resistance training in germ cell cancer patients undergoing chemotherapy: a randomized controlled trial**. *Br J Cancer* 111:8-16.

45. Christensen JF, Bandak M, Campbell A*, et al.* (2015): **Treatment-related cardiovascular late effects and exercise training countermeasures in testicular germ cell cancer survivorship**. *Acta Oncol* 54:592-9.

46. Irwin ML, Cartmel B, Harrigan M*, et al.* (2017): **Effect of the LIVESTRONG at the YMCA exercise program on physical activity, fitness, quality of life, and fatigue in cancer survivors**. *Cancer* 123:1249-1258.

47. Rajotte EJ, Yi JC, Baker KS*, et al.* (2012): **Community-based exercise program effectiveness and safety for cancer survivors**. *J Cancer Surviv* 6:219-28.

48. Jones LW, Courneya KS, Fairey AS*, et al.* (2004): **Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: a single-blind, randomized controlled trial**. *Ann Behav Med* 28:105-13.

49. Canadian Cancer Society's Advisory Committee on Cancer Statistics (2014): **Canadian cancer statistics 2014**, in Society CC (ed). Toronto, ON., pp 132.

50. Siegel R, Naishadham D, Jemal A (2013): **Cancer statistics 2013**. *CA Cancer J Clin* 63:11-30.

51. World Health Organization (2004): **The global burden of disease 2004 update: disability weights for diseases and conditions**. Geneva.

52. Weston KS, Wisloff U, Coombes JS (2014): **High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis**. *Br J Sports Med* 48:1227-34.

53. American College of Sports Medicine (2013): **ACSM's guidelines for exercise testing and prescription** (ed 9), *Lippincott Williams & Wilkins*,

54. Anderson TJ, Gregoire J, Pearson GJ*, et al.* (2016): **2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult**. *Can J Cardiol* 32:1263-1282.

55. D'Agostino RB, Sr., Vasan RS, Pencina MJ*, et al.* (2008): **General cardiovascular risk profile for use in primary care: the Framingham Heart Study**. *Circulation* 117:743-53.

56. Engelen L, Bossuyt J, Ferreira I*, et al.* (2015): **Reference values for local arterial stiffness. Part A: carotid artery**. *J Hypertens* 33:1981-96.

57. Engelen L, Ferreira I, Stehouwer CD*, et al.* (2013): **Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors**. *Eur Heart J* 34:2368-80.

58. Jones LW, Eves ND, Haykowsky M*, et al.* (2008): **Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations**. *Lancet Oncol* 9:757-65.

59. Thijssen DH, Black MA, Pyke KE*, et al.* (2011): **Assessment of flow-mediated dilation in humans: a methodological and physiological guideline**. *Am J Physiol Heart Circ Physiol* 300:H2-12.

60. Touboul PJ, Hennerici MG, Meairs S*, et al.* (2012): **Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011**. *Cerebrovasc Dis* 34:290-6.

61. Low PA (1993): **Autonomic nervous system function**. *J Clin Neurophysiol* 10:14-27.

62. Low PA, Sletten DM (2008): **Laboratory evaluation of autonomic failure**, in Low PA, Benarroch EE (eds): Clinical Autonomic Disorders (ed 3rd). Baltimore, MD, *Lippincott Williams & Wilkins*, pp 130-163.

Bibliography

(including Appendices)

1. Aass N, Fossa SD, Aas M*, et al.* (1990): **Renal function related to different treatment modalities for malignant germ cell tumours**. *Br J Cancer* 62:842-6.

2. Abouassaly R, Fossa SD, Giwercman A*, et al.* (2011): **Sequelae of treatment in long-term survivors of testis cancer**. *Eur Urol* 60:516-26.

3. Adamopoulos S, Ponikowski P, Cerquetani E*, et al.* (1995): **Circadian pattern of heart rate variability in chronic heart failure patients. Effects of physical training**. *Eur Heart J* 16:1380-6.

4. Adams SC, DeLorey DS, Davenport MH*, et al.* (2017): **Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: a phase II randomized controlled trial**. *Cancer* in press.

5. Adams SC, Schondorf R, Benoit J*, et al.* (2015): **Impact of cancer and chemotherapy on autonomic nervous system function and cardiovascular reactivity in young adults with cancer: a case-controlled feasibility study**. *BMC Cancer* 15:414.

6. Adamson IY (1976): **Pulmonary toxicity of bleomycin**. *Environ Health Perspect* 16:119-26.

7. Airaksinen KE, Ikaheimo MJ, Linnaluoto MK*, et al.* (1987): **Impaired vagal heart rate control in coronary artery disease**. *Br Heart J* 58:592-7.

8. Albers P, Albrecht W, Algaba F*, et al.* (2011): **EAU guidelines on testicular cancer: 2011 update**. *Eur Urol* 60:304-19.

9. Allgayer H, Owen RW, Nair J*, et al.* (2008): **Short-term moderate exercise programs reduce oxidative DNA damage as determined by high-performance liquid**

chromatography-electrospray ionization-mass spectrometry in patients with colorectal carcinoma following primary treatment. *Scand J Gastroenterol* 43:971-8.

10. Altena R, de Haas EC, Nuver J*, et al.* (2009): **Evaluation of sub-acute changes in cardiac function after cisplatin-based combination chemotherapy for testicular cancer**. *Br J Cancer* 100:1861-6.

11. Altena R, Hummel YM, Nuver J*, et al.* (2011): **Longitudinal changes in cardiac function after cisplatin-based chemotherapy for testicular cancer**. *Ann Oncol* 22:2286-93.

12. Altena R, Perik PJ, van Veldhuisen DJ*, et al.* (2009): **Cardiovascular toxicity caused by cancer treatment: strategies for early detection**. *Lancet Oncol* 10:391-9.

13. Amara CE, Koval JJ, Johnson PJ*, et al.* (2000): **Modelling the influence of fat-free mass and physical activity on the decline in maximal oxygen uptake with age in older humans**. *Exp Physiol* 85:877-86.

14. American College of Sports Medicine (2013): **ACSM's guidelines for exercise testing and prescription** (ed 9), *Lippincott Williams & Wilkins*,

15. Anderson TJ, Charbonneau F, Title LM*, et al.* (2011): **Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study**. *Circulation* 123:163-9.

16. Anderson TJ, Gregoire J, Hegele RA*, et al.* (2013): **2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult**. *Can J Cardiol* 29:151-67.

17. Anderson TJ, Gregoire J, Pearson GJ*, et al.* (2016): **2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult**. *Can J Cardiol* 32:1263-1282.

18. Anderson TJ, Uehata A, Gerhard MD*, et al.* (1995): **Close relation of endothelial function in the human coronary and peripheral circulations**. *J Am Coll Cardiol* 26:1235-41.

19. Andresen EM, Malmgren JA, Carter WB*, et al.* (1994): **Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale)**. *Am J Prev Med* 10:77-84.

20. Andrews TC, Fenton T, Toyosaki N*, et al.* (1993): **Subsets of ambulatory myocardial ischemia based on heart rate activity. Circadian distribution and response to anti-ischemic medication. The Angina and Silent Ischemia Study Group (ASIS)**. *Circulation* 88:92-100.

21. Argyriou AA, Koutras A, Polychronopoulos P*, et al.* (2005): **The impact of paclitaxel or cisplatin-based chemotherapy on sympathetic skin response: a prospective study**. *Eur J Neurol* 12:858-61.

22. Armenian SH, Lacchetti C, Barac A*, et al.* (2017): **Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline**. *J Clin Oncol* 35:893-911.

23. Armstrong T, Almadrones L, Gilbert MR (2005): **Chemotherapy-induced peripheral neuropathy**. *Oncol Nurs Forum* 32:305-11.

24. Aupetit JF, Frassati D, Bui-Xuan B*, et al.* (1998): **Efficacy of a beta-adrenergic receptor antagonist, propranolol, in preventing ischaemic ventricular fibrillation: dependence on heart rate and ischaemia duration**. *Cardiovasc Res* 37:646-55.

25. Babyak M, Blumenthal JA, Herman S*, et al.* (2000): **Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months**. *Psychosom Med* 62:633-638.

26. Ballard-Barbash R, Friedenreich CM, Courneya KS*, et al.* (2012): **Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review**. *J Natl Cancer Inst* 104:815-40.

27. Barney JA, Ebert TJ, Groban L*, et al.* (1988): **Carotid baroreflex responsiveness in high-fit and sedentary young men**. *J Appl Physiol* 65:2190-4.

28. Bartlett JD, Close GL, MacLaren DP*, et al.* (2011): **High-intensity interval running is perceived to be more enjoyable than moderate-intensity continuous exercise: implications for exercise adherence**. *J Sports Sci* 29:547-53.

29. Beck SL, Schwartz AL, Towsley G*, et al.* (2004): **Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients**. *J Pain Symptom Manage* 27:140-8.

30. Belardinelli R, Georgiou D, Cianci G*, et al.* (1999): **Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome**. *Circulation* 99:1173-82.

31. Belotti D, Vergani V, Drudis T*, et al.* (1996): **The microtubule-affecting drug paclitaxel has antiangiogenic activity**. *Clin Cancer Res* 2:1843-1849.

32. Berger CC, Bokemeyer C, Schneider M*, et al.* (1995): **Secondary Raynaud's phenomenon and other late vascular complications following chemotherapy for testicular cancer**. *Eur J Cancer* 31A:2229-38.

33. Berntson GG, Cacioppo JT, Quigley KS (1993): **Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications**. *Psychophysiology* 30:183-96.

34. Betik AC, Hepple RT (2008): **Determinants of VO2 max decline with aging: an integrated perspective**. *Appl Physiol Nutr Metab* 33:130-140.

35. Billman GE (2002): **Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention**. *J Appl Physiol* 92:446-54.

36. Billman GE (2009): **Cardiac autonomic neural remodeling and susceptibility to sudden cardiac death: effect of endurance exercise training**. *Am J Physiol Heart Circ Physiol* 297:H1171-93.

37. Billman GE, Cagnoli KL, Csepe T*, et al.* (2015): **Exercise training induced bradycardia: evidence for enhanced parasympathetic regulation without changes in" intrinsic" sinoatrial node function**. *J Appl Physiol* jap. 01111.2014-jap. 01111.2014.

38. Bissett D, Kunkeler L, Zwanenburg L*, et al.* (1990): **Long-term sequelae of treatment for testicular germ cell tumours**. *Br J Cancer* 62:655-9.

39. Blair SN, Kohl HW, Paffenbarger RS*, et al.* (1989): **Physical fitness and all-cause mortality. A prospective study of healthy men and women.** *JAMA* 262:2395-401.

40. Boer H, Proost JH, Nuver J*, et al.* (2015): **Long-term exposure to circulating platinum is associated with late effects of treatment in testicular cancer survivors**. *Ann Oncol* 26:2305-10.

41. Bokemeyer C, Berger CC, Kuczyk MA*, et al.* (1996): **Evaluation of long-term toxicity after chemotherapy for testicular cancer**. *J Clin Oncol* 14:2923-32.

42. Bolli R, Fisher DJ, Entman ML (1986): **Factors that determine the occurrence of arrhythmias during acute myocardial ischemia**. *Am Heart J* 111:261-270.

43. Bonaduce D, Petretta M, Cavallaro V*, et al.* (1998): **Intensive training and cardiac autonomic control in high level athletes**. *Med Sci Sports Exerc* 30:691-6.

44. Boogerd W, ten Bokkel Huinink WW, Dalesio O*, et al.* (1990): **Cisplatin induced neuropathy: central, peripheral and autonomic nerve involvement**. *J Neurooncol* 9:255-63.

45. Borm GF, Fransen J, Lemmens WA (2007): **A simple sample size formula for analysis of covariance in randomized clinical trials**. *J Clin Epidemiol* 60:1234-8.

46. Bower JE (2007): **Cancer-related fatigue: links with inflammation in cancer patients and survivors**. *Brain Behav Immun* 21:863-71.

47. Bower JE (2014): **Cancer-related fatigue--mechanisms, risk factors, and treatments**. *Nat Rev Clin Oncol* 11:597-609.

48. Bower JE, Lamkin DM (2013): **Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications**. *Brain Behav Immun* 30 Suppl:S48-57.

49. Brennemann W, Stoffel-Wagner B, Helmers A*, et al.* (1997): **Gonadal function of patients treated with cisplatin based chemotherapy for germ cell cancer**. *J Urol* 158:844-50.

50. Brown JC, Huedo-Medina TB, Pescatello LS*, et al.* (2012): **The efficacy of exercise in reducing depressive symptoms among cancer survivors: a meta-analysis**. *PLoS One* 7:e30955.

51. Buffart LM, De Backer IC, Schep G*, et al.* (2013): **Fatigue mediates the relationship between physical fitness and quality of life in cancer survivors**. *J Sci Med Sport* 16:99-104.

52. Buffart LM, Galvao DA, Chinapaw MJ*, et al.* (2014): **Mediators of the resistance and aerobic exercise intervention effect on physical and general health in men undergoing androgen deprivation therapy for prostate cancer**. *Cancer* 120:294-301.

53. Buffart LM, Newton RU, Chinapaw MJ*, et al.* (2015): **The effect, moderators, and mediators of resistance and aerobic exercise on health-related quality of life in older long-term survivors of prostate cancer**. *Cancer* 121:2821-30.

54. Burgomaster KA, Howarth KR, Phillips SM*, et al.* (2008): **Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans**. *J Physiol* 586:151-60.

55. Buskirk ER, Hodgson JL (1987): **Age and aerobic power: the rate of change in men and women**, Federation proceedings, pp 1824-1829.

56. Canadian Cancer Society's Advisory Committee on Cancer Statistics (2014): **Canadian cancer statistics 2014**, in Society CC (ed). Toronto, ON., pp 132.

57. Cancer Care Ontario (2017): **Cisplatin**, Drug formulary.

58. Carnethon MR, Jacobs DR, Jr., Sidney S*, et al.* (2003): **Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: the CARDIA study**. *Diabetes Care* 26:3035-41.

59. Carter JB, Banister EW, Blaber AP (2003): **Effect of endurance exercise on autonomic control of heart rate**. *Sports Med* 33:33-46.

60. Cassady JR (1995): **Clinical radiation nephropathy**. *Int J Radiat Oncol Biol Phys* 31:1249-56.

61. Celermajer DS, Sorensen KE, Georgakopoulos D*, et al.* (1993): **Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults**. *Circulation* 88:2149-2155.

62. Celermajer DS, Sorensen KE, Gooch VM*, et al.* (1992): **Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis**. *The Lancet* 340.

63. Cella D, Eton DT, Lai JS*, et al.* (2002): **Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales**. *J Pain Symptom Manage* 24:547-61.

64. Christensen JF, Bandak M, Campbell A*, et al.* (2015): **Treatment-related cardiovascular late effects and exercise training countermeasures in testicular germ cell cancer survivorship**. *Acta Oncol* 54:592-9.

65. Christensen JF, Jones LW, Tolver A*, et al.* (2014): **Safety and efficacy of resistance training in germ cell cancer patients undergoing chemotherapy: a randomized controlled trial**. *Br J Cancer* 111:8-16.

66. Christensen JF, Tolver A, Andersen JL*, et al.* (2014): **Resistance training does not protect against increases in plasma cytokine levels among germ cell cancer patients during and after chemotherapy**. *J Clin Endocrinol Metab* 99:2967-76.

67. Coats AJ, Adamopoulos S, Radaelli A*, et al.* (1992): **Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function**. *Circulation* 85:2119-31.

68. Coburn AF, Grey RM, Rivera SM (1971): **Observations on the relation of heart rate, life span, weight and mineralization in the digoxin-treated A-J mouse**. *Johns Hopkins Med J* 128:169-93.

69. Cohen S, Kamarck T, Mermelstein R (1983): **A global measure of perceived stress**. *J Health Soc Behav* 24:385-96.

70. Cole CR, Foody JM, Blackstone EH*, et al.* (2000): **Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort**. *Ann Intern Med* 132:552-555.

71. Coote JH (2010): **Recovery of heart rate following intense dynamic exercise**. *Exp Physiol* 95:431-40.

72. Cormie P, Galvao DA, Spry N*, et al.* (2015): **Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial**. *BJU Int* 115:256-66.

73. Corn BW, Trock BJ, Goodman RL (1990): **Irradiation-related ischemic heart disease**. *J Clin Oncol* 8:741-50.

74. Corretti MC, Anderson TJ, Benjamin EJ*, et al.* (2002): **Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force**. *J Am Coll Cardiol* 39:257-65.

75. Courneya KS (2014): **Physical activity and cancer survivorship: a simple framework for a complex field**. *Exerc Sport Sci Rev* 42:102-9.

76. Courneya KS, Booth CM, Gill S*, et al.* (2008): **The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group**. *Curr Oncol* 15:279-85.

77. Courneya KS, Crawford JJ, Adams SC (2015): **Physical activity and exercise interventions in cancer survivors.**, in Holland JC, Breitbart WS, Jacobsen PB, et al (eds): Psychooncology (ed 3rd). New York, , *Oxford University Press.*

78. Courneya KS, Jones LW, Peddle CJ*, et al.* (2008): **Effects of aerobic exercise training in anemic cancer patients receiving darbepoetin alfa: a randomized controlled trial**. *Oncologist* 13:1012-20.

79. Courneya KS, Mackey JR, Bell GJ*, et al.* (2003): **Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes**. *J Clin Oncol* 21:1660-8.

80. Courneya KS, McKenzie DC, Gelmon K*, et al.* (2014): **A multicenter randomized trial of the effects of exercise dose and type on psychosocial distress in breast cancer patients undergoing chemotherapy**. *Cancer Epidemiol Biomarkers Prev* 23:857-64.

81. Courneya KS, Segal RJ, Gelmon K*, et al.* (2007): **Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy**. *Cancer Epidemiol Biomarkers Prev* 16:2572-8.

82. Courneya KS, Segal RJ, Mackey JR*, et al.* (2007): **Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial**. *J Clin Oncol* 25:4396-404.

83. Courneya KS, Sellar CM, Stevinson C*, et al.* (2009): **Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients**. *J Clin Oncol* 27:4605-12.

84. Courneya KS, Sellar CM, Trinh L*, et al.* (2012): **A randomized trial of aerobic exercise and sleep quality in lymphoma patients receiving chemotherapy or no treatments**. *Cancer Epidemiol Biomarkers Prev*.

85. Craft LL, Vaniterson EH, Helenowski IB*, et al.* (2012): **Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis**. *Cancer Epidemiol Biomarkers Prev* 21:3-19.

86. Cruickshank K, Riste L, Anderson SG*, et al.* (2002): **Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function?** *Circulation* 106:2085-90.

87. Cunha RS, Pannier B, Benetos A*, et al.* (1997): **Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects**. *J Hypertens* 15:1423-1430.

88. Curado M-P, Edwards B, Shin HR*, et al.* (2007): **Cancer incidence in five continents**, *International Agency for Research on Cancer*, pp. 896.

89. Currie KD, Dubberley JB, McKelvie RS*, et al.* (2013): **Low-volume, high-intensity interval training in patients with CAD**. *Med Sci Sports Exerc* 45:1436-42.

90. Currie KD, McKelvie RS, Macdonald MJ (2012): **Flow-mediated dilation is acutely improved after high-intensity interval exercise**. *Med Sci Sports Exerc* 44:2057-64.

91. Custodis F, Baumhakel M, Schlimmer N*, et al.* (2008): **Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice**. *Circulation* 117:2377-87.

92. D'Agostino RB, Sr., Vasan RS, Pencina MJ*, et al.* (2008): **General cardiovascular risk profile for use in primary care: the Framingham Heart Study**. *Circulation* 117:743-53.

93. Dahl AA, Haaland CF, Mykletun A*, et al.* (2005): **Study of anxiety disorder and depression in long-term survivors of testicular cancer**. *J Clin Oncol* 23:2389-95.

94. Dahl CF, Haugnes HS, Bremnes R*, et al.* (2010): **A controlled study of risk factors for disease and current problems in long-term testicular cancer survivors**. *J Cancer Surviv* 4:256-65.

95. Daugaard G, Rossing N, Rorth M (1988): **Effects of cisplatin on different measures of glomerular function in the human kidney with special emphasis on high-dose**. *Cancer Chemother Pharmacol* 21:163-7.

96. Daussin FN, Zoll J, Dufour SP*, et al.* (2008): **Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects**. *Am J Physiol Regul Integr Comp Physiol* 295:R264-72.

97. Davies CT, Neilson JM (1967): **Disturbance of heart rhythm during recovery from exercise in man**. *J Appl Physiol* 22:943-6.

98. Davies CTM, Neilson JMM (1967): **Sinus arrhythmia in man at rest**. *J Appl Physiol* 22:947-955.

99. Davy KP, Miniclier NL, Taylor JA*, et al.* (1996): **Elevated heart rate variability in physically active postmenopausal women: a cardioprotective effect?** *Am J Physiol* 271:H455-60.

100. Dawber TR, Meadors GF, Moore FE, Jr. (1951): **Epidemiological approaches to heart disease: the Framingham Study**. *Am J Public Health Nations Health* 41:279-81.

101. De Angelis K, Wichi RB, Jesus WR*, et al.* (2004): **Exercise training changes autonomic cardiovascular balance in mice**. *J Appl Physiol* 96:2174-8.

102. de Haas EC, Altena R, Boezen HM*, et al.* (2013): **Early development of the metabolic syndrome after chemotherapy for testicular cancer**. *Ann Oncol* 24:749-55.

103. De Meersman RE (1992): **Respiratory sinus arrhythmia alteration following training in endurance athletes**. *Eur J Appl Physiol Occup Physiol* 64:434-6.

104. De Meersman RE (1993): **Heart rate variability and aerobic fitness**. *Am Heart J* 125:726-31.

105. de Vos FY, Nuver J, Willemse PH*, et al.* (2004): **Long-term survivors of ovarian malignancies after cisplatin-based chemotherapy; cardiovascular risk factors and signs of vascular damage**. *Eur J Cancer* 40:696-700.

106. DeSouza CA, Shapiro LF, Clevenger CM*, et al.* (2000): **Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men**. *Circulation* 102:1351-7.

107. Devin JL, Sax AT, Hughes GI*, et al.* (2016): **The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial**. *J Cancer Surviv* 10:467-79.

108. Dewit L, Anninga JK, Hoefnagel CA*, et al.* (1990): **Radiation injury in the human kidney: a prospective analysis using specific scintigraphic and biochemical endpoints**. *Int J Radiat Oncol Biol Phys* 19:977-983.

109. Dieckmann KP, Gerl A, Witt J*, et al.* (2010): **Myocardial infarction and other major vascular events during chemotherapy for testicular cancer**. *Ann Oncol* 21:1607-11.

110. Dinenno FA, Tanaka H, Monahan KD*, et al.* (2001): **Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men**. *J Physiol* 534:287-95.

111. Dixon EM, Kamath MV, McCartney N*, et al.* (1992): **Neural regulation of heart rate variability in endurance athletes and sedentary controls**. *Cardiovasc Res* 26:713-9.

112. Doll DC, Ringenberg QS, Yarbro JW (1986): **Vascular toxicity associated with antineoplastic agents**. *J Clin Oncol* 4:1405-17.

113. Dormann AJ, Grunewald T, Wigginghaus B*, et al.* (1998): **Gemcitabine-associated autonomic neuropathy**. *Lancet* 351:644.

114. Dorr RT (1992): **Bleomycin pharmacology: mechanism of action and resistance, and clinical pharmacokinetics**, Semin Oncol, pp 3-8.

115. Duprez DA, Cohn JN (2007): **Detection of early cardiovascular disease**, in Willerson JT, Wellens HJJ, Cohn JN, et al (eds): Cardiovascular Medicine, *Springer London*, pp 1615-1622.

116. Eble JN (2004): **WHO histological classification of testis tumours**, Pathology and genetics of tumours of the urinary system and male genital organs, *International Agency for Research on Cancer*, pp 359.

117. Ebrahim S, Papacosta O, Whincup P*, et al.* (1999): **Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study**. *Stroke* 30:841-50.

118. Edwards DG, Schofield RS, Magyari PM*, et al.* (2004): **Effect of exercise training on central aortic pressure wave reflection in coronary artery disease**. *Am J Hypertens* 17:540-3.

119. Einhorn LH, Donohue J (1977): **Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer**. *Ann Intern Med* 87:293-8.

120. Ekholm E, Rantanen V, Antila K*, et al.* (1997): **Paclitaxel changes sympathetic control of blood pressure**. *Eur J Cancer* 33:1419-24.

121. Ekholm EM, Salminen EK, Huikuri HV*, et al.* (2000): **Impairment of heart rate variability during paclitaxel therapy**. *Cancer* 88:2149-53.

122. Engelen L, Bossuyt J, Ferreira I*, et al.* (2015): **Reference values for local arterial stiffness. Part A: carotid artery**. *J Hypertens* 33:1981-96.

123. Engelen L, Ferreira I, Stehouwer CD*, et al.* (2013): **Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors**. *Eur Heart J* 34:2368-80.

124. European Heart Failure Training Group (1998): **Experience from controlled trials of physical training in chronic heart failure. Protocol and patient factors in effectiveness in the improvement in exercise tolerance.** *Eur Heart J* 19:466-75.

125. Ewer MS, Lenihan DJ (2008): **Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground?** *J Clin Oncol* 26:1201-3.

126. Ewing DJ, Clarke BF (1986): **Autonomic neuropathy: its diagnosis and prognosis**. *Clin Endocrinol Metab* 15:855-88.

127. Falah M, Schiff D, Burns TM (2005): **Neuromuscular complications of cancer diagnosis and treatment**. *J Support Oncol* 3:271-82.

128. Feldman DR, Bosl GJ, Sheinfeld J*, et al.* (2008): **Medical treatment of advanced testicular cancer**. *JAMA* 299:672-84.

129. Feldman JL, Ellenberger HH (1988): **Central coordination of respiratory and cardiovascular control in mammals**. *Annu Rev Physiol* 50:593-606.

130. Fjeldborg P, Sorensen J, Helkjaer PE (1986): **The long-term effect of cisplatin on renal function**. *Cancer* 58:2214-7.

131. Fossa SD, Aass N, Winderen M*, et al.* (2002): **Long-term renal function after treatment for malignant germ-cell tumours**. *Ann Oncol* 13:222-8.

132. Fossa SD, Dahl AA, Haaland CF (1999): **Health-related quality of life in patients treated for testicular cancer**. *Curr Opin Urol* 9:425-9.

133. Fossa SD, Dahl AA, Loge JH (2003): **Fatigue, anxiety, and depression in long-term survivors of testicular cancer**. *J Clin Oncol* 21:1249-54.

134. Fossa SD, Gilbert E, Dores GM*, et al.* (2007): **Noncancer causes of death in survivors of testicular cancer**. *J Natl Cancer Inst* 99:533-44.

135. Fouad FM, Tarazi RC, Ferrario CM*, et al.* (1984): **Assessment of parasympathetic control of heart rate by a noninvasive method**. *Am J Physiol* 246:H838-42.

136. Fox K, Borer JS, Camm AJ*, et al.* (2007): **Resting heart rate in cardiovascular disease**. *J Am Coll Cardiol* 50:823-30.

137. Franklin SS, Gustin Wt, Wong ND*, et al.* (1997): **Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study**. *Circulation* 96:308-15.

138. Franklin SS, Khan SA, Wong ND*, et al.* (1999): **Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study**. *Circulation* 100:354-360.

139. Franklin SS, Larson MG, Khan SA*, et al.* (2001): **Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study**. *Circulation* 103:1245-1249.

140. Franklin SS, Pio JR, Wong ND*, et al.* (2005): **Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study**. *Circulation* 111:1121-7.

141. Freeman RL (2008): **Noninvasive evaluation of heart rate: time and frequency domains.**, in Low PA, Benarroch EE (eds): Clinical Autonomic Disorders. (ed 3rd). Philadelphia, *Lippincott Williams & Wilkins*, pp 185-197.

142. Friedenreich CM, Neilson HK, Farris MS*, et al.* (2016): **Physical activity and cancer outcomes: a precision medicine approach**. *Clin Cancer Res* 22:4766-4775.

143. Fu Q, Levine BD (2013): **Exercise and the autonomic nervous system**. *Handb Clin Neurol* 117:147-60.

144. Fu TC, Wang CH, Lin PS*, et al.* (2013): **Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure**. *Int J Cardiol* 167:41-50.

145. Fuertes MA, Castilla J, Alonso C*, et al.* (2003): **Cisplatin biochemical mechanism of action: from cytotoxicity to induction of cell death through interconnections between apoptotic and necrotic pathways**. *Curr Med Chem* 10:257-266.

146. Fung C, Fossa SD, Williams A*, et al.* (2015): **Long-term morbidity of testicular cancer treatment**. *Urol Clin North Am* 42:393-408.

147. Fung C, Sesso HD, Williams AM*, et al.* (2017): **Multi-institutional assessment of adverse health outcomes among north american testicular cancer survivors after modern cisplatin-based chemotherapy**. *J Clin Oncol* 35:1211-1222.

148. Gandaglia G, Becker A, Trinh QD*, et al.* (2014): **Long-term survival in patients with germ cell testicular cancer: a population-based competing-risks regression analysis**. *Eur J Surg Oncol* 40:103-12.

149. Genest J, McPherson R, Frohlich J*, et al.* (2009): **2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations**. *Can J Cardiol* 25:567-79.

150. Gerritsen JK, Vincent AJ (2016): **Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials**. *Br J Sports Med* 50:796-803.

151. Giese-Davis J, Wilhelm FH, Tamagawa R*, et al.* (2015): **Higher vagal activity as related to survival in patients with advanced breast cancer: an analysis of autonomic dysregulation**. *Psychosom Med* 77:346-55.

152. Gietema JA, Meinardi MT, Messerschmidt J*, et al.* (2000): **Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer**. *The Lancet* 355:1075-1076.

153. Gietema JA, Meinardi MT, van der Graaf WTA*, et al.* (2001): **Syndrome X in testicular cancer survivors**. *The Lancet* 357:228-229.

154. Gietema JA, Sleijfer DT, Willemse PH*, et al.* (1992): **Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated nonseminomatous testicular cancer**. *Ann Intern Med* 116:709-15.

155. Gnasso A, Carallo C, Irace C*, et al.* (1996): **Association between intima-media thickness and wall shear stress in common carotid arteries in healthy male subjects**. *Circulation* 94:3257-3262.

156. Godia EC, Madhok R, Pittman J*, et al.* (2007): **Carotid artery distensibility: a reliability study**. *J Ultrasound Med* 26:1157-65.

157. Godin G, Shephard RJ (1985): **A simple method to assess exercise behavior in the community**. *Can J Appl Sport Sci* 10:141-6.

158. Goldsmith RL, Bigger JT, Jr., Steinman RC*, et al.* (1992): **Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men**. *J Am Coll Cardiol* 20:552-8.

159. Golemati S, Sassano A, Lever MJ*, et al.* (2003): **Carotid artery wall motion estimated from B-mode ultrasound using region tracking and block matching**. *Ultrasound Med Biol* 29:387-399.

160. Gomber S, Dewan P, Chhonker D (2010): **Vincristine induced neurotoxicity in cancer patients**. *Indian J Pediatr* 77:97-100.

161. Gomez D, Owens GK (2012): **Smooth muscle cell phenotypic switching in atherosclerosis**. *Cardiovasc Res* 95:156-64.

162. Green DJ (2005): **Point: flow-mediated dilation does reflect nitric oxide-mediated endothelial function**. *J Appl Physiol* 99:1233-8.

163. Green DJ (2009): **Exercise training as vascular medicine: direct impacts on the vasculature in humans**. *Exerc Sport Sci Rev* 37:196-202.

164. Green DJ, O'Driscoll G, Joyner MJ*, et al.* (2008): **Exercise and cardiovascular risk reduction: time to update the rationale for exercise?** *J Appl Physiol* 105:766-8.

165. Gregoire J, Tuck S, Hughson RL*, et al.* (1996): **Heart rate variability at rest and exercise: influence of age, gender, and physical training**. *Can J Appl Physiol* 21:455-470.

166. Grossman P (1983): **Respiration, stress, and cardiovascular function**. *Psychophysiology* 20:284-300.

167. Groth S, Nielsen H, Sorensen JB*, et al.* (1986): **Acute and long-term nephrotoxicity of cis-platinum in man**. *Cancer Chemother Pharmacol* 17:191-6.

168. Guo Y, Koshy S, Hui D*, et al.* (2015): **Prognostic value of heart rate variability in patients with cancer**. *J Clin Neurophysiol* 32:516-20.

169. Guyton AC, Hall JE (2006): **Textbook of medical physiology** (ed 11th). Philadelphia, *Elsevier Saunders*, pp. 748-760.

170. Hagberg JM, Hickson RC, Ehsani AA*, et al.* (1980): **Faster adjustment to and recovery from submaximal exercise in the trained state**. *J Appl Physiol Respir Environ Exerc Physiol* 48:218-24.

171. Hagberg JM, Hickson RC, McLane JA*, et al.* (1979): **Disappearance of norepinephrine from the circulation following strenuous exercise**. *J Appl Physiol Respir Environ Exerc Physiol* 47:1311-4.

172. Haider AW, Larson MG, Franklin SS*, et al.* (2003): **Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study**. *Ann Intern Med* 138:10-16.

173. Hambrecht R, Adams V, Erbs S*, et al.* (2003): **Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase**. *Circulation* 107:3152-8.

174. Hamilton CR, Bliss JM, Horwich A (1989): **The late effects of cis-platinum on renal function**. *Eur J Cancer Clin Oncol* 25:185-9.

175. Hann D, Winter K, Jacobsen P (1999): **Measurement of depressive symptoms in cancer patients: evaluation of the Center for Epidemiological Studies Depression Scale (CES-D)**. *J Psychosom Res* 46:437-43.

176. Hansen SW (1990): **Autonomic neuropathy after treatment with cisplatin, vinblastine, and bleomycin for germ cell cancer**. *BMJ* 300:511-2.

177. Hansen SW, Groth S, Daugaard G*, et al.* (1988): **Long-term effects on renal function and blood pressure of treatment with cisplatin, vinblastine, and bleomycin in patients with germ cell cancer**. *J Clin Oncol* 6:1728-31.

178. Hansen SW, Olsen N (1989): **Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin for germ cell cancer: measurement of vasoconstrictor response to cold**. *J Clin Oncol* 7:940-2.

179. Hartley LH, Mason JW, Hogan RP*, et al.* (1972): **Multiple hormonal responses to graded exercise in relation to physical training**. *J Appl Physiol* 33:602-6.

180. Hartmann JT, Kollmannsberger C, Kanz L*, et al.* (1999): **Platinum organ toxicity and possible prevention in patients with testicular cancer**. *Int J Cancer* 83:866-9.

181. Haugnes HS, Aass N, Fossa SD*, et al.* (2007): **Components of the metabolic syndrome in long-term survivors of testicular cancer**. *Ann Oncol* 18:241-8.

182. Haugnes HS, Bosl GJ, Boer H*, et al.* (2012): **Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up**. *J Clin Oncol* 30:3752-63.

183. Haugnes HS, Oldenburg J, Bremnes RM (2015): **Pulmonary and cardiovascular toxicity in long-term testicular cancer survivors**, Urol Oncol Semin Ori, *Elsevier*, pp 399-406.

184. Haugnes HS, Wethal T, Aass N*, et al.* (2010): **Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study**. *J Clin Oncol* 28:4649-57.

185. Hawkins S, Wiswell R (2003): **Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training**. *Sports Med* 33:877-88.

186. Hayano J, Sakakibara Y, Yamada M*, et al.* (1990): **Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity**. *Circulation* 81:1217-24.

187. Hayashi K, Sugawara J, Komine H*, et al.* (2005): **Effects of aerobic exercise training on the stiffness of central and peripheral arteries in middle-aged sedentary men**. *Jpn J Physiol* 55:235-9.

188. Hayes AF (2013): **Introduction to mediation, moderation, and conditional process analysis: a regression-based approach**, *Guilford Press.*,

189. Hecht SM (2000): **Bleomycin: new perspectives on the mechanism of action**. *J Nat Prod* 63:158-68.

190. Hegbom F, Stavem K, Sire S*, et al.* (2007): **Effects of short-term exercise training on symptoms and quality of life in patients with chronic atrial fibrillation**. *Int J Cardiol* 116:86-92.

191. Heidland UE, Strauer BE (2001): **Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption**. *Circulation* 104:1477-82.

192. Heier MS, Nilsen T, Graver V*, et al.* (1991): **Raynaud's phenomenon after combination chemotherapy of testicular cancer, measured by laser Doppler flowmetry. A pilot study**. *Br J Cancer* 63:550-2.

193. Hejazi SM, Rashidlamir A, Jebelli A*, et al.* (2013): **The effects of 8 weeks aerobic exercise on levels of homocysteine, HS-CRP serum and plasma fibrinogen in type II diabetic women**. *Life Sci*:430-435.

194. Hirvonen HE, Salmi TT, Heinonen E*, et al.* (1989): **Vincristine treatment of acute lymphoblastic leukemia induces transient autonomic cardioneuropathy**. *Cancer* 64:801-5.

195. Hjalmarson A, Elmfeldt D, Herlitz J*, et al.* (1981): **Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial**. *Lancet* 2:823-7.

196. Hjelle LV, Gundersen PO, Oldenburg J*, et al.* (2015): **Long-term platinum retention after platinum-based chemotherapy in testicular cancer survivors: a 20-year follow-up study**. *Anticancer Res* 35:1619-25.

197. Hodis HN, Mack WJ, LaBree L*, et al.* (1998): **The role of carotid arterial intima-media thickness in predicting clinical coronary events**. *Ann Intern Med* 128:262-9.

198. Hoeks AP, Brands PJ, Smeets FA*, et al.* (1990): **Assessment of the distensibility of superficial arteries**. *Ultrasound Med Biol* 16:121-8.

199. Hoffman J (2014): **Physiological aspects of sport training and performance** (ed 2), *Human Kinetics*,

200. Hornsby WE, Douglas PS, West MJ*, et al.* (2014): **Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial**. *Acta Oncol* 53:65-74.

201. Hrushesky WJ, Fader D, Schmitt O*, et al.* (1984): **The respiratory sinus arrhythmia: a measure of cardiac age**. *Science* 224:1001-4.

202. Hrushesky WJ, Fader DJ, Berestka JS*, et al.* (1991): **Diminishment of respiratory sinus arrhythmia foreshadows doxorubicin-induced cardiomyopathy**. *Circulation* 84:697-707.

203. Huddart RA, Norman A, Moynihan C*, et al.* (2005): **Fertility, gonadal and sexual function in survivors of testicular cancer**. *Br J Cancer* 93:200-7.

204. Huddart RA, Norman A, Shahidi M*, et al.* (2003): **Cardiovascular disease as a long-term complication of treatment for testicular cancer**. *J Clin Oncol* 21:1513-23.

205. Huikuri HV, Jokinen V, Syvanne M*, et al.* (1999): **Heart rate variability and progression of coronary atherosclerosis**. *Arterioscler Thromb Vasc Biol* 19:1979-85.

206. Hull SS, Jr., Vanoli E, Adamson PB*, et al.* (1994): **Exercise training confers anticipatory protection from sudden death during acute myocardial ischemia**. *Circulation* 89:548-52.

207. Huybrechts SA, Devos DG, Vermeersch SJ*, et al.* (2011): **Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path lengths determined by MRI and superficial measurements**. *J Hypertens* 29:1577-82.

208. Huyghe E, Matsuda T, Daudin M*, et al.* (2004): **Fertility after testicular cancer treatments: results of a large multicenter study**. *Cancer* 100:732-7.

209. Iellamo F, Legramante JM, Massaro M*, et al.* (2000): **Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: a randomized, controlled study**. *Circulation* 102:2588-92.

210. Imai K, Sato H, Hori M*, et al.* (1994): **Vagally mediated heart-rate recovery after exercise is accelerated in athletes but alunted in aatients with chronic heart-failure**. *J Am Coll Cardiol* 24:1529-1535.

211. Inaba Y, Chen JA, Bergmann SR (2010): **Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis**. *Int J Cardiovasc Imaging* 26:631-40.

212. Inaba Y, Chen JA, Bergmann SR (2012): **Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis**. *Atherosclerosis* 220:128-33.

213. Irace C, Cortese C, Fiaschi E*, et al.* (2004): **Wall shear stress is associated with intima-media thickness and carotid atherosclerosis in subjects at low coronary heart disease risk**. *Stroke* 35:464-8.

214. Irwin ML, Cartmel B, Harrigan M*, et al.* (2017): **Effect of the LIVESTRONG at the YMCA exercise program on physical activity, fitness, quality of life, and fatigue in cancer survivors**. *Cancer* 123:1249-1258.

215. Izawa K, Hirano Y, Yamada S*, et al.* (2004): **Improvement in physiological outcomes and health-related quality of life following cardiac rehabilitation in patients with acute myocardial infarction**. *Circ J* 68:315-20.

216. Jarvela LS, Niinikoski H, Heinonen OJ*, et al.* (2013): **Endothelial function in long-term survivors of childhood acute lymphoblastic leukemia: effects of a home-based exercise program**. *Pediatr Blood Cancer* 60:1546-51.

217. Jensen BV, Skovsgaard T, Nielsen SL (2002): **Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients**. *Ann Oncol* 13:699-709.

218. Jerian SM, Sarosy GA, Link CJ, Jr.*, et al.* (1993): **Incapacitating autonomic neuropathy precipitated by taxol**. *Gynecol Oncol* 51:277-80.

219. Jolly MA, Brennan DM, Cho L (2011): **Impact of exercise on heart rate recovery**. *Circulation* 124:1520-6.

220. Joly F, Heron JF, Kalusinski L*, et al.* (2002): **Quality of life in long-term survivors of testicular cancer: a population-based case-control study**. *J Clin Oncol* 20:73-80.

221. Jones LW (2015): **A precision oncology framework for investigation of exercise as treatment for cancer**. *J Clin Oncol* 33:4134-4137.

222. Jones LW, Courneya KS, Fairey AS*, et al.* (2004): **Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: a single-blind, randomized controlled trial**. *Ann Behav Med* 28:105-13.

223. Jones LW, Courneya KS, Mackey JR*, et al.* (2012): **Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum**. *J Clin Oncol* 30:2530-7.

224. Jones LW, Eves ND, Haykowsky M*, et al.* (2008): **Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations**. *Lancet Oncol* 9:757-65.

225. Jones LW, Liang Y, Pituskin EN*, et al.* (2011): **Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis**. *Oncologist* 16:112-20.

226. Jones LW, Watson D, Herndon JE, 2nd*, et al.* (2010): **Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer**. *Cancer* 116:4825-32.

227. Joseph AM, Adhihetty PJ, Leeuwenburgh C (2016): **Beneficial effects of exercise on age-related mitochondrial dysfunction and oxidative stress in skeletal muscle**. *J Physiol* 594:5105-23.

228. Jouven X, Empana JP, Schwartz PJ*, et al.* (2005): **Heart-rate profile during exercise as a predictor of sudden death**. *N Engl J Med* 352:1951-8.

229. Kadoglou NP, Moustardas P, Kapelouzou A*, et al.* (2013): **The anti-inflammatory effects of exercise training promote atherosclerotic plaque stabilization in apolipoprotein E knockout mice with diabetic atherosclerosis**. *Eur J Histochem* 57:e3.

230. Kaminsky LA, Arena R, Beckie TM*, et al.* (2013): **The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association**. *Circulation* 127:652-62.

231. Kannankeril PJ, Le FK, Kadish AH*, et al.* (2004): **Parasympathetic effects on heart rate recovery after exercise**. *J Investig Med* 52:394-401.

232. Kaplan JR, Manuck SB, Clarkson TB (1987): **The influence of heart rate on coronary artery atherosclerosis**. *J Cardiovasc Pharmacol* 10 Suppl 2:S100-2; discussion S103.

233. Katona PG, Jih F (1975): **Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control**. *J Appl Physiol* 39:801-5.

234. Katona PG, McLean M, Dighton DH*, et al.* (1982): **Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest**. *J Appl Physiol* 52:1652-1657.

235. Kavanagh T, Mertens DJ, Hamm LF*, et al.* (2002): **Prediction of long-term prognosis in 12,169 men referred for cardiac rehabilitation**. *Circulation* 106:666-71.

236. Kawasaki T, Sasayama S, Yagi S*, et al.* (1987): **Non-invasive assessment of the age related changes in stiffness of major branches of the human arteries**. *Cardiovasc Res* 21:678-87.

237. Kero AE, Jarvela LS, Arola M*, et al.* (2014): **Cardiovascular morbidity in long-term survivors of early-onset cancer: a population-based study**. *Int J Cancer* 134:664-73.

238. Kessler HS, Sisson SB, Short KR (2012): **The potential for high-intensity interval training to reduce cardiometabolic disease risk**. *Sports Med* 42:489-509.

239. Keteyian SJ, Brawner CA, Schairer JR*, et al.* (1999): **Effects of exercise training on chronotropic incompetence in patients with heart failure**. *Am Heart J* 138:233-40.

240. Kiilavuori K, Naveri H, Leinonen H*, et al.* (1999): **The effect of physical training on hormonal status and exertional hormonal response in patients with chronic congestive heart failure**. *Eur Heart J* 20:456-64.

241. Kiilavuori K, Toivonen L, Naveri H*, et al.* (1995): **Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability**. *Eur Heart J* 16:490-5.

242. Kim C, McGlynn KA, McCorkle R*, et al.* (2011): **Quality of life among testicular cancer survivors: a case-control study in the United States**. *Qual Life Res* 20:1629-37.

243. Kim TH, Somerville PJ, Freeman CR (1984): **Unilateral radiation nephropathy--the long-term significance**. *Int J Radiat Oncol Biol Phys* 10:2053-9.

244. Kingwell BA, Sherrard B, Jennings GL*, et al.* (1997): **Four weeks of cycle training increases basal production of nitric oxide from the forearm**. *Am J Physiol* 272:H1070-7.

245. Kitta Y, Obata JE, Nakamura T*, et al.* (2009): **Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease**. *J Am Coll Cardiol* 53:323-30.

246. Kobayashi K, Akishita M, Yu W*, et al.* (2004): **Interrelationship between non-invasive measurements of atherosclerosis: flow-mediated dilation of brachial artery, carotid intima-media thickness and pulse wave velocity**. *Atherosclerosis* 173:13-8.

247. Kohout FJ, Berkman LF, Evans DA*, et al.* (1993): **Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index**. *J Aging Health* 5:179-93.

248. La Rovere MT, Mortara A, Sandrone G*, et al.* (1992): **Autonomic nervous system adaptations to short-term exercise training**. *Chest* 101:299S-303S.

249. La Vecchia C, Bosetti C, Lucchini F*, et al.* (2010): **Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975**. *Ann Oncol* 21:1323-60.

250. Lackner JE, Koller A, Schatzl G*, et al.* (2009): **Androgen deficiency symptoms in testicular cancer survivors are associated with sexual problems but not with serum testosterone or therapy**. *Urology* 74:825-9.

251. Lahiri MK, Kannankeril PJ, Goldberger JJ (2008): **Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications**. *J Am Coll Cardiol* 51:1725-33.

252. Lakoski SG, Eves ND, Douglas PS*, et al.* (2012): **Exercise rehabilitation in patients with cancer**. *Nat Rev Clin Oncol* 9:288-96.

253. Lauer MS (2009): **Autonomic function and prognosis**. *Cleve Clin J Med* 76 Suppl 2:S18-22.

254. Lauer MS (2011): **Heart rate recovery: what now?** *J Intern Med* 270:597-9.

255. Laurent S, Cockcroft J, Van Bortel L*, et al.* (2006): **Expert consensus document on arterial stiffness: methodological issues and clinical applications**. *Eur Heart J* 27:2588-605.

256. Le Cornet C, Lortet-Tieulent J, Forman D*, et al.* (2014): **Testicular cancer incidence to rise by 25% by 2025 in Europe? Model-based predictions in 40 countries using population-based registry data**. *Eur J Cancer* 50:831-9.

257. Lechner D, Kollars M, Gleiss A*, et al.* (2007): **Chemotherapy-induced thrombin generation via procoagulant endothelial microparticles is independent of tissue factor activity**. *J Thromb Haemost* 5:2445-52.

258. Lederman GS, Sheldon TA, Chaffey JT*, et al.* (1987): **Cardiac disease after mediastinal irradiation for seminoma**. *Cancer* 60:772-6.

259. Lehmann M, Schmid P, Keul J (1984): **Age- and exercise-related sympathetic activity in untrained volunteers, trained athletes and patients with impaired left-ventricular contractility**. *Eur Heart J* 5 Suppl E:1-7.

260. Lenneman CG, Sawyer DB (2016): **Cardio-oncology: an update on cardiotoxicity of cancer-related treatment**. *Circ Res* 118:1008-20.

261. Lester SJ, Tajik AJ, Nishimura RA*, et al.* (2008): **Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later**. *J Am Coll Cardiol* 51:679-89.

262. Levine HJ (1997): **Rest heart rate and life expectancy**. *J Am Coll Cardiol* 30:1104-6.

263. Levy D, DeStefano AL, Larson MG*, et al.* (2000): **Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the framingham heart study**. *Hypertension* 36:477-83.

264. Levy WC, Cerqueira MD, Harp GD*, et al.* (1998): **Effect of endurance exercise training on heart rate variability at rest in healthy young and older men**. *Am J Cardiol* 82:1236-1241.

265. Lewis SF, Nylander E, Gad P*, et al.* (1980): **Non‐autonomic component in bradycardia of endurance trained men at rest and during exercise**. *Acta Physiologica Scandinavica* 109:297-305.

266. Liao JK, Bettmann MA, Sandor T*, et al.* (1991): **Differential impairment of vasodilator responsiveness of peripheral resistance and conduit vessels in humans with atherosclerosis**. *Circ Res* 68:1027-34.

267. Libby P (2012): **Inflammation in atherosclerosis**. *Arterioscler Thromb Vasc Biol* 32:2045-51.

268. Lieberman EH, Gerhard MD, Uehata A*, et al.* (1996): **Flow-induced vasodilation of the human brachial artery is impaired in patients < 40 years of age with coronary artery disease**. *Am J Cardiol* 78:1210-1214.

269. Lind L, Andrén B (2002): **Heart rate recovery after exercise is related to the insulin resistance syndrome and heart rate variability in elderly men**. *Am Heart J* 144:666-672.

270. Lishner M, Akselrod S, Avi VM*, et al.* (1987): **Spectral analysis of heart rate fluctuations. A non-invasive, sensitive method for the early diagnosis of autonomic neuropathy in diabetes mellitus**. *J Auton Nerv Syst* 19:119-25.

271. Lorenz MW, Markus HS, Bots ML*, et al.* (2007): **Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis**. *Circulation* 115:459-67.

272. Lorenz MW, Schaefer C, Steinmetz H*, et al.* (2010): **Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS)**. *Eur Heart J* 31:2041-8.

273. Low PA (1993): **Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure**. *Mayo Clin Proc* 68:748-52.

274. Low PA (1993): **Autonomic nervous system function**. *J Clin Neurophysiol* 10:14-27.

275. Low PA, Sletten DM (2008): **Laboratory evaluation of autonomic failure**, in Low PA, Benarroch EE (eds): Clinical Autonomic Disorders (ed 3rd). Baltimore, MD, *Lippincott Williams & Wilkins*, pp 130-163.

276. Lubberts S, Boer H, Altena R*, et al.* (2016): **Vascular fingerprint and vascular damage markers associated with vascular events in testicular cancer patients during and after chemotherapy**. *Eur J Cancer* 63:180-8.

277. Mabeta P, Pepper MS (2009): **A comparative study on the anti-angiogenic effects of DNA-damaging and cytoskeletal-disrupting agents**. *Angiogenesis* 12:81-90.

278. MacKinnon DP (2008): **Introduction to statistical mediation analysis**. New York, *Routledge.*, pp. 477.

279. MacLeod PM, Tyrell CJ, Keeling DH (1988): **The effect of cisplatin on renal function in patients with testicular tumours**. *Clin Radiol* 39:190-2.

280. Madden KM, Lockhart C, Cuff D*, et al.* (2009): **Short-term aerobic exercise reduces arterial stiffness in older adults with type 2 diabetes, hypertension, and hypercholesterolemia**. *Diabetes Care* 32:1531-5.

281. Maddox TM, Ross C, Ho PM*, et al.* (2009): **Impaired heart rate recovery is associated with new-onset atrial fibrillation: a prospective cohort study**. *BMC Cardiovasc Disord* 9:11.

282. Malfatto G, Facchini M, Bragato R*, et al.* (1996): **Short and long term effects of exercise training on the tonic autonomic modulation of heart rate variability after myocardial infarction**. *Eur Heart J* 17:532-8.

283. Malfatto G, Facchini M, Sala L*, et al.* (1998): **Effects of cardiac rehabilitation and beta-blocker therapy on heart rate variability after first acute myocardial infarction**. *Am J Cardiol* 81:834-40.

284. Mangoni AA, Mircoli L, Giannattasio C*, et al.* (1996): **Heart rate-dependence of arterial distensibility in vivo**. *J Hypertens* 14:897-901.

285. Maruish ME (2011): **User's manual for the SF-36v2 Health Survey**, *Quality Metric Incorporated.*,

286. Masi CM, Hawkley LC, Rickett EM*, et al.* (2007): **Respiratory sinus arrhythmia and diseases of aging: obesity, diabetes mellitus, and hypertension**. *Biol Psychol* 74:212-23.

287. Mathiesen EB, Johnsen SH, Wilsgaard T*, et al.* (2011): **Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromso Study**. *Stroke* 42:972-8.

288. Mattace-Raso FU, van der Cammen TJ, Hofman A*, et al.* (2006): **Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study**. *Circulation* 113:657-63.

289. McArdle WD, Katch FI, Katch VL (2007): **Exercise physiology: energy, nutrition & human performance** (ed 6), *Lippincott Williams & Wilkins.*,

290. McEniery CM, Wallace S, Mackenzie IS*, et al.* (2006): **Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans**. *Hypertension* 48:602-8.

291. McGlynn KA, Cook MB (2009): **Etiologic factors in testicular germ-cell tumors**. *Future Oncol* 5:1389-402.

292. Meinardi MT, Gietema JA, van der Graaf WT*, et al.* (2000): **Cardiovascular morbidity in long-term survivors of metastatic testicular cancer**. *J Clin Oncol* 18:1725-32.

293. Meinardi MT, Gietema JA, van Veldhuisen DJ*, et al.* (2000): **Long-term chemotherapy-related cardiovascular morbidity**. *Cancer Treat Rev* 26:429-47.

294. Mezzani A, Hamm LF, Jones AM*, et al.* (2013): **Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation**. *Eur J Prev Cardiol* 20:442-67.

295. Minotti G (2013): **Pharmacology at work for cardio-oncology: ranolazine to treat early cardiotoxicity induced by antitumor drugs**. *J Pharmacol Exp Ther* 346:343-9.

296. Mishra SI, Scherer RW, Snyder C*, et al.* (2014): **Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis**. *Oncol Nurs Forum* 41:E326-42.

297. Mitchell GF, Hwang SJ, Vasan RS*, et al.* (2010): **Arterial stiffness and cardiovascular events: the Framingham Heart Study**. *Circulation* 121:505-11.

298. Mitchell GF, Parise H, Benjamin EJ*, et al.* (2004): **Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study**. *Hypertension* 43:1239-45.

299. Mitchell GF, Parise H, Vita JA*, et al.* (2004): **Local shear stress and brachial artery flow-mediated dilation: the Framingham Heart Study**. *Hypertension* 44:134-9.

300. Mitchell GF, Wang N, Palmisano JN*, et al.* (2010): **Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study**. *Circulation* 122:1379-86.

301. Mock V, Atkinson A, Barsevick A*, et al.* (2000): **NCCN practice guidelines for cancer-related fatigue**. *Oncology* 14:151-61.

302. Moholdt TT, Amundsen BH, Rustad LA*, et al.* (2009): **Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life**. *Am Heart J* 158:1031-7.

303. Molinari F, Zeng G, Suri JS (2010): **A state of the art review on intima-media thickness (IMT) measurement and wall segmentation techniques for carotid ultrasound**. *Comput Methods Programs Biomed* 100:201-21.

304. Molmen-Hansen HE, Stolen T, Tjonna AE*, et al.* (2012): **Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients**. *Eur J Prev Cardiol* 19:151-60.

305. Motl RW, Birnbaum AS, Kubik MY*, et al.* (2004): **Naturally occurring changes in physical activity are inversely related to depressive symptoms during early adolescence**. *Psychosom Med* 66:336-42.

306. Mousavi N, Nohria A (2013): **Radiation-induced cardiovascular disease**. *Curr Treat Options Cardiovasc Med* 15:507-17.

307. Mulrooney DA, Blaes AH, Duprez D (2012): **Vascular injury in cancer survivors**. *J Cardiovasc Transl Res* 5:287-95.

308. Mustian KM, Alfano CM, Heckler C*, et al.* (2017): **Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis**. *JAMA Oncol*.

309. Myers GA, Martin GJ, Magid NM*, et al.* (1986): **Power spectral analysis of heart rate varability in sudden cardiac death: comparison to other methods**. *IEEE Trans Biomed Eng* BME-33:1149-1156.

310. Myers J, Prakash M, Froelicher V*, et al.* (2002): **Exercise capacity and mortality among men referred for exercise testing**. *N Engl J Med* 346:793-801.

311. Mykletun A, Dahl AA, Haaland CF*, et al.* (2005): **Side effects and cancer-related stress determine quality of life in long-term survivors of testicular cancer**. *J Clin Oncol* 23:3061-8.

312. Nichols CR, Roth BJ, Williams SD*, et al.* (1992): **No evidence of acute cardiovascular complications of chemotherapy for testicular cancer - an analysis of the Testicular-Cancer-Intergroup Study**. *J Clin Oncol* 10:760-765.

313. Nichols W, O'Rourke M, Vlachopoulos C (2011): **McDonald's blood flow in arteries: theoretical, experimental and clinical principles**, *CRC Press.*,

314. Niederer D, Vogt L, Gonzalez-Rivera J*, et al.* (2015): **Heart rate recovery and aerobic endurance capacity in cancer survivors: interdependence and exercise-induced improvements**. *Support Care Cancer* 23:3513-20.

315. Nigam M, Aschebrook-Kilfoy B, Shikanov S*, et al.* (2015): **Increasing incidence of testicular cancer in the United States and Europe between 1992 and 2009**. *World J Urol* 33:623-31.

316. Nissinen SI, Mäkikallio TH, Seppänen T*, et al.* (2003): **Heart rate recovery after exercise as a predictor of mortality among survivors of acute myocardial infarction**. *J Am Coll Cardiol* 91:711-714.

317. Nord C, Bjoro T, Ellingsen D*, et al.* (2003): **Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer**. *Eur Urol* 44:322-8.

318. Norwegian Multicenter Study Group (1981): **Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction**. *N Engl J Med* 304:801-807.

319. Nuver J, De Haas EC, Van Zweeden M*, et al.* (2010): **Vascular damage in testicular cancer patients: a study on endothelial activation by bleomycin and cisplatin in vitro**. *Oncol Rep* 23:247-53.

320. Nuver J, Smit AJ, Sleijfer DT*, et al.* (2004): **Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer**. *Eur J Cancer* 40:701-6.

321. Nuver J, Smit AJ, Sleijfer DT*, et al.* (2005): **Left ventricular and cardiac autonomic function in survivors of testicular cancer**. *Eur J Clin Invest* 35:99-103.

322. Nuver J, Smit AJ, van der Meer J*, et al.* (2005): **Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer**. *J Clin Oncol* 23:9130-7.

323. Nuver J, Smit AJ, Wolffenbuttel BH*, et al.* (2005): **The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer**. *J Clin Oncol* 23:3718-25.

324. Oechsle K, Hartmann M, Mehnert A*, et al.* (2016): **Symptom burden in long-term germ cell tumor survivors**. *Support Care Cancer* 24:2243-50.

325. Oh JH, Baum DD, Pham S*, et al.* (2007): **Long-term complications of platinum-based chemotherapy in testicular cancer survivors**. *Med Oncol* 24:175-81.

326. Onufrak S, Abramson J, Vaccarino V (2007): **Adult-onset asthma is associated with increased carotid atherosclerosis among women in the Atherosclerosis Risk in Communities (ARIC) study**. *Atherosclerosis* 195:129-37.

327. Ordway GA, Charles JB, Randall DC*, et al.* (1982): **Heart rate adaptation to exercise training in cardiac-denervated dogs**. *J Appl Physiol Respir Environ Exerc Physiol* 52:1586-90.

328. Orre IJ, Fossa SD, Murison R*, et al.* (2008): **Chronic cancer-related fatigue in long-term survivors of testicular cancer**. *J Psychosom Res* 64:363-71.

329. Orre IJ, Murison R, Dahl AA*, et al.* (2009): **Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue**. *Brain Behav Immun* 23:868-74.

330. Oya M, Itoh H, Kato K*, et al.* (1999): **Effects of exercise training on the recovery of the autonomic nervous system and exercise capacity after acute myocardial infarction**. *Jpn Circ J* 63:843-8.

331. Packer M, Bristow MR, Cohn JN*, et al.* (1996): **The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group**. *N Engl J Med* 334:1349-55.

332. Panza JA, Diodati JG, Callahan TS*, et al.* (1992): **Role of increases in heart rate in determining the occurrence and frequency of myocardial ischemia during daily life in patients with stable coronary artery disease**. *J Am Coll Cardiol* 20:1092-8.

333. Patterson H, Norman AR, Mitra SS*, et al.* (2001): **Combination carboplatin and radiotherapy in the management of stage II testicular seminoma: comparison with radiotherapy treatment alone**. *Radiother Oncol* 59:5-11.

334. Pecanha T, Silva-Junior ND, Forjaz CL (2014): **Heart rate recovery: autonomic determinants, methods of assessment and association with mortality and cardiovascular diseases**. *Clin Physiol Funct Imaging* 34:327-39.

335. Pedersen AF, Rossen P, Olesen F*, et al.* (2012): **Fear of recurrence and causal attributions in long-term survivors of testicular cancer**. *Psychooncology* 21:1222-8.

336. Peltola M, Tulppo MP, Kiviniemi A*, et al.* (2008): **Respiratory sinus arrhythmia as a predictor of sudden cardiac death after myocardial infarction**. *Ann Med* 40:376-382.

337. Penedo FJ, Dahn JR (2005): **Exercise and well-being: a review of mental and physical health benefits associated with physical activity**. *Curr Opin Psychiatry* 18:189-93.

338. Perini R, Orizio C, Comande A*, et al.* (1989): **Plasma norepinephrine and heart rate dynamics during recovery from submaximal exercise in man**. *Eur J Appl Physiol Occup Physiol* 58:879-83.

339. Peters SA, den Ruijter HM, Bots ML (2012): **The incremental value of brachial flow-mediated dilation measurements in risk stratification for incident cardiovascular events: a systematic review**. *Ann Med* 44:305-12.

340. Petersen PM, Skakkebæk NE, Vistisen K*, et al.* (1999): **Semen quality and reproductive hormones before orchiectomy in men with testicular cancer**. *J Clin Oncol* 17:941.

341. Philpott AC, Lonn E, Title LM*, et al.* (2009): **Comparison of new measures of vascular function to flow mediated dilatation as a measure of cardiovascular risk factors**. *Am J Cardiol* 103:1610-5.

342. Pierce GL, Eskurza I, Walker AE*, et al.* (2011): **Sex-specific effects of habitual aerobic exercise on brachial artery flow-mediated dilation in middle-aged and older adults**. *Clin Sci* 120:13-23.

343. Pignoli P, Tremoli E, Poli A*, et al.* (1986): **Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging**. *Circulation* 74:1399-406.

344. Piper BF, Borneman T, Sun VC*, et al.* (2008): **Cancer-related fatigue: role of oncology nurses in translating National Comprehensive Cancer Network assessment guidelines into practice**. *Clin J Oncol Nurs* 12:37-47.

345. Pollock ML, Mengelkoch LJ, Graves JE*, et al.* (1997): **Twenty-year follow-up of aerobic power and body composition of older track athletes**. *J Appl Physiol* 82:1508-16.

346. Pratt CM, McMahon RP, Goldstein S*, et al.* (1996): **Comparison of subgroups assigned to medical regimens used to suppress cardiac ischemia (the Asymptomatic Cardiac Ischemia Pilot [ACIP] study)**. *Am J Cardiol* 77:1302-1309.

347. Preacher KJ, Hayes AF (2004): **SPSS and SAS procedures for estimating indirect effects in simple mediation models**. *Behav Res Methods Instrum Comput* 36:717-31.

348. Public Health Agency of Canada (2010): **The Chronic Disease Infobase website.**,

349. Pyke KE, Dwyer EM, Tschakovsky ME (2004): **Impact of controlling shear rate on flow-mediated dilation responses in the brachial artery of humans**. *J Appl Physiol* 97:499-508.

350. Pyke KE, Tschakovsky ME (2005): **The relationship between shear stress and flow-mediated dilatation: implications for the assessment of endothelial function**. *J Physiol* 568:357-69.

351. Pyke KE, Tschakovsky ME (2007): **Peak vs. total reactive hyperemia: which determines the magnitude of flow-mediated dilation?** *J Appl Physiol* 102:1510-1519.

352. Quarmby S, Kumar P, Kumar S (1999): **Radiation-induced normal tissue injury: role of adhesion molecules in leukocyte-endothelial cell interactions**. *Int J Cancer* 82:385-95.

353. Quasthoff S, Hartung HP (2002): **Chemotherapy-induced peripheral neuropathy**. *J Neurol* 249:9-17.

354. Raghavan D, Cox K, Childs A*, et al.* (1992): **Hypercholesterolemia after chemotherapy for testis cancer**. *J Clin Oncol* 10:1386-9.

355. Rajotte EJ, Yi JC, Baker KS*, et al.* (2012): **Community-based exercise program effectiveness and safety for cancer survivors**. *J Cancer Surviv* 6:219-28.

356. Rakobowchuk M, Tanguay S, Burgomaster KA*, et al.* (2008): **Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans**. *Am J Physiol Regul Integr Comp Physiol* 295:R236-42.

357. Reference Values for Arterial Stiffness Collaboration (2010): **Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'**. *Eur Heart J* 31:2338-50.

358. Reilley MJ, Jacobs LA, Vaughn DJ*, et al.* (2014): **Health behaviors among testicular cancer survivors**. *J Community Support Oncol* 12:121-8.

359. Reynolds RD, Calzadilla SV, Lee RJ (1978): **Spontaneous heart rate, propranolol, and ischaemia-induced ventricular fibrillation in the dog**. *Cardiovasc Res* 12:653-8.

360. Ribeiro F, Alves AJ, Duarte JA*, et al.* (2010): **Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation?** *Int J Cardiol* 141:214-21.

361. Riley WA, Evans GW, Sharrett AR*, et al.* (1997): **Variation of common carotid artery elasticity with intimal-medial thickness: the ARIC Study. Atherosclerosis Risk in Communities**. *Ultrasound Med Biol* 23:157-64.

362. Robinson D, Moller H, Horwich A (2007): **Mortality and incidence of second cancers following treatment for testicular cancer**. *Br J Cancer* 96:529-33.

363. Rogers LQ, Hopkins-Price P, Vicari S*, et al.* (2009): **Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects**. *Cancer Epidemiol Biomarkers Prev* 18:1410-8.

364. Rognmo O, Hetland E, Helgerud J*, et al.* (2004): **High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease**. *Eur J Cardiovasc Prev Rehabil* 11:216-222.

365. Rognmo O, Moholdt T, Bakken H*, et al.* (2012): **Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients**. *Circulation* 126:1436-40.

366. Rosenberg M (1965): **Society and the adolescent self-image**. NJ, *Princeton university press Princeton*,

367. Ross CE, Hayes D (1988): **Exercise and psychologic well-being in the community**. *Am J Epidemiol* 127:762-71.

368. Rossen P, Pedersen AF, Zachariae R*, et al.* (2012): **Sexuality and body image in long-term survivors of testicular cancer**. *Eur J Cancer* 48:571-8.

369. Rossen PB, Pedersen AF, Zachariae R*, et al.* (2009): **Health-related quality of life in long-term survivors of testicular cancer**. *J Clin Oncol* 27:5993-9.

370. Rush JW, Denniss SG, Graham DA (2005): **Vascular nitric oxide and oxidative stress: determinants of endothelial adaptations to cardiovascular disease and to physical activity**. *Can J Appl Physiol* 30:442-74.

371. Sagstuen H, Aass N, Fossa SD*, et al.* (2005): **Blood pressure and body mass index in long-term survivors of testicular cancer**. *J Clin Oncol* 23:4980-90.

372. Saltin B, Essén B, Pedersen PK (1976): **Intermittent exercise: its physiology and some practical applications**, *Karger Publishers.*,

373. Sambuceti G, Marzilli M, Marraccini P*, et al.* (1997): **Coronary vasoconstriction during myocardial ischemia induced by rises in metabolic demand in patients with coronary artery disease**. *Circulation* 95:2652-9.

374. Sasso JP, Eves ND, Christensen JF*, et al.* (2015): **A framework for prescription in exercise-oncology research**. *J Cachexia Sarcopenia Muscle* 6:115-24.

375. Saul JP, Rea RF, Eckberg DL*, et al.* (1990): **Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity**. *Am J Physiol* 258:H713-21.

376. Schillaci G, Sarchielli P, Corbelli I*, et al.* (2010): **Aortic stiffness and pulse wave reflection in young subjects with migraine: a case-control study**. *Neurology* 75:960-6.

377. Schjerve IE, Tyldum GA, Tjonna AE*, et al.* (2008): **Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults**. *Clin Sci* 115:283-93.

378. Schmitt DP, Allik J (2005): **Simultaneous administration of the Rosenberg Self-Esteem Scale in 53 nations: exploring the universal and culture-specific features of global self-esteem**. *J Pers Soc Psychol* 89:623-42.

379. Schmitz KH, Courneya KS, Matthews C*, et al.* (2010): **American College of Sports Medicine roundtable on exercise guidelines for cancer survivors**. *Med Sci Sports Exerc* 42:1409-26.

380. Schnohr P, Marott JL, Jensen JS*, et al.* (2012): **Intensity versus duration of cycling, impact on all-cause and coronary heart disease mortality: the Copenhagen City Heart Study**. *Eur J Prev Cardiol* 19:73-80.

381. Schwartz PJ, La Rovere MT, Vanoli E (1992): **Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification**. *Circulation* 85:I77-91.

382. Schwartz PJ, Vanoli E, Strambabadiale M*, et al.* (1988): **Autonomic mechanisms and sudden-death - New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial-infarction**. *Circulation* 78:969-979.

383. Scott J (2004): **Pathophysiology and biochemistry of cardiovascular disease**. *Curr Opin Genet Dev* 14:271-9.

384. Scott JM, Adams SC, Koelwyn GJ*, et al.* (2016): **Cardiovascular late effects and exercise treatment in breast cancer: current evidence and future directions**. *Can J Cardiol* 32:881-90.

385. Scott JM, Koelwyn GJ, Hornsby WE*, et al.* (2013): **Exercise therapy as treatment for cardiovascular and oncologic disease after a diagnosis of early-stage cancer**. *Semin Oncol* 40:218-28.

386. Seals DR, Chase PB (1989): **Influence of physical training on heart rate variability and baroreflex circulatory control**. *J Appl Physiol* 66:1886-95.

387. Selzer RH, Mack WJ, Lee PL*, et al.* (2001): **Improved common carotid elasticity and intima-media thickness measurements from computer analysis of sequential ultrasound frames**. *Atherosclerosis* 154:185-93.

388. Senkus E, Jassem J (2011): **Cardiovascular effects of systemic cancer treatment**. *Cancer Treat Rev* 37:300-11.

389. Shahani BT, Halperin JJ, Boulu P*, et al.* (1984): **Sympathetic skin response--a method of assessing unmyelinated axon dysfunction in peripheral neuropathies**. *J Neurol Neurosurg Psychiatry* 47:536-42.

390. Shechter M, Matetzky S, Arad M*, et al.* (2009): **Vascular endothelial function predicts mortality risk in patients with advanced ischaemic chronic heart failure**. *Eur J Heart Fail* 11:588-93.

391. Shetler K, Marcus R, Froelicher VF*, et al.* (2001): **Heart rate recovery: validation and methodologic issues**. *J Am Coll Cardiol* 38:1980-7.

392. Shi X, Stevens GH, Foresman BH*, et al.* (1995): **Autonomic nervous system control of the heart: endurance exercise training**. *Med Sci Sports Exerc* 27:1406-13.

393. Shinn EH, Swartz RJ, Thornton BB*, et al.* (2010): **Testis cancer survivors' health behaviors: comparison with age-matched relative and demographically matched population controls**. *J Clin Oncol* 28:2274-9.

394. Shock NW (1984): **Normal human aging: the Baltimore longitudinal study of aging**. Bethesda, MD, *National Institute on Aging*

395. Siegel R, Naishadham D, Jemal A (2013): **Cancer statistics 2013**. *CA Cancer J Clin* 63:11-30.

396. Simons PC, Algra A, Bots ML*, et al.* (1999): **Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease)**. *Circulation* 100:951-7.

397. Sinclair SJ, Blais MA, Gansler DA*, et al.* (2010): **Psychometric properties of the Rosenberg Self-Esteem Scale: overall and across demographic groups living within the United States**. *Eval Health Prof* 33:56-80.

398. Skaali T, Fossa SD, Andersson S*, et al.* (2011): **Self-reported cognitive problems in testicular cancer patients: relation to neuropsychological performance, fatigue, and psychological distress**. *J Psychosom Res* 70:403-10.

399. Skaali T, Fossa SD, Bremnes R*, et al.* (2009): **Fear of recurrence in long-term testicular cancer survivors**. *Psychooncology* 18:580-8.

400. Skakkebaek NE, Rajpert-De Meyts E, Main KM (2001): **Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects**. *Hum Reprod* 16:972-8.

401. Smith AB, Butow P, Olver I*, et al.* (2016): **The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study**. *J Cancer Surviv* 10:223-33.

402. Smith DL, Fernhall B (2011): **Advanced cardiovascular exercise physiology**, *Human Kinetics.*,

403. Smith LL, Kukielka M, Billman GE (2005): **Heart rate recovery after exercise: a predictor of ventricular fibrillation susceptibility after myocardial infarction**. *Am J Physiol Heart Circ Physiol* 288:H1763-9.

404. Smith ML, Hudson DL, Graitzer HM*, et al.* (1989): **Exercise training bradycardia: the role of autonomic balance**. *Med Sci Sports Exerc* 21:40-4.

405. Sonnenschein K, Horvath T, Mueller M*, et al.* (2011): **Exercise training improves in vivo endothelial repair capacity of early endothelial progenitor cells in subjects with metabolic syndrome**. *Eur J Cardiovasc Prev Rehabil* 18:406-14.

406. Soultati A, Mountzios G, Avgerinou C*, et al.* (2012): **Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications**. *Cancer Treat Rev* 38:473-83.

407. Spielberger CD, Gorsuch RL, Lushene R*, et al.* (1983): **Manual for the state-trait anxiety inventory**. Palo Alto, CA, *Consulting Psychologists Press.*,

408. Sprauten M, Darrah TH, Peterson DR*, et al.* (2012): **Impact of long-term serum platinum concentrations on neuro- and ototoxicity in cisplatin-treated survivors of testicular cancer**. *J Clin Oncol* 30:300-7.

409. Sprauten M, Haugnes HS, Brydøy M*, et al.* (2015): **Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: increasing prevalence and risk factors**. *Ann Oncol* 26:2133-2140.

410. Stefenelli T, Kuzmits R, Ulrich W*, et al.* (1988): **Acute vascular toxicity after combination chemotherapy with cisplatin, vinblastine, and bleomycin for testicular cancer**. *Eur Heart J* 9:552-6.

411. Stehouwer CD, Henry RM, Dekker JM*, et al.* (2004): **Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: further evidence for a link between microalbuminuria and endothelial dysfunction--the Hoorn Study**. *Kidney Int Suppl* 66:S42-4.

412. Stein PK, Ehsani AA, Domitrovich PP*, et al.* (1999): **Effect of exercise training on heart rate variability in healthy older adults**. *Am Heart J* 138:567-76.

413. Stein R, Medeiros CM, Rosito GA*, et al.* (2002): **Intrinsic sinus and atrioventricular node electrophysiologic adaptations in endurance athletes**. *J Am Coll Cardiol* 39:1033-8.

414. Stickland MK, Butcher SJ, Marciniuk DD*, et al.* (2012): **Assessing exercise limitation using cardiopulmonary exercise testing**. *Pulmonary medicine* 2012:13.

415. Stoter G, Koopman A, Vendrik CP*, et al.* (1989): **Ten-year survival and late sequelae in testicular cancer patients treated with cisplatin, vinblastine, and bleomycin**. *J Clin Oncol* 7:1099-104.

416. Strumberg D, Brugge S, Korn MW*, et al.* (2002): **Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer**. *Ann Oncol* 13:229-36.

417. Stuart NS, Woodroffe CM, Grundy R*, et al.* (1990): **Long-term toxicity of chemotherapy for testicular cancer--the cost of cure**. *Br J Cancer* 61:479-84.

418. Sundaram S, Shoushtari C, Carnethon M*, et al.* (2004): **Autonomic and nonautonomic determinants of heart rate recovery**. *Heart Rhythm* 1:S100-S101.

419. Sutton-Tyrrell K, Najjar SS, Boudreau RM*, et al.* (2005): **Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults**. *Circulation* 111:3384-90.

420. Swain SM, Whaley FS, Ewer MS (2003): **Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials**. *Cancer* 97:2869-79.

421. Takamochi K, Nagai K, Yoshida J*, et al.* (2000): **The role of computed tomographic scanning in diagnosing mediastinal node involvement in non-small cell lung cancer**. *J Thorac Cardiovasc Surg* 119:1135-40.

422. Talbot LA, Metter EJ, Fleg JL (2000): **Leisure-time physical activities and their relationship to cardiorespiratory fitness in healthy men and women 18-95 years old**. *Med Sci Sports Exerc* 32:417-425.

423. Tanaka H, Dinenno FA, Monahan KD*, et al.* (2000): **Aging, habitual exercise, and dynamic arterial compliance**. *Circulation* 102:1270-5.

424. Tanaka H, Seals DR, Monahan KD*, et al.* (2002): **Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men**. *J Appl Physiol* 92:1458-64.

425. Tanaka N, Nozawa T, Yasumura Y*, et al.* (1990): **Heart-rate-proportional oxygen consumption for constant cardiac work in dog heart**. *Jpn J Physiol* 40:503-21.

426. Tang YD, Dewland TA, Wencker D*, et al.* (2009): **Post-exercise heart rate recovery independently predicts mortality risk in patients with chronic heart failure**. *J Card Fail* 15:850-5.

427. Taniwaki H, Kawagishi T, Emoto M*, et al.* (1999): **Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes**. *Diabetes Care* 22:1851-1857.

428. Task Force of the European Society of Cardiology & North American Society of Pacing Electrophysiology (1996): **Heart rate variability: standards of measurement, physiological interpretation, and clinical use**. *Circulation* 93:1043-1065.

429. Taylor JA, Myers CW, Halliwill JR*, et al.* (2001): **Sympathetic restraint of respiratory sinus arrhythmia: implications for vagal-cardiac tone assessment in humans**. *Am J Physiol Heart Circ Physiol* 280:H2804-14.

430. Thayer JF, Lane RD (2007): **The role of vagal function in the risk for cardiovascular disease and mortality**. *Biol Psychol* 74:224-42.

431. Thijssen DH, Black MA, Pyke KE*, et al.* (2011): **Assessment of flow-mediated dilation in humans: a methodological and physiological guideline**. *Am J Physiol Heart Circ Physiol* 300:H2-12.

432. Thompson PD, Buchner D, Pina IL*, et al.* (2003): **Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)**. *Circulation* 107:3109-16.

433. Thorsen L, Nystad W, Stigum H*, et al.* (2005): **The association between self-reported physical activity and prevalence of depression and anxiety disorder in long-term survivors of testicular cancer and men in a general population sample**. *Support Care Cancer* 13:637-46.

434. Tian L, Lu HJ, Lin L*, et al.* (2016): **Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials**. *Support Care Cancer* 24:969-83.

435. Tinken TM, Thijssen DH, Black MA*, et al.* (2008): **Time course of change in vasodilator function and capacity in response to exercise training in humans**. *J Physiol* 586:5003-12.

436. Tjonna AE, Lee SJ, Rognmo O*, et al.* (2008): **Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study**. *Circulation* 118:346-54.

437. Toth MJ, Gardner AW, Ades PA*, et al.* (1994): **Contribution of body composition and physical activity to age-related decline in peak VO2 in men and women**. *J Appl Physiol* 77:647-52.

438. Touboul PJ, Hennerici MG, Meairs S*, et al.* (2012): **Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011**. *Cerebrovasc Dis* 34:290-6.

439. Toumbis-Ioannou E, Cohen PR (1994): **Chemotherapy-induced Raynaud's phenomenon**. *Cleve Clin J Med* 61:195-9.

440. Tracey KJ (2009): **Reflex control of immunity**. *Nat Rev Immunol* 9:418-28.

441. Traub O, Berk BC (1998): **Laminar shear stress: mechanisms by which endothelial cells transduce an atheroprotective force**. *Arterioscler Thromb Vasc Biol* 18:677-85.

442. Travis LB, Fossa SD, Schonfeld SJ*, et al.* (2005): **Second cancers among 40,576 testicular cancer patients: focus on long-term survivors**. *J Natl Cancer Inst* 97:1354-65.

443. Trombold JR, Christmas KM, Machin DR*, et al.* (2013): **Acute high-intensity endurance exercise is more effective than moderate-intensity exercise for attenuation of postprandial triglyceride elevation**. *J Appl Physiol* 114:792-800.

444. Turner ML, Boland OM, Parker AC*, et al.* (1993): **Subclinical autonomic dysfunction in patients with Hodgkin's disease and non-Hodgkin's lymphoma**. *Br J Haematol* 84:623-6.

445. van Basten JP, Jonker-Pool G, van Driel MF*, et al.* (1996): **Fantasies and facts of the testes**. *Br J Urol* 78:756-62.

446. Van Bortel LM, Laurent S, Boutouyrie P*, et al.* (2012): **Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity**. *J Hypertens* 30:445-448.

447. van den Belt-Dusebout AW, de Wit R, Gietema JA*, et al.* (2007): **Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer**. *J Clin Oncol* 25:4370-8.

448. van den Belt-Dusebout AW, Nuver J, de Wit R*, et al.* (2006): **Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer**. *J Clin Oncol* 24:467-75.

449. van Popele NM, Grobbee DE, Bots ML*, et al.* (2001): **Association between arterial stiffness and atherosclerosis: the Rotterdam Study**. *Stroke* 32:454-460.

450. van Schinkel LD, Willemse PM, van der Meer RW*, et al.* (2013): **Chemotherapy for testicular cancer induces acute alterations in diastolic heart function**. *Br J Cancer* 109:891-6.

451. van Tol BA, Huijsmans RJ, Kroon DW*, et al.* (2006): **Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis**. *Eur J Heart Fail* 8:841-50.

452. Vanoli E, De Ferrari GM, Stramba-Badiale M*, et al.* (1991): **Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction**. *Circ Res* 68:1471-81.

453. Vaughn DJ, Palmer SC, Carver JR*, et al.* (2008): **Cardiovascular risk in long-term survivors of testicular cancer**. *Cancer* 112:1949-53.

454. Verheij M, Dewit LG, Valdes Olmos RA*, et al.* (1994): **Evidence for a renovascular component in hypertensive patients with late radiation nephropathy**. *Int J Radiat Oncol Biol Phys* 30:677-83.

455. Verhoeven RH, Karim-Kos HE, Coebergh JW*, et al.* (2014): **Markedly increased incidence and improved survival of testicular cancer in the Netherlands**. *Acta Oncol* 53:342-50.

456. Verrier RL, Tan A (2009): **Heart rate, autonomic markers, and cardiac mortality**. *Heart Rhythm* 6:S68-75.

457. Vidrine DJ, Hoekstra-Weebers JE, Hoekstra HJ*, et al.* (2010): **The effects of testicular cancer treatment on health-related quality of life**. *Urology* 75:636-41.

458. Viniegra M, Marchetti M, Losso M*, et al.* (1990): **Cardiovascular autonomic function in anthracycline-treated breast cancer patients**. *Cancer Chemother Pharmacol* 26:227-31.

459. Vlachopoulos C, Aznaouridis K, Stefanadis C (2010): **Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis**. *J Am Coll Cardiol* 55:1318-27.

460. Vogelzang NJ, Bosl GJ, Johnson K*, et al.* (1981): **Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer**. *Ann Intern Med* 95:288-92.

461. Ware JE, Kosinski M, Bjorner JB*, et al.* (2008): **User's manual for the SF-36v2 Health Survey**, *Quality Metric.*,

462. Weisbrod RM, Shiang T, Al Sayah L*, et al.* (2013): **Arterial stiffening precedes systolic hypertension in diet-induced obesity**. *Hypertension* 62:1105-10.

463. Weston KS, Wisloff U, Coombes JS (2014): **High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis**. *Br J Sports Med* 48:1227-34.

464. Wethal T, Haugnes HS, Kjekshus J*, et al.* (2010): **C-reactive protein; a potential marker of second cancer and cardiovascular disease in testicular cancer survivors?** *Eur J Cancer* 46:3425-33.

465. Weuve J, Kang JH, Manson JE*, et al.* (2004): **Physical activity, including walking, and cognitive function in older women**. *JAMA* 292:1454-61.

466. Wiechno P, Demkow T, Kubiak K*, et al.* (2007): **The quality of life and hormonal disturbances in testicular cancer survivors in the cisplatin era**. *Eur Urol* 52:1448-54.

467. Wienbergen H, Hambrecht R (2013): **Physical exercise and its effects on coronary artery disease**. *Curr Opin Pharmacol* 13:218-25.

468. Willemse PM, Burggraaf J, Hamdy NA*, et al.* (2013): **Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors**. *Br J Cancer* 109:60-7.

469. Willemse PP, van der Meer RW, Burggraaf J*, et al.* (2014): **Abdominal visceral and subcutaneous fat increase, insulin resistance and hyperlipidemia in testicular cancer patients treated with cisplatin-based chemotherapy**. *Acta Oncol* 53:351-60.

470. Wisloff U, Stoylen A, Loennechen JP*, et al.* (2007): **Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study**. *Circulation* 115:3086-94.

471. Woodward M, Webster R, Murakami Y*, et al.* (2014): **The association between resting heart rate, cardiovascular disease and mortality: evidence from 112,680 men and women in 12 cohorts**. *Eur J Prev Cardiol* 21:719-26.

472. World Health Organization (2004): **The global burden of disease 2004 update: disability weights for diseases and conditions**. Geneva.

473. Yasuma F, Hayano J (2004): **Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm?** *Chest* 125:683-90.

474. Yeap BB (2009): **Testosterone and ill-health in aging men**. *Nat Clin Pract Endocrinol Metab* 5:113-121.

475. Yellen SB, Cella DF, Webster K*, et al.* (1997): **Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system**. *J Pain Symptom Manage* 13:63-74.

476. Yokoyama H, Emoto M, Fujiwara S*, et al.* (2004): **Short-term aerobic exercise improves arterial stiffness in type 2 diabetes**. *Diabetes Res Clin Pract* 65:85-93.

477. Yoshikawa A, Saura R, Matsubara T*, et al.* (1997): **A mechanism of cisplatin action: antineoplastic effect through inhibition of neovascularization**. *Kobe J Med Sci* 43:109-120.

478. Zagars GK, Ballo MT, Lee AK*, et al.* (2004): **Mortality after cure of testicular seminoma**. *J Clin Oncol* 22:640-7.

479. Zanesco A, Antunes E (2007): **Effects of exercise training on the cardiovascular system: pharmacological approaches**. *Pharmacol Ther* 114:307-17.

480. Zuanetti G, De Ferrari GM, Priori SG*, et al.* (1987): **Protective effect of vagal stimulation on reperfusion arrhythmias in cats**. *Circ Res* 61:429-35.

481. β-Blocker Heart Attack Trial Research Group (1982): **A randomized trial of propranolol in patients with acute myocardial infarction**. *JAMA* 247:1707-1714.

Appendix A: TC Diagnostic and Prognostic Information

	pT	Primary tumour*
	pTX	Primary tumour cannot be assessed
	pT0	No evidence of primary tumour (eg, histologic scar in testis)
	pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)
	pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: Tumour may invade tunica albuginea but not tunica vaginalis
	pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion or tumour extending through tunica albuginea with involvement of tunica vaginalis
	pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
	pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N – Regional lymph nodes clinical		
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis with a lymph node mass ≤2 cm in greatest dimension or multiple lymph nodes; none >2 cm in greatest dimension
	N2	Metastasis with a lymph node mass >2 cm but ≤5 cm in greatest dimension or multiple lymph nodes; any one mass >2 cm but ≤5 cm in greatest dimension
	N3	Metastasis with a lymph node mass >5 cm in greatest dimension
pN – Pathologic regional lymph nodes		
	pNX	Regional lymph nodes cannot be assessed
	pN0	No regional lymph node metastasis
	pN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension and ≤5 positive nodes; none >2 cm in greatest dimension
	pN2	Metastasis with a lymph node mass >2 cm but <5 cm in greatest dimension; or >5 nodes positive, none >5 cm; or evidence of extranodal extension of tumour
	pN3	Metastasis with a lymph node mass >5 cm in greatest dimension
M – Distant metastasis		
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
		M1a Nonregional lymph node(s) or lung
		M1b Other sites
pM – Pathologic distant metastasis		
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
		M1a Nonregional lymph node(s) or lung
		M1b Other sites
S – Serum tumour markers		
Sx		Serum markers studies not available or not performed
S0		Serum marker study levels within normal limits

	LDH, U/l	hCG, mIU/ml	AFP, ng/ml
S1	<1.5 × N and	<5000 and	<1000
S2	1.5–10 × N or	5000–50,000 or	1000–10,000
S3	>10 × N or	>50,000 or	>10,000

LDH = lactate dehydrogenase; N = upper limit of normal for the LDH assay; hCG = human gonadotrophin; AFP = α-fetoprotein.
* Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

Figure A1: TNM classification for testicular cancer[1]

Good-prognosis group	
Nonseminoma (56% of cases)	All of the following criteria:
5-yr PFS 89%	Testis/retroperitoneal primary
5-yr survival 92%	No nonpulmonary visceral metastases
	AFP <1000 ng/ml
	hCG <5000 IU/l (1000 ng/ml)
	LDH <1.5 × ULN
Seminoma (90% of cases)	All of the following criteria:
5-yr PFS 82%	Any primary site
5-yr survival 86%	No nonpulmonary visceral metastases
	Normal AFP
	Any hCG
	Any LDH
Intermediate-prognosis group	
Nonseminoma (28% of cases)	All of the following criteria:
5-yr PFS 75%	Testis/retroperitoneal primary
5-yr survival 80%	No nonpulmonary visceral metastases
	AFP 1000–10,000 ng/ml, or
	hCG 5000–50,000 IU/l, or
	LDH 1.5–10 × ULN
Seminoma (10% of cases)	Any of the following criteria:
5-yr PFS 67%	Any primary site
5-yr survival 72%	Nonpulmonary visceral metastases
	Normal AFP
	Any hCG
	Any LDH
Poor-prognosis group	
Nonseminoma (16% of cases)	Any of the following criteria:
5-yr PFS 41%	Mediastinal primary
5-yr survival 48%	Nonpulmonary visceral metastases
	AFP >10,000 ng/ml, or
	hCG >50,000 IU/l (10,000 ng/ml), or
	LDH >10 × ULN
Seminoma	
No patients classified as poor prognosis	

PFS = progression-free survival; AFP = α-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; ULN = upper limit of normal range.

Figure A2: Prognostic-based staging system for metastatic germ cell cancer[1]

Reference:

1. Albers P, Albrecht W, Algaba F*, et al.* (2011): **EAU guidelines on testicular cancer: 2011 update**. *Eur Urol* 60:304-19.

Appendix B: Methods of Cardiovascular Health Assessment

Methods of Cardiovascular Health Assessment

The pathophysiological processes underlying the clinical manifestations of CVD are pro-atherosclerotic, -thrombotic, -arrhythmic and -inflammatory disease states/conditions. Traditional risk factors for CVD are categorized as modifiable (i.e., high cholesterol, obesity, high blood pressure, physical inactivity, unhealthy diets, diabetes, tobacco exposure and harmful use of alcohol) and non-modifiable (i.e., age, ethnicity and family history). Recently, an increasing number of investigations have examined the clinical utility of additional CVD risk factors that may add important prognostic information in the identification and management of individuals at-risk of CVD. Through large cohort investigations, like the Framingham Heart Study,[1] patterns of negative age-related changes to the cardiovascular system (i.e., arterial stiffening/distensibility-blood pressure relationships,[2,3] blood pressure and pulse pressure-cardiovascular morbidity risks,[4-6] age-specific risk factor fluctuations,[7] body mass index -blood pressure relationships,[8] genetic components of morbidity risks,[9] and pulse wave reflection-cardiovascular morbidity risks[10]) have been identified. The following sections provide a brief review of the evidence supporting the evaluation of, and theoretical considerations for, the novel CVD risk factors used in the HIITTS trial.

Assessments of Vascular Health

Pulse-Wave Velocity

Numerous studies have demonstrated that arterial stiffness is a strong, independent predictor of CVD risk.[11,12] As reported in the Framingham Heart Study, the predictive value of arterial stiffness for future cardiovascular events was greatly superior when assessed by carotid-femoral pulse-wave velocity (PWV) compared to carotid-radial PWV, central pulse pressure, pulse pressure amplification, and the augmentation index.[6] Accordingly, carotid-femoral PWV

has become the gold standard assessment of arterial stiffness[11] and was our primary measure of vascular stiffness. Furthermore, we also attempted to characterize peripheral arterial stiffness by assessing femoral-toe PWV. The addition of femoral-toe PWV provided additional insight into the pattern of arterial stiffening throughout the arterial tree.

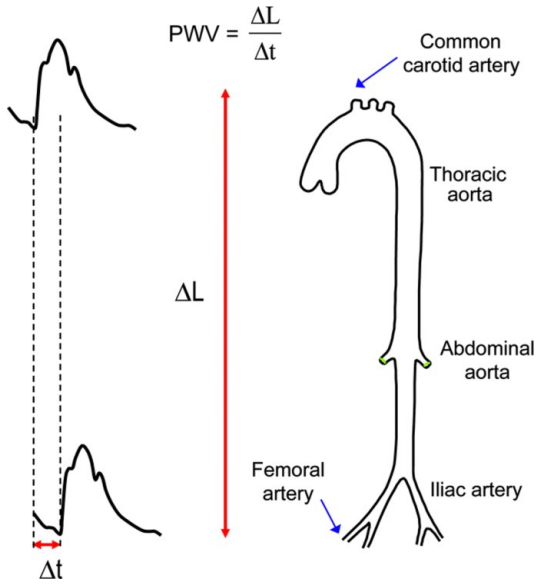


Figure B1: Assessment of carotid-femoral PWV using the foot-to-foot method[13]

A recent expert consensus report[14] highlighted a number of key theoretical and methodological considerations for carotid-femoral PWV assessment, described below. Carotid-femoral PWV is determined by measuring and dividing the traveled distance by the transit time of a vascular pulse wave (**Figure B1**).[14] The measurement can be ascertained directly from a single pulse wave, or indirectly by subtracting the time delay of the electrocardiogram-derived Rtop at the common carotid from the Rtop at the common femoral artery.[11,15] Until recently, the full measured distance between the common carotid and common femoral arteries was used in PWV calculations. However, a magnetic resonance imaging-based correction factor[16] has been proposed which has been shown to overestimate the real traveled distance of a vascular pulse

wave by only 0.4%. The corrected equation for real traveled distance = (0.286 · (common carotid artery (cm) – common femoral artery (cm)) + (0.101 · age) + (0.159 · weight (kg)) + 16.165. However, the recently published normative PWV data was derived using a simplified version of this correction factor:[15]

$$PWV = (Common\ carotid\ artery - Common\ femoral\ artery) \times 0.8.$$

Importantly, age and blood pressure are established determinants of carotid-femoral PWV.[15] Although a 10 m/s cut-off has been proposed as the risk factor criteria for carotid-femoral PWV,[14] it may not be appropriate to apply the criteria to samples with highly variable ages and blood pressures.[15] Therefore, for the purposes of this investigation, the simplified carotid-femoral PWV correction equation and age-/blood pressure-adjusted carotid-femoral PWV risk factor cut-offs will be used.

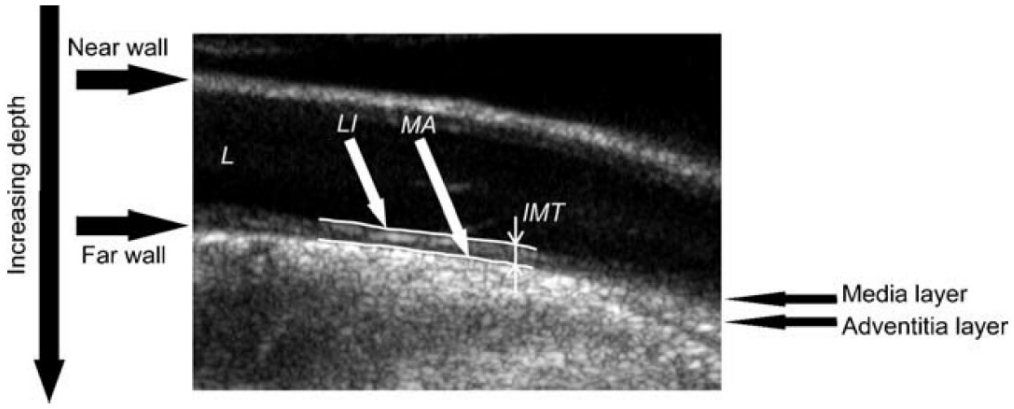


Figure B2: Longitudinal projection of common carotid artery
Notes: (L) artery lumen. (LI) lumen-intima. (MA) media-adventitia. Intima-media thickness calculated as the distance between the LI and MA.[17]

Carotid Plaque and Intima-Media Thickness

In atherogenesis, B-mode ultrasonography can be used to visualize the first morphological abnormalities within the arterial walls and is suggested to be one of the best non-invasive techniques available to detect early atherosclerotic development.[18] Evidence from recent meta-analyses and diagnostic cohort studies suggests that the assessment of carotid plaque is a stronger predictor of CVD events than intima-media thickness;[19-21] however, intima-media thickness assessment remains prognostically useful when augmented by thorough scans of the carotid arteries for carotid plaque.[19,20] According to the guidelines,[18] the following definitions of intima-media thickness and plaque boundaries are used to classify any observed carotid artery lesions. First, intima-media thickness is a double-line pattern visualized by echography on both walls of the common carotid artery in a longitudinal image. The leading edges of the two

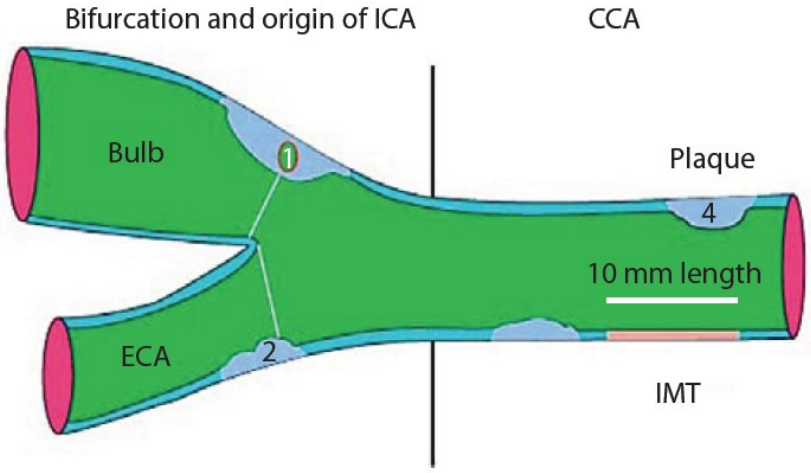


Figure B3: Carotid tree with intima-media thickness and plaque measurements according to Mannheim consensus

Notes: 1) >1.5 mm thickness, 2) >0.5 mm lumen encroaching, 4) 50% of the surrounding intima-media thickness value. [18]

anatomical boundaries of interest (i.e., lumen-intima and media-adventitia interfaces) are visualized as two parallel lines (**Figure B2**). This definition complies with intima-media thickness correlation studies comparing this ultrasound pattern to carotid anatomy specimens.[22] Second, plaques are focal structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness value, or demonstrates a thickness >1.5mm as measured from the intima-lumen interface to the media-adventitia interface (**Figure B3**). Overall carotid artery plaque burden was assessed by totaling the number of plaque-present sites and generating a total plaque score, based on a total of 12 possible affected locations (i.e., 6 measurement sites per side). Subsequently, the severity of arterial plaque development was classified according to participants having no plaque (0 sites), mild plaque (1-4 sites), moderate plaque (5-8 sites) and severe plaque (9-12 sites).[23]

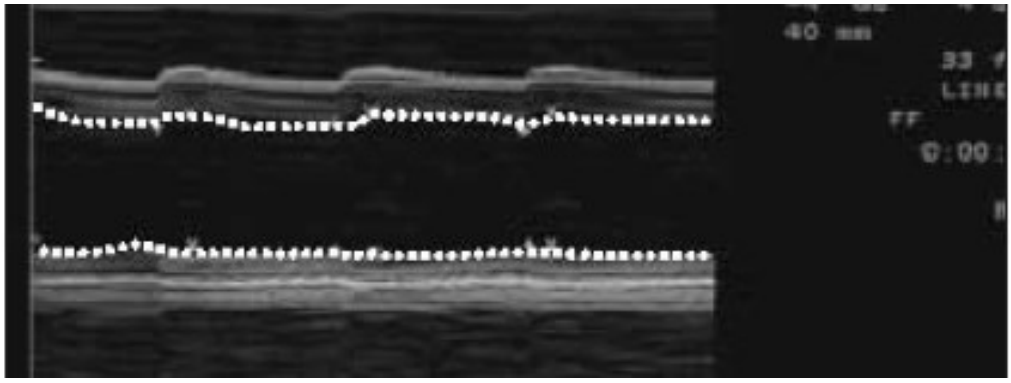


Figure B4: Common carotid artery diameter changes across cardiac cycles[24]

Carotid Distensibility

In general, arterial distensibility reflects an artery's ability to expand and recoil according to, or in-phase with, cardiac pulse pressures (**Figure B4**).[25] A functional loss of arterial distensibility (i.e., an increase in artery wall stiffness) has been associated with early

atherosclerotic CVD development and progression, and may precede structural wall changes and clinical CVD symptoms.[26,27] Of note, carotid distensibility is only an estimate of the strain and modulus because of its interdependence on the movement of the surrounding tissue and limitations to vessel wall boundary identification.[28] Technical limitations aside, carotid distensibility is recognized as a novel CVD risk factor for central and peripheral vascular disease as well as cerebrovascular events.[23,29-32]

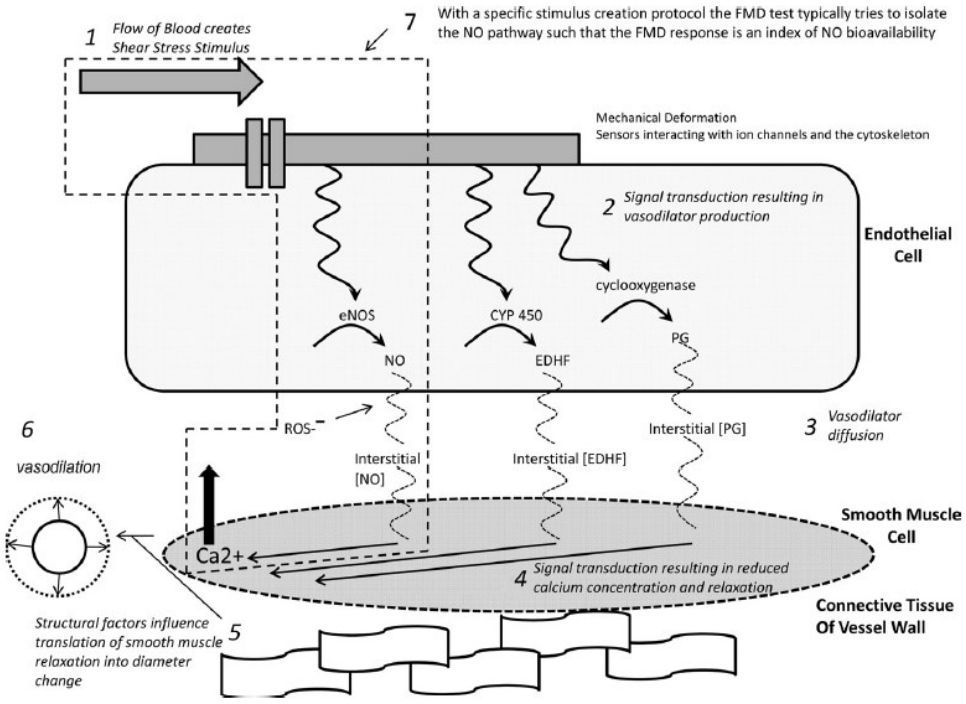


Figure B5: Mechanisms of flow-mediated dilation – sheer stress to vasodilation[33]

Flow-Mediated Dilation and Microvascular Function

On a physiological level, flow-mediated dilation reflects any artery's capacity to vasodilate in response to increased arterial wall sheer stress (**Figure B5**).[34] First introduced by Celermajer et al.,[35] numerous studies have employed variations of this technique as a non-

invasive means to assess endothelial function and its relation to the development, severity, and progression of CVD.[36] The flow-mediated dilation response was initially thought to be exclusively dependent on the production and action of a vasodilator substance called endothelial-derived hyperpolarizing factor, now known as nitric oxide.[35] However, it is now understood that subtle protocol variations can alter the mechanisms driving the resultant vasodilatory response,[33] which extend beyond the nitric oxide pathway. Accordingly, and in order to preserve the

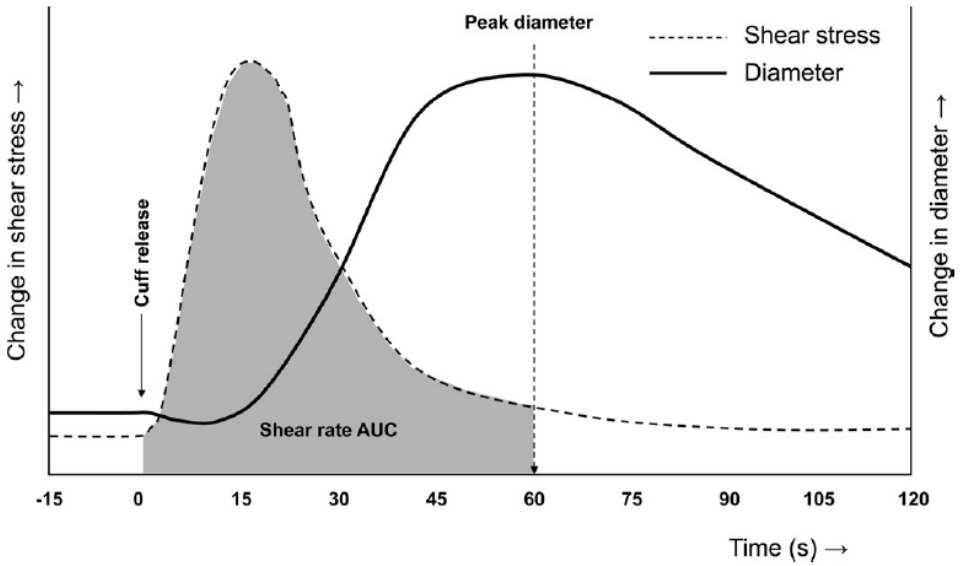


Figure B6: Vascular diameter/sheer stress profiles following cuff-release after 5-minute occlusion[33]

endothelial-specific nature of the technique, strict adherence to specific protocol components is essential. The key protocol considerations include i) occlusion location and duration, ii) timing of baseline diameter, iii) timing and duration of peak dilatory response, iv) simultaneous assessment of vessel diameter and blood velocity, v) velocity signal analysis, vi) measurement of, and normalization for, the response stimulus (i.e., shear force) (**Figure B6**).[33] Moreover, whereas flow-mediated dilation is a measure of conduit vessel function, measures of microvascular function (i.e., velocity time integral and shear stress during reactive hyperemia) have been shown

to independently predict and provide stronger correlations to CVD risk.[37-40] Brachial artery occlusion elicits a vasodilatory response within healthy microvasculature. The accompanying decrease in vascular resistance permits greater blood flow during reactive hyperemia and, therein, higher velocity time integral and shear stress during reactive hyperemia are expected from healthier vasculature.

Assessment of Autonomic Function

As simple measures of autonomic nervous system function (*primarily the parasympathetic branch*), resting HR, HR variability (e.g., respiratory sinus arrhythmia), and post-exercise HRR are strong predictors of CVD risk and all-cause mortality in the primary prevention and secondary prevention settings.[41-44]

Resting Heart Rate

Resting HR is the simplest indirect measure of resting parasympathetic tone.[42] In humans, HR is intrinsically driven by the sino-atrial node at a variably fixed pace of between 60 to 100 beats per minute (bpm) and is externally gated by the parasympathetic and sympathetic branches of the autonomic nervous system.[34] In healthy resting individuals, it is widely accepted that the heart rhythm is predominantly under parasympathetic (vagal) control (**Figure B7**).[34] After more than 50 years studying the associations between resting HR and mortality outcomes in healthy and clinical populations, our understanding of resting HR has evolved from treating it as a simple pathophysiological phenomenon to a viable treatment target for interventional research.[45] Epidemiological research reports strong and inverse relationships between resting HR and overall life expectancy[41,42] which extends across most invertebrate species.[46] Importantly, evidence suggests that the role of resting HR may extend beyond these associations as a causal factor in CVD development. Indeed, on the basis of preclinical[47-54] and clinical models,[55-62]

pathophysiological links between high resting HRs and atherosclerosis, arteriosclerosis, myocardial ischemia, and ventricular arrhythmias in humans have been proposed.[63]

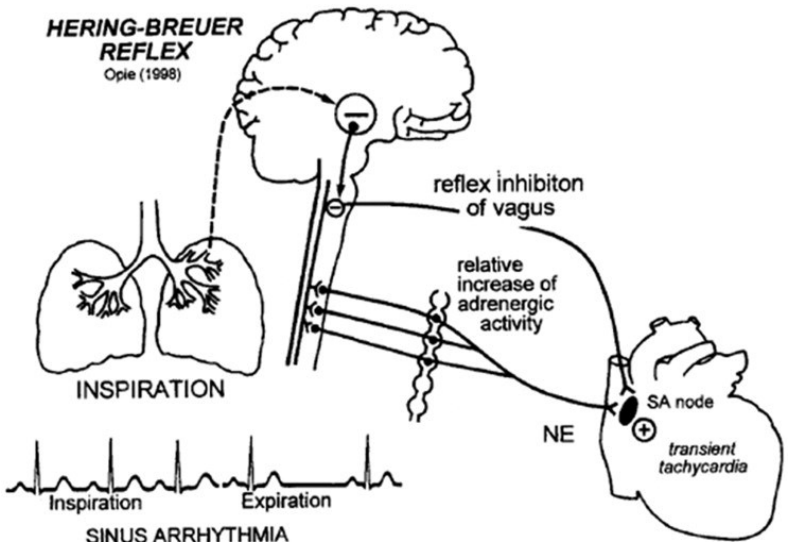


Figure B7: Cardiac-autonomic innervation & respiratory sinus arrhythmia physiology[64]

Respiratory Sinus Arrhythmia

Respiration (both depth and frequency of breathing) strongly modulates HR rhythmicity generating a rhythm known as respiratory sinus arrhythmia.[65] The HR rhythm results from, and is modulated by, complex interactions of factors originating in the heart (i.e., the Bainbridge stretch reflex), lungs (i.e., the Hering-Breuer stretch reflex), central autonomic network (i.e., inspiration-associated inhibition of vagal efferents within the medullary respiratory center) and vasculature (i.e., respiration-associated tonic and phasic baroreceptor and chemoreceptor modulations), as well as local metabolic and mechanical factors.[66-72]

Respiratory sinus arrhythmia naturally occurs across a range of respiratory frequencies and is most commonly assessed through the analysis of the frequency and amplitude of HR variability during controlled deep breathing. An indirect index of cardiovagal function,

respiratory sinus arrhythmia is specific, sensitive and reproducible.[73] First described in dogs,[74] and later in humans,[75] parasympathetic cardiac control is characterized as the decrease in HR period resulting from eliminated parasympathetic influence (with preserved sympathetic influence). In general, R-R intervals shorten when the cardiac vagal nerve activity is nearly arrested during inspiration and lengthened during expiration when cardiac vagal nerve activity reaches its peak (**Figure B7**). Although some groups have generally consider respiratory sinus arrhythmia as a reliable, clinical index of cardiac vagal activity,[76,77] several other factors have been shown to modify this reflex response including central and peripheral chemoreceptor stimuli, respiratory-linked mechanical factors (i.e., atrial stretch), state-dependent sympathetic influences, and circulating catecholamine levels.[77,78]

Defined as the peak-to-trough difference in R-R intervals across a series of respiratory cycles,[73] respiratory sinus arrhythmia is typically performed with the subject supine, where, due to a decrease in baroreceptor-mediated sympathetic activity, vagal influence is greatest. Although the greatest amplitude of respiratory sinus arrhythmia-mediated HR response is achieved with a maximal respiratory effort and with a respiratory rate of four cycles per minute, respiratory sinus arrhythmia is most commonly assessed using a comfortably slow respiration rate of six cycles per minute by taking the average peak-to-trough difference from the largest six sequential responses.[73] Age-related trends indicate the amplitude of respiratory sinus arrhythmia is greatest in younger populations and is attenuated with age.[79] Within a given age group, highly conditioned individuals have greater respiratory sinus arrhythmia amplitude than their unconditioned counterparts.[80,81] Suggested to be one of the most easily quantified markers of autonomic neuropathy in the diabetic population,[82] reductions in respiratory sinus arrhythmia (**Figure B8**) have also been reported in patients with coronary artery disease and congestive heart failure.[83-85]

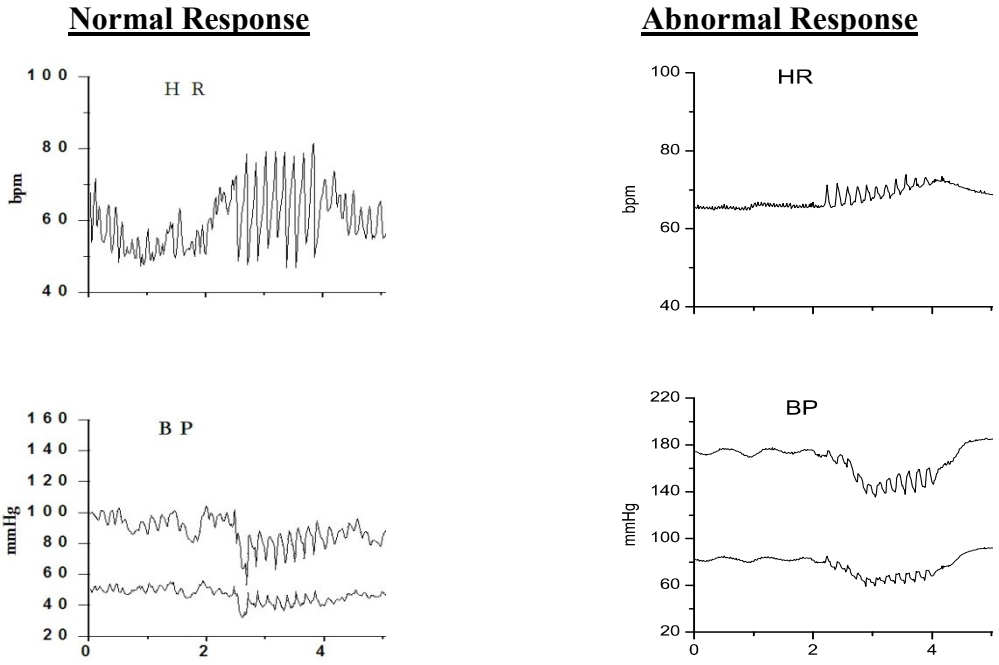


Figure B8: Normal and abnormal HR and blood pressure responses to respiratory sinus arrhythmia challenge

(Clinical data – Adams SC, 2013)

Heart Rate Recovery

Heart rate recovery (HRR) is a simple and inexpensive tool to evaluate post-exercise cardiac autonomic function.[45] Post-exercise HRR can be characterized into two principle components (i.e., a fast phase and a slow phase; **Figure B9**).[86] First described in an atropine blockade study by Imai et al.,[87] and later confirmed by similar single and double blockade studies,[88,89] the HRR within the first minute post exercise (i.e., the fast phase) is primarily driven by parasympathetic reactivation; whereas, HRR beyond the first minute (i.e., the slow phase) is caused by the combination of parasympathetic activation and sympathetic withdrawl.[90,91] Although our understanding of the cardiovascular control mechanisms underlying post-exercise HRR remains incomplete, several factors have been proposed as key mediators of the fast and

slow phases of this response (**Figure B10**). The fast phase of HRR may be partially explained by the deactivation of two principle mechanisms of cardiovascular control (i.e., central command

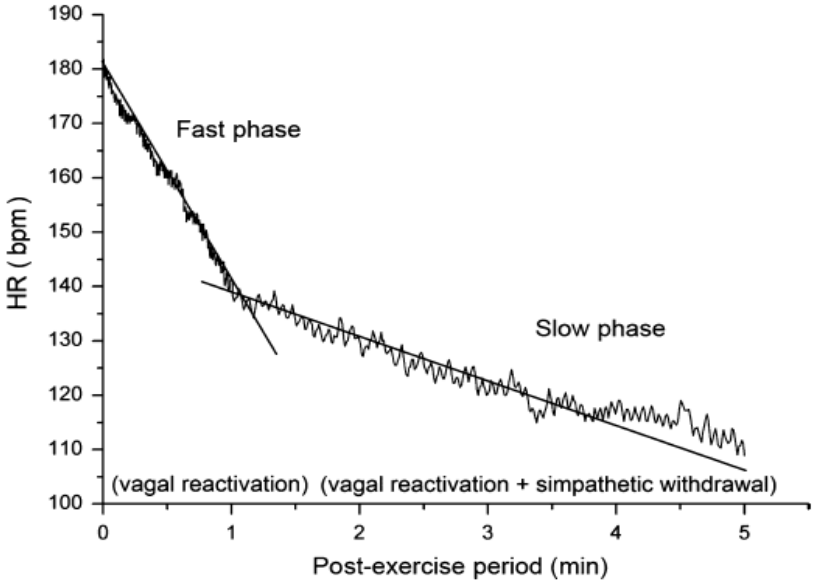


Figure B9: Post-exercise HRR kinetics[86]

and the mechanoreflex).[91] Later into recovery, the deactivation of two additional mechanisms of cardiovascular control may contribute to further decreases in HR (i.e., the muscle metaboreflex and thermoregulation).

Unfortunately, there is no internationally accepted standard for assessing post-exercise HRR and protocols differ greatly in terms of the use of an active vs. passive recovery and optimal body position (i.e., standing vs. supine).[86] Similarly, the duration of HRR tracking (e.g., 60 seconds vs. 120 seconds) and the risk factor cut-off points (e.g., 12 beats per minute vs. 30 beats per minute) also vary considerably. Notably, the assessment methods used to assess HRR may have a direct impact on the cardiovascular control mechanisms underlying the fast phase of HRR (e.g., less deactivation of central command and the mechanoreflex with active recovery).

Despite the lack of standardization, HRR is consistently found to independently predict of cardiovascular morbidity (e.g., atrial fibrillation[92] and insulin resistance[93]) as well as cardiovascular-[94-96] and overall-mortality[97-99] in both men and women. Experimental evidence in animal models of myocardial infarction has demonstrated that HRR predicts susceptibility to ventricular fibrillation.[100] A related finding in humans is that HRR is a stronger predictor of sudden cardiac death than other types of cardiac mortality.[95] As a marker of the rapid parasympathetic reactivation, these HRR findings suggest a protective role of the parasympathetic nervous system in protecting the heart from ischemia-related arrhythmias.[45]

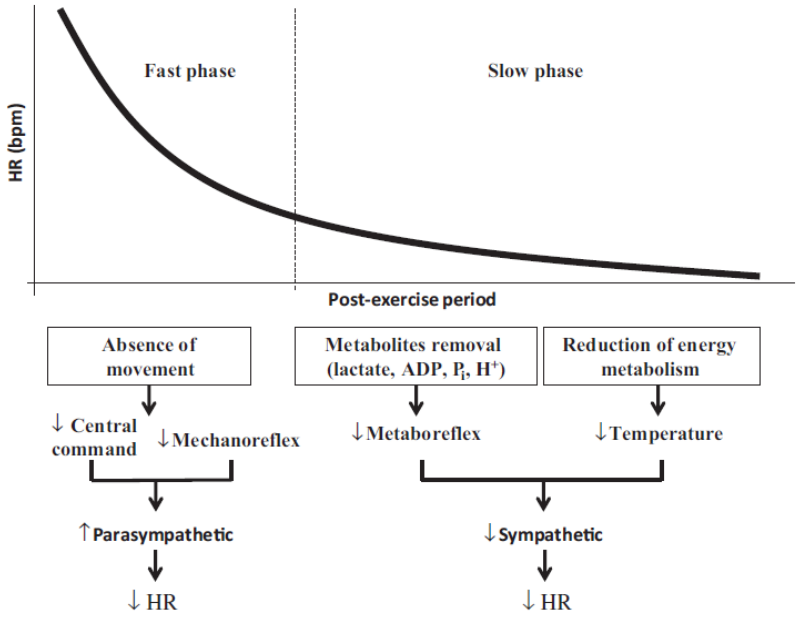


Figure B10: Proposed cardiovascular control mechanisms in HRR[86]

References

1. Dawber TR, Meadors GF, Moore FE, Jr. (1951): **Epidemiological approaches to heart disease: the Framingham Study**. *Am J Public Health Nations Health* 41:279-81.

2. Franklin SS, Gustin Wt, Wong ND*, et al.* (1997): **Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study**. *Circulation* 96:308-15.

3. Mitchell GF, Parise H, Benjamin EJ*, et al.* (2004): **Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study**. *Hypertension* 43:1239-45.

4. Franklin SS, Khan SA, Wong ND*, et al.* (1999): **Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study**. *Circulation* 100:354-360.

5. Haider AW, Larson MG, Franklin SS*, et al.* (2003): **Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study**. *Ann Intern Med* 138:10-16.

6. Mitchell GF, Hwang SJ, Vasan RS*, et al.* (2010): **Arterial stiffness and cardiovascular events: the Framingham Heart Study**. *Circulation* 121:505-11.

7. Franklin SS, Larson MG, Khan SA*, et al.* (2001): **Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study**. *Circulation* 103:1245-1249.

8. Franklin SS, Pio JR, Wong ND*, et al.* (2005): **Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study**. *Circulation* 111:1121-7.

9. Levy D, DeStefano AL, Larson MG*, et al.* (2000): **Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal**

blood pressure phenotypes in subjects from the framingham heart study. *Hypertension* 36:477-83.

10. Mitchell GF, Wang N, Palmisano JN*, et al.* (2010): **Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study**. *Circulation* 122:1379-86.

11. Laurent S, Cockcroft J, Van Bortel L*, et al.* (2006): **Expert consensus document on arterial stiffness: methodological issues and clinical applications**. *Eur Heart J* 27:2588-605.

12. Vlachopoulos C, Aznaouridis K, Stefanadis C (2010): **Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis**. *J Am Coll Cardiol* 55:1318-27.

13. Schillaci G, Sarchielli P, Corbelli I*, et al.* (2010): **Aortic stiffness and pulse wave reflection in young subjects with migraine: a case-control study**. *Neurology* 75:960-6.

14. Van Bortel LM, Laurent S, Boutouyrie P*, et al.* (2012): **Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity**. *J Hypertens* 30:445-448.

15. Reference Values for Arterial Stiffness Collaboration (2010): **Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'**. *Eur Heart J* 31:2338-50.

16. Huybrechts SA, Devos DG, Vermeersch SJ*, et al.* (2011): **Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path lengths determined by MRI and superficial measurements**. *J Hypertens* 29:1577-82.

17. Molinari F, Zeng G, Suri JS (2010): **A state of the art review on intima-media thickness (IMT) measurement and wall segmentation techniques for carotid ultrasound**. *Comput Methods Programs Biomed* 100:201-21.

18. Touboul PJ, Hennerici MG, Meairs S*, et al.* (2012): **Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011**. *Cerebrovasc Dis* 34:290-6.

19. Inaba Y, Chen JA, Bergmann SR (2012): **Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis**. *Atherosclerosis* 220:128-33.

20. Lorenz MW, Schaefer C, Steinmetz H*, et al.* (2010): **Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS)**. *Eur Heart J* 31:2041-8.

21. Mathiesen EB, Johnsen SH, Wilsgaard T*, et al.* (2011): **Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromso Study**. *Stroke* 42:972-8.

22. Pignoli P, Tremoli E, Poli A*, et al.* (1986): **Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging**. *Circulation* 74:1399-406.

23. van Popele NM, Grobbee DE, Bots ML*, et al.* (2001): **Association between arterial stiffness and atherosclerosis: the Rotterdam Study**. *Stroke* 32:454-460.

24. Godia EC, Madhok R, Pittman J*, et al.* (2007): **Carotid artery distensibility: a reliability study**. *J Ultrasound Med* 26:1157-65.

25. Kawasaki T, Sasayama S, Yagi S*, et al.* (1987): **Non-invasive assessment of the age related changes in stiffness of major branches of the human arteries**. *Cardiovasc Res* 21:678-87.

26. Hoeks AP, Brands PJ, Smeets FA*, et al.* (1990): **Assessment of the distensibility of superficial arteries**. *Ultrasound Med Biol* 16:121-8.

27. Selzer RH, Mack WJ, Lee PL*, et al.* (2001): **Improved common carotid elasticity and intima-media thickness measurements from computer analysis of sequential ultrasound frames**. *Atherosclerosis* 154:185-93.

28. Golemati S, Sassano A, Lever MJ*, et al.* (2003): **Carotid artery wall motion estimated from B-mode ultrasound using region tracking and block matching**. *Ultrasound Med Biol* 29:387-399.

29. Haugnes HS, Wethal T, Aass N*, et al.* (2010): **Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study**. *J Clin Oncol* 28:4649-57.

30. Riley WA, Evans GW, Sharrett AR*, et al.* (1997): **Variation of common carotid artery elasticity with intimal-medial thickness: the ARIC Study. Atherosclerosis Risk in Communities**. *Ultrasound Med Biol* 23:157-64.

31. Shock NW (1984): **Normal human aging: the Baltimore longitudinal study of aging**. Bethesda, MD, *National Institute on Aging*

32. Simons PC, Algra A, Bots ML*, et al.* (1999): **Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease)**. *Circulation* 100:951-7.

33. Thijssen DH, Black MA, Pyke KE*, et al.* (2011): **Assessment of flow-mediated dilation in humans: a methodological and physiological guideline**. *Am J Physiol Heart Circ Physiol* 300:H2-12.

34. Smith DL, Fernhall B (2011): **Advanced cardiovascular exercise physiology**, *Human Kinetics.*,

35. Celermajer DS, Sorensen KE, Gooch VM*, et al.* (1992): **Non-invasive detection of endothelial dysfunction in children and adults at risk of atherscleroses**. *The Lancet* 340.

36. Inaba Y, Chen JA, Bergmann SR (2010): **Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis**. *Int J Cardiovasc Imaging* 26:631-40.

37. Anderson TJ, Charbonneau F, Title LM*, et al.* (2011): **Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study**. *Circulation* 123:163-9.

38. Irace C, Cortese C, Fiaschi E*, et al.* (2004): **Wall shear stress is associated with intima-media thickness and carotid atherosclerosis in subjects at low coronary heart disease risk**. *Stroke* 35:464-8.

39. Mitchell GF, Parise H, Vita JA*, et al.* (2004): **Local shear stress and brachial artery flow-mediated dilation: the Framingham Heart Study**. *Hypertension* 44:134-9.

40. Philpott AC, Lonn E, Title LM*, et al.* (2009): **Comparison of new measures of vascular function to flow mediated dilatation as a measure of cardiovascular risk factors**. *Am J Cardiol* 103:1610-5.

41. Lahiri MK, Kannankeril PJ, Goldberger JJ (2008): **Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications**. *J Am Coll Cardiol* 51:1725-33.

42. Lauer MS (2009): **Autonomic function and prognosis**. *Cleve Clin J Med* 76 Suppl 2:S18-22.

43. Masi CM, Hawkley LC, Rickett EM*, et al.* (2007): **Respiratory sinus arrhythmia and diseases of aging: obesity, diabetes mellitus, and hypertension**. *Biol Psychol* 74:212-23.

44. Peltola M, Tulppo MP, Kiviniemi A*, et al.* (2008): **Respiratory sinus arrhythmia as a predictor of sudden cardiac death after myocardial infarction**. *Ann Med* 40:376-382.

45. Lauer MS (2011): **Heart rate recovery: what now?** *J Intern Med* 270:597-9.

46. Levine HJ (1997): **Rest heart rate and life expectancy**. *J Am Coll Cardiol* 30:1104-6.

47. Aupetit JF, Frassati D, Bui-Xuan B*, et al.* (1998): **Efficacy of a beta-adrenergic receptor antagonist, propranolol, in preventing ischaemic ventricular fibrillation: dependence on heart rate and ischaemia duration**. *Cardiovasc Res* 37:646-55.

48. Bolli R, Fisher DJ, Entman ML (1986): **Factors that determine the occurrence of arrhythmias during acute myocardial ischemia**. *Am Heart J* 111:261-270.

49. Coburn AF, Grey RM, Rivera SM (1971): **Observations on the relation of heart rate, life span, weight and mineralization in the digoxin-treated A-J mouse**. *Johns Hopkins Med J* 128:169-93.

50. Custodis F, Baumhakel M, Schlimmer N*, et al.* (2008): **Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice**. *Circulation* 117:2377-87.

51. Kaplan JR, Manuck SB, Clarkson TB (1987): **The influence of heart rate on coronary artery atherosclerosis**. *J Cardiovasc Pharmacol* 10 Suppl 2:S100-2; discussion S103.

52. Mangoni AA, Mircoli L, Giannattasio C*, et al.* (1996): **Heart rate-dependence of arterial distensibility in vivo**. *J Hypertens* 14:897-901.

53. Reynolds RD, Calzadilla SV, Lee RJ (1978): **Spontaneous heart rate, propranolol, and ischaemia-induced ventricular fibrillation in the dog**. *Cardiovasc Res* 12:653-8.

54. Tanaka N, Nozawa T, Yasumura Y*, et al.* (1990): **Heart-rate-proportional oxygen consumption for constant cardiac work in dog heart**. *Jpn J Physiol* 40:503-21.

55. Andrews TC, Fenton T, Toyosaki N*, et al.* (1993): **Subsets of ambulatory myocardial ischemia based on heart rate activity. Circadian distribution and response to anti-ischemic medication. The Angina and Silent Ischemia Study Group (ASIS)**. *Circulation* 88:92-100.

56. Cunha RS, Pannier B, Benetos A*, et al.* (1997): **Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects**. *J Hypertens* 15:1423-1430.

57. Heidland UE, Strauer BE (2001): **Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption**. *Circulation* 104:1477-82.

58. Huikuri HV, Jokinen V, Syvanne M*, et al.* (1999): **Heart rate variability and progression of coronary atherosclerosis**. *Arterioscler Thromb Vasc Biol* 19:1979-85.

59. Panza JA, Diodati JG, Callahan TS*, et al.* (1992): **Role of increases in heart rate in determining the occurrence and frequency of myocardial ischemia during daily life in patients with stable coronary artery disease**. *J Am Coll Cardiol* 20:1092-8.

60. Pratt CM, McMahon RP, Goldstein S*, et al.* (1996): **Comparison of subgroups assigned to medical regimens used to suppress cardiac ischemia (the Asymptomatic Cardiac Ischemia Pilot [ACIP] study)**. *Am J Cardiol* 77:1302-1309.

61. Sambuceti G, Marzilli M, Marraccini P*, et al.* (1997): **Coronary vasoconstriction during myocardial ischemia induced by rises in metabolic demand in patients with coronary artery disease**. *Circulation* 95:2652-9.

62. Traub O, Berk BC (1998): **Laminar shear stress: mechanisms by which endothelial cells transduce an atheroprotective force**. *Arterioscler Thromb Vasc Biol* 18:677-85.

63. Fox K, Borer JS, Camm AJ*, et al.* (2007): **Resting heart rate in cardiovascular disease**. *J Am Coll Cardiol* 50:823-30.

64. Verrier RL, Tan A (2009): **Heart rate, autonomic markers, and cardiac mortality**. *Heart Rhythm* 6:S68-75.

65. Berntson GG, Cacioppo JT, Quigley KS (1993): **Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications**. *Psychophysiology* 30:183-96.

66. Davies CT, Neilson JM (1967): **Disturbance of heart rhythm during recovery from exercise in man**. *J Appl Physiol* 22:943-6.

67. Davies CTM, Neilson JMM (1967): **Sinus arrhythmia in man at rest**. *J Appl Physiol* 22:947-955.

68. Feldman JL, Ellenberger HH (1988): **Central coordination of respiratory and cardiovascular control in mammals**. *Annu Rev Physiol* 50:593-606.

69. Guyton AC, Hall JE (2006): **Textbook of medical physiology** (ed 11th). Philadelphia, *Elsevier Saunders*, pp. 748-760.

70. McArdle WD, Katch FI, Katch VL (2007): **Exercise physiology: energy, nutrition & human performance** (ed 6), *Lippincott Williams & Wilkins.*,

71. Saul JP, Rea RF, Eckberg DL*, et al.* (1990): **Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity**. *Am J Physiol* 258:H713-21.

72. Grossman P (1983): **Respiration, stress, and cardiovascular function**. *Psychophysiology* 20:284-300.

73. Freeman RL (2008): **Noninvasive evaluation of heart rate: time and frequency domains.**, in Low PA, Benarroch EE (eds): Clinical Autonomic Disorders. (ed 3rd). Philadelphia, *Lippincott Williams & Wilkins*, pp 185-197.

74. Katona PG, Jih F (1975): **Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control**. *J Appl Physiol* 39:801-5.

75. Fouad FM, Tarazi RC, Ferrario CM*, et al.* (1984): **Assessment of parasympathetic control of heart rate by a noninvasive method**. *Am J Physiol* 246:H838-42.

76. Task Force of the European Society of Cardiology & North American Society of Pacing Electrophysiology (1996): **Heart rate variability: standards of measurement, physiological interpretation, and clinical use**. *Circulation* 93:1043-1065.

77. Yasuma F, Hayano J (2004): **Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm?** *Chest* 125:683-90.

78. Taylor JA, Myers CW, Halliwill JR*, et al.* (2001): **Sympathetic restraint of respiratory sinus arrhythmia: implications for vagal-cardiac tone assessment in humans**. *Am J Physiol Heart Circ Physiol* 280:H2804-14.

79. Hrushesky WJ, Fader D, Schmitt O*, et al.* (1984): **The respiratory sinus arrhythmia: a measure of cardiac age**. *Science* 224:1001-4.

80. Dixon EM, Kamath MV, McCartney N*, et al.* (1992): **Neural regulation of heart rate variability in endurance athletes and sedentary controls**. *Cardiovasc Res* 26:713-9.

81. Goldsmith RL, Bigger JT, Jr., Steinman RC*, et al.* (1992): **Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men**. *J Am Coll Cardiol* 20:552-8.

82. Lishner M, Akselrod S, Avi VM*, et al.* (1987): **Spectral analysis of heart rate fluctuations. A non-invasive, sensitive method for the early diagnosis of autonomic neuropathy in diabetes mellitus**. *J Auton Nerv Syst* 19:119-25.

83. Airaksinen KE, Ikaheimo MJ, Linnaluoto MK*, et al.* (1987): **Impaired vagal heart rate control in coronary artery disease**. *Br Heart J* 58:592-7.

84. Hayano J, Sakakibara Y, Yamada M*, et al.* (1990): **Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity**. *Circulation* 81:1217-24.

85. Myers GA, Martin GJ, Magid NM*, et al.* (1986): **Power spectral analysis of heart rate varability in sudden cardiac death: comparison to other methods**. *IEEE Trans Biomed Eng* BME-33:1149-1156.

86. Pecanha T, Silva-Junior ND, Forjaz CL (2014): **Heart rate recovery: autonomic determinants, methods of assessment and association with mortality and cardiovascular diseases**. *Clin Physiol Funct Imaging* 34:327-39.

87. Imai K, Sato H, Hori M*, et al.* (1994): **Vagally mediated heart-rate recovery after exercise is accelerated in athletes but alunted in aatients with chronic heart-failure**. *J Am Coll Cardiol* 24:1529-1535.

88. Kannankeril PJ, Le FK, Kadish AH*, et al.* (2004): **Parasympathetic effects on heart rate recovery after exercise**. *J Investig Med* 52:394-401.

89. Sundaram S, Shoushtari C, Carnethon M*, et al.* (2004): **Autonomic and nonautonomic determinants of heart rate recovery**. *Heart Rhythm* 1:S100-S101.

90. Perini R, Orizio C, Comande A*, et al.* (1989): **Plasma norepinephrine and heart rate dynamics during recovery from submaximal exercise in man**. *Eur J Appl Physiol Occup Physiol* 58:879-83.

91. Coote JH (2010): **Recovery of heart rate following intense dynamic exercise**. *Exp Physiol* 95:431-40.

92. Maddox TM, Ross C, Ho PM*, et al.* (2009): **Impaired heart rate recovery is associated with new-onset atrial fibrillation: a prospective cohort study**. *BMC Cardiovasc Disord* 9:11.

93. Lind L, Andrén B (2002): **Heart rate recovery after exercise is related to the insulin resistance syndrome and heart rate variability in elderly men**. *Am Heart J* 144:666-672.

94. Cole CR, Foody JM, Blackstone EH*, et al.* (2000): **Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort**. *Ann Intern Med* 132:552-555.

95. Jouven X, Empana JP, Schwartz PJ*, et al.* (2005): **Heart-rate profile during exercise as a predictor of sudden death**. *N Engl J Med* 352:1951-8.

96. Tang YD, Dewland TA, Wencker D*, et al.* (2009): **Post-exercise heart rate recovery independently predicts mortality risk in patients with chronic heart failure**. *J Card Fail* 15:850-5.

97. Jolly MA, Brennan DM, Cho L (2011): **Impact of exercise on heart rate recovery**. *Circulation* 124:1520-6.

98. Nissinen SI, Mäkikallio TH, Seppänen T*, et al.* (2003): **Heart rate recovery after exercise as a predictor of mortality among survivors of acute myocardial infarction**. *J Am Coll Cardiol* 91:711-714.

99. Shetler K, Marcus R, Froelicher VF*, et al.* (2001): **Heart rate recovery: validation and methodologic issues**. *J Am Coll Cardiol* 38:1980-7.

100. Smith LL, Kukielka M, Billman GE (2005): **Heart rate recovery after exercise: a predictor of ventricular fibrillation susceptibility after myocardial infarction**. *Am J Physiol Heart Circ Physiol* 288:H1763-9.

Appendix C: Methods of Psychosocial and HRQoL Health Assessment

Methods of Psychosocial and HRQoL Health Assessment

In addition to the increased CVD risks described previously, TCS are also at increased risk of psychosocial distress and HRQoL impairments related to their diagnoses and treatments.[1,2] However, unlike the objective assessment techniques employed in CVD disease research, psychosocial function and HRQoL are assessed using well-validated subjective self-report questionnaires. The following section provides a brief overview of the use of, and the theory underlying, these PRO inventories.

Assessment of Psychosocial Health

CRF is defined by the National Comprehensive Cancer Network as "a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning".[3] Of the numerous single- and multi-item CRF assessment scales have been validated in cancer patients, the Functional Assessment of Cancer Therapy-Fatigue scale[4] among the most commonly used in large-scale national and international clinical trials.[5] A 13-item inventory, the Functional Assessment of Cancer Therapy-Fatigue is based on a 1-week recall and requires participants to rate their fatigue symptoms on a scale of 0-4. Functional Assessment of Cancer Therapy-Fatigue scores range between 0 and 52 with higher scores reflecting lower CRF.[4]

Depression was assessed using the well-validated Center for Epidemiologic Studies Depression Scale[6] which has been shown to have high internal consistency (Cronbach's $\alpha = 0.89$) and a test-retest score of 0.57 in cancer patients.[7] A 10-item inventory, the Center for Epidemiologic Studies Depression Scale is based on a 1-week recall and requires participants to rate the frequency of depressive symptoms on a 0-3 scale. Center for Epidemiologic Studies Depression Scale scores range from 0 to 30 with higher scores reflecting higher depressive symptom frequency.[8]

Anxiety was evaluated using the validated Spielberger State Anxiety Scale.[9] A 10-item inventory, the Spielberger State Anxiety Scale is based on a 1-week recall and requires participants to rate the severity of their anxiety symptoms on a 1-4 scale. Spielberger State Anxiety Scale scores range from 10 to 40 with higher scores reflecting increased anxiety symptom severity.[9]

Stress was evaluated using the Perceived Stress Scale which has a demonstrated reliability range of 0.84 to 0.86.[10] A 14-item inventory, the Perceived Stress Scale is based on a 1-month recall and requires participants to assess the frequency of stress symptoms on a 0-4 scale. Perceived Stress Scale scores range from 0 to 56 with higher scores reflecting greater stress symptom frequency.[10]

Self-esteem was assessed using the Rosenberg Self-Esteem Scale[11] which has been shown to have high internal consistency (Cronbach's $\alpha = 0.81$ to 0.91) and test-retest reliability.[12,13] A 10-item inventory, Rosenberg Self-Esteem Scale assesses overall self-esteem on a 1-4 scale. Rosenberg Self-Esteem Scale scores range from 10 to 40 with higher scores reflect greater self-esteem.[11]

Sleep quality was assessed using the Pittsburgh Sleep Quality Index[14] which has a good internal consistency (Cronbach's $\alpha = 0.77$ to 0.81).[14] An 8-item inventory, the Pittsburgh Sleep Quality Index assesses 1-month subjective sleep quality with lower scores reflecting better sleep quality.[14]

Assessment of Health-Related Quality of Life

Overall HRQoL was assessed using the Short-Form 36 (SF-36)® which has been validated and demonstrated strong reliability in a number of clinical and nonclinical populations.[15] A 36-

item scale, the SF-36 assesses eight health domains including physical functioning (i.e., physical activity limitations), role-physical (i.e., difficulties with activities of daily living or work caused by physical problems), bodily pain (i.e., pain-related limitations), general health (i.e., perception and expectation of changes in health), vitality (i.e., energy levels and tiredness), social functioning (i.e., effect of physical and mental health on social activities), role-emotional (i.e., difficulties with activities of daily living or work caused by emotional problems), and mental health (i.e., happiness, nervousness, and depression). Two additional scores [i.e., the mental component score and physical component score] are then calculated by adding the prespecified weighted contributions of each of the eight subscale scores. The scores for each subscale are transformed into norm-based scores ranging from 0 to 100 with higher scores reflecting better functioning.[15]

References

1. Smith AB, Butow P, Olver I*, et al.* (2016): **The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study**. *J Cancer Surviv* 10:223-33.

2. Sprauten M, Haugnes HS, Brydøy M*, et al.* (2015): **Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: increasing prevalence and risk factors**. *Ann Oncol* 26:2133-2140.

3. Mock V, Atkinson A, Barsevick A*, et al.* (2000): **NCCN practice guidelines for cancer-related fatigue**. *Oncology* 14:151-61.

4. Yellen SB, Cella DF, Webster K*, et al.* (1997): **Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system**. *J Pain Symptom Manage* 13:63-74.

5. Piper BF, Borneman T, Sun VC*, et al.* (2008): **Cancer-related fatigue: role of oncology nurses in translating National Comprehensive Cancer Network assessment guidelines into practice**. *Clin J Oncol Nurs* 12:37-47.

6. Andresen EM, Malmgren JA, Carter WB*, et al.* (1994): **Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale)**. *Am J Prev Med* 10:77-84.

7. Hann D, Winter K, Jacobsen P (1999): **Measurement of depressive symptoms in cancer patients: evaluation of the Center for Epidemiological Studies Depression Scale (CES-D)**. *J Psychosom Res* 46:437-43.

8. Kohout FJ, Berkman LF, Evans DA*, et al.* (1993): **Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index**. *J Aging Health* 5:179-93.

9. Spielberger CD, Gorsuch RL, Lushene R*, et al.* (1983): **Manual for the state-trait anxiety inventory**. Palo Alto, CA, *Consulting Psychologists Press.*,

10. Cohen S, Kamarck T, Mermelstein R (1983): **A global measure of perceived stress**. *J Health Soc Behav* 24:385-96.

11. Rosenberg M (1965): **Society and the adolescent self-image**. NJ, *Princeton university press Princeton*,

12. Schmitt DP, Allik J (2005): **Simultaneous administration of the Rosenberg Self-Esteem Scale in 53 nations: exploring the universal and culture-specific features of global self-esteem**. *J Pers Soc Psychol* 89:623-42.

13. Sinclair SJ, Blais MA, Gansler DA*, et al.* (2010): **Psychometric properties of the Rosenberg Self-Esteem Scale: overall and across demographic groups living within the United States**. *Eval Health Prof* 33:56-80.

14. Beck SL, Schwartz AL, Towsley G*, et al.* (2004): **Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients**. *J Pain Symptom Manage* 27:140-8.

15. Ware JE, Kosinski M, Bjorner JB*, et al.* (2008): **User's manual for the SF-36v2 Health Survey**, *Quality Metric.*,

Appendix D: CVD Risk Screening & Treatment-Related CVD Risks in TCS

Traditional CVD Screening in Oncology

Assessed by multi-gated acquisition scintigraphy and echocardiography, left ventricular ejection fraction (LVEF) is the most reported cardiac monitoring endpoint in cancer patients and survivors.[1] However, LVEF may not be sensitive to early cardiac damage because, despite myocyte damage, the compensatory reserve capacity of the myocardium is able to maintain adequate cardiac output.[2] In the case of left ventricular dysfunction, the decline of diastolic cardiac function may occur in the absence of systolic changes. Furthermore, many patients may experience diastolic disturbances in advance of systolic dysfunction.[3] In a retrospective analysis of 630 anthracycline-treated cancer patients, decreased LVEF was only present in 11 of the 32 patients who developed chronic heart failure.[4] Another study prospectively followed 120 anthracycline-treated breast cancer patients with LVEF assessments for up to three years.[5] The authors reported that 91.67% of the most drastic treatment-related reductions in LVEF (>35% decrease from baseline) occurred more than three months post therapy, suggesting that LVEF was unable to detect early cardiomyocyte injury.[5] Together, the evidence suggests that adequate LVEF may conceal early cardiomyocyte damage and, therefore, more sensitive CVD risk screening measures are needed.[2]

Novel Cardiovascular Screening Techniques in Oncology

Anticancer therapies are known to cause cardiovascular injuries beyond the heart. Indices of endothelial and vascular structure and function (i.e., brachial flow-mediation dilation, carotid intima-media thickness, carotid distensibility, and central/peripheral PWV) and parasympathetic autonomic nervous system function (i.e., resting HR, respiratory sinus arrhythmia, and HRR) have been used to assess cardiovascular health in general,[6-8] high CVD risk,[9-13] and CVD populations including diabetics,[14-18] asthmatics,[19] persons with coronary artery disease,[13,20-23] and

individuals with atherosclerosis.[13,24-26] These indices may have greater sensitivity to subtle cardiovascular perturbations, and, therefore, may be more effective in detecting early treatment-related cardiovascular injury than LVEF.[27]

Table D1: CVD Risk and Development Summary in TCS

Reported Outcome	# Studies (RSF vs. ASO (%))	Subjects (#)	Age (Avg. years)	Months Follow-Up (Avg. (*Range*))
Cardiac Toxicity	5 of 5 (*100*)	212	35.5	116.9 (*2.6-180*)
Cerebral Infarction	3 of 6 (*50*)	9,511	36.8	128.0 (*0-228*)
CVD Risk	14 of 15 (*93*)	57,538	41.5	158.0 (*0-228*)
Endothelial Dysfunction				
FMD	1 of 2 (*50*)	129	40.5	41.0 (*7-75*)
Biomarkers*	5 of 5 (*100*)	343	38.2	63.1 (*2.5-168*)
Gonadal Toxicity	14 of 15 (*93*)	4,044	37.6	100.7 (*9-228*)
Metabolic Syndrome				
Diabetic/IR	6 of 7 (*86*)	1,671	40.2	99.8 (*2.6-228*)
Hypertension	19 of 20 (*95*)	45,083	38.4	103.6 (*7-228*)
Lipid Imbalance	15 of 15 (*100*)	3,534	38.0	97.1 (*2.6-228*)
Obesity/↑ BMI	13 of 13 (*100*)	4,241	36.9	78.4 (*2.6-180*)
Raynaud's Phenomenon	11 of 11 (*100*)	667	33.4	93.2 (*0-180*)
Renal Toxicity	11 of 11 (*100*)	531	28.5	36.4 (*0-65*)
Systemic Inflammation	3 of 3 (*100*)	959	41	122.3 (*7-228*)
Vascular Injury**	10 of 12 (*83*)	12,649	36.6	91.8 (*0-228*)

RSF: reported significant findings; ASO: assessing specific outcome; Avg.: average; FMD: flow-mediated dilation; IR: insulin resistant; BMI: body mass index

* includes microalbuminuria, fibrinogen, intracellular adhesion molecule-1, plasminogen activator inhibitor-1, tissue plasminogen activator, PAI-1/t-PA, von Willebrand factor, endothelial progenitor cell, and circulating endothelial cell measures

**includes atherogenesis, coronary artery disease, cardiac ischemia, carotid stiffness, intima-media thickness, myocardial infarction, pulse-wave velocity and thrombogenesis measures

Treatment-related CVD risks in TCS

In general, the primary mechanisms of CVD-related mortality include cerebral and cardiac ischemic and occlusive events. The principle pathophysiological processes underlying these events are pro-atherosclerotic, -thrombotic, -arrhythmic and -inflammatory in nature.[28] TCS are susceptible to developing a variety of treatment-related cardiovascular deficits which may drastically impair their HRQoL and limit long-term survival (see **Table D1** for a summary of 47

studies reporting cardiovascular complications in TCS[16,29-73]). This summary highlights three important trends in CVD development in TCS. First, 44 (93%) of the 47 studies reviewed reported significantly elevated CVD risk or incidence in TC patients and survivors. Second, the pooled data from 61,442 TC patients and survivors demonstrated the average age of CVD development as 37.4 years (range 28.5 – 41.5 years). Third, all of the reported cardiovascular morbidities manifested within the first 19 years post treatment. Notably, all of the common anti-cancer therapies used to treat and control TC are implicated in the increased CVD risks in TCS.

Surgery

In general, TCS demonstrate low to normal testosterone levels, with the prevalence of below normal levels varying from 11% to 34%.[35,49,74] Provided TCS retain the normal functioning of their contralateral testicle, serum testosterone levels in TCS treated with unilateral orchiectomy-only often remain relatively unaffected.[75] However, hypogonadism develops if the remaining testicle is unable to compensate and maintain adequate levels of testosterone production. A multicenter survey of 1235 TC survivors reported an elevated age-adjusted odds ratio for hypogonadism of 3.8 (95% CI, 2.0-7.3) compared to controls, which increased with treatment intensity and was highest in patients who had received cumulative doses of cisplatin >850 mg (*odds ratio*: 7.9; 95% CI, 3.6-17.4).[55] Hypogonadism-related risks may include CVD, metabolic syndrome, osteoporosis, type II diabetes, premature aging, and decreased HRQoL.[76] Moreover, in the only study to date to compare markers of endothelial activation and inflammation in TCS treated with orchidectomy-only to healthy controls, Nuver et al.[56] reported significantly elevated levels of fibrinogen, von Willebrand factor, tissue plasminogen activator, and hsCRP in TCS.

Radiotherapy

Patients with seminoma have been identified as being at a particularly high risk of CVD, due to their additional radiation exposure. Individuals receiving radiotherapy, alone or in combination with chemotherapy and especially with mediastinal involvement, are reported to have an approximately doubled CVD-risk, owing to direct injury of the coronary vasculature and microvasculature.[77-80] Although mediastinal radiotherapy is no longer common in TC treatment, elevated CVD risk has also been identified in patients treated with infradiaphragmatic radiotherapy[81] such as increased risks for peripheral vascular disease (i.e., vascular stenosis, thromboembolism and accelerated or premature atherosclerosis),[82] and renal dysfunction.[83-85] In addition to conduit vessel damage, abdominal irradiation, involving one or both kidneys, has been shown to cause nephropathy-related hypertension[83-85] through what is believed to be a renovascular effect involving the renin-angiotensin system.[83,84,86]

Chemotherapy

Of the six chemotherapeutic agents listed previously, bleomycin and cisplatin are known to cause a variety of acute and long-term cardiovascular complications in TCS.

Bleomycin belongs to a family of anticancer drugs called antitumor antibiotics. Although the exact mechanisms of action for this drug are partially unknown, bleomycin induces apoptosis by causing DNA strand breaks through targeted DNA binding and free radical production.[87,88] Bleomycin, like other cytoskeletal-disrupting agents, has anti-angiogenic effects (decreases endothelial growth and induces apoptosis).[89] Bleomycin, either alone or in combination with cisplatin, etoposide or vinca alkaloids, may cause pulmonary fibrosis,[90] and is associated with myocardial ischemia and infarction, Raynaud's phenomenon and thromboembolic events.[53,69,91] An established marker of endothelial dysfunction, Raynaud's phenomenon has been reported in approximately one third of patients treated with bleomycin.[32,92]

Cisplatin is a platinum compound belonging to another family of anticancer drugs called alkylating agents.[93] Through DNA binding, cisplatin's antitumor effect involves the disruption of cellular transcription and replication mechanisms.[94] In vitro investigations of cisplatin-related effects on vascular endothelium have demonstrated an inhibition of endothelial cell proliferation, which may enhance its antitumor effects.[95,96] The most common adverse cardiovascular events associated with the administration of platinum compounds include hypertension, Raynaud's phenomenon and thrombotic events (e.g., cerebrovascular events, cardiac ischemia and myocardial infarction).[53,97,98] Cisplatin is thought to contribute to late-onset occlusive vascular disease by triggering a degenerative process in vessel walls (medium-thickness);[99] and, it is biologically plausible that ongoing platinum-induced vascular damage extends well into survivorship by promoting endothelial injury and atherosclerotic plaque development – representing the greatest treatment-related contributor to the elevated CVD risk in TCS.[99-101]

Compared to general population, chemotherapy-treated TCS have an increased coronary artery disease observed-to-expected ratio of 7:1[91] and a 19-year increased risk of myocardial infarction for patients treated with chemotherapy-only (*hazard ratio*: 3.1; 95% CI, 1.2-7.7) or combined chemotherapy and radiotherapy (*hazard ratio*: 4.8; 95% CI, 1.6-13.9).[48] In TCS treated with cisplatin-based therapy, early diastolic dysfunction has been reported as early as 10 months post treatment.[30] In TCS, specific CVD risk factors (i.e., obesity and hypertension) have also been associated with diastolic dysfunction due to related increases in cardiac pre- and afterload demands. Altena et al.[31] demonstrated the relationship between hypertension and tissue velocity imaging of early diastole (TVI Et) as well as follow-up Δ TVI Et, and went on to suggest the treatment of obesity and hypertension may be effective in preventing or mitigating the observed diastolic dysfunction. Moreover, cumulative cisplatin doses exceeding 400 mg/m^2 have been

associated with increased hypertension in TCS,[34] which may have longer-term atherogenic consequences.

Treatment-related Vascular Injuries in TCS

Compared to other high-risk CVD populations, very little research has focused on the vascular health of cancer patients and survivors, including TCS. Nuver et al.[73] assessed the effects of cisplatin on human microvascular endothelial cell activation, proliferation and apoptosis and reported a cisplatin-induced decrease in endothelial cell survival concurrent with the induction of apoptosis. In a related study, Nuver et al.[56] assessed markers of subclinical atherosclerosis in 90 cisplatin-treated TCS, 44 TCS treated with orchiectomy alone, and 47 healthy controls. Compared to healthy controls, TCS in both groups had elevated plasma endothelial inflammatory markers (i.e., fibrinogen, hsCRP, von Willebrand factor, and plasminogen activator inhibitor-1) and a higher prevalence of microalbuminuria a median of seven years post therapy.[56] Cisplatin-treated TCS also had elevated low-density lipoprotein plasma activator initiator-1, and carotid artery stiffness.[56] However, the authors reported no difference between groups in carotid intima-media thickness or brachial flow-mediated dilation.[56] In a subsequent prospective follow-up of 65 cisplatin-treated TC patients, Nuver et al.[57] reported an increased carotid intima-media thickness, compared to pretreatment values, a median of 10 weeks post treatment. However, the authors were unclear as to whether the increased carotid intima-media thickness was due to atherosclerotic changes or a consequence of blood pressure changes.[57] Unlike the previously described null flow-mediated dilation results, Vaughn et al.[68] demonstrated impaired brachial artery flow-mediated dilation in long-term TCS who received cisplatin-based chemotherapy in comparison to chemo-naïve patients (8.8% vs. 5.6%, p=0.05). The authors also confirmed that the difference was, in fact, endothelial-mediated and not due to

changes in vascular smooth muscle.[68] However, a study of young ovarian cancer survivors revealed that cisplatin also causes impairments in the function of vascular smooth muscle a median of 14 years post treatment.[102] Moreover, several studies have identified cisplatin-induced increases in tissue-dependent procoagulant endothelial particles,[103] as well as superoxide-mediated coagulation defects and endothelial injury.[104] Very recently, a prospective cohort study assessed markers of vascular damage and related vascular events in 73 TC patients during, immediately following, and 1 year post-chemotherapy.[105] They reported an 11% incidence of vascular events and a related increase in markers of endothelial injury and upregulated pro-coagulant activity (e.g., von Willebrand factor and coagulation factor VIII) during chemotherapy in these patients.[105] Together, this evidences highlights a consistent pattern of treatment-related vascular injury in TCS, and reinforces the importance of including novel vascular markers of subclinical CVD in the screening and follow-up of TCS.

Treatment-related Autonomic Dysfunction in TCS

Relatively few studies have assessed autonomic nervous system function in cancer patients and survivors. Autonomic dysfunction, resulting from primary (i.e., paraneoplastic disease and metastatic invasion)[106] and secondary (i.e., treatment-related)[106-115] mechanisms of injury, may contribute to the observed CVD risks/development in cancer survivors – as is becoming increasingly recognized in other populations.[13] The majority of autonomic evaluations completed in cancer patients and survivors have assessed cardiovagal (i.e., parasympathetic) or adrenergic (i.e., sympathetic) function based on the test battery described by Ewing and Clarke.[116]

Three studies have assessed autonomic function in homogeneous groups of TC patients and survivors. Steen W. Hansen[113] assessed autonomic function in 28 cisplatin-treated TCS

(median age 35 years) after a median follow-up period of 83 months. Parasympathetic dysfunction was assessed via participants' HR response to standing, the Valsalva maneuver, and respiratory sinus arrhythmia.[22] He reported mild parasympathetic impairment in eight participants and definitive impairment in two others.[113] Evidence of sympathetic dysfunction, as assessed by measuring blood pressure changes to an orthostatic challenge, was not present in any participant.[113] In a more recent series of studies by Nuver et al., they reported little[57] and no[117] evidence of autonomic impairment, as assessed via baroreflex sensitivity, both acutely and up to seven years post therapy, respectively.

Studies of autonomic function in other cancer populations have reported diminished HR variability, during both respiratory sinus arrhythmia and 24-hour recordings, in patients treated with vincristine,[118] paclitaxel,[111] doxorubicin,[114] as well as patient groups treated with various combination therapies (including cisplatin).[113,119] Maladaptive orthostatic responses and aberrant blood pressure variability have been observed in patients treated with paclitaxel, taxanes, vinca alkaloids, and cisplatin.[110,120,121] Using a protocol described by Shahani et al.,[122] another study assessed sympathetic-mediated sweat function of the hand and foot in a mixed group of cancer survivors and reported a prolonged skin response latency.[123] Adams et al.,[124] using a more modern clinical battery of tests (i.e., the composite autonomic scoring scale[125]), conducted a case-controlled pilot study assessing the autonomic function of a mixed diagnoses group of young patients (median age of 35.5 years; prior to and following four cycles of chemotherapy). They reported evidence of autonomic impairment in 5 of 13 (38.5%) patients at baseline, which persisted in 4 of 12 (33.3%) patients following four cycles of chemotherapy. Consistent with the findings of Hansen[113] and Nuver et al.,[57,117] they reported no evidence of sympathetic impairment, as evidenced by normal blood pressure responses to an orthostatic tilt table challenge. Finally, they proposed a potential cholinergic mechanism of autonomic dysfunction

indicated by abnormal HR responses to respiratory sinus arrhythmia, Valsalva maneuver, and sweat responses using a quantitative sudomotor axon reflex test.[124] However, the reporting from, and methods employed across, these trials was inconsistent.[124] Despite the frequent use of the Ewing and Clarke protocol, these studies lacked sufficient consistency in the selection and execution of their autonomic challenges, in the application of their eligibility and test criteria and most failed to include key methodological detail required to compare between trials. As such, there remains insufficient evidence to make any conclusions regarding the presence or specific nature of cancer- and treatment-related autonomic dysfunction.

Overall, disease and treatment-related parasympathetic dysfunction may be an important contributor to the increased CVD risks in TCS and, given TCS' high survival rates and the great number years potentially affected by the resultant CVD, represents an important therapeutic target for future exercise intervention research.

Summary

Together, this evidence strongly supports the contention that TCS are at high risk of developing chronic CVD within the first two decades post treatment. Compared to national estimates of the average age of onset for chronic diseases in Canadian males (i.e., heart disease (65+ years), diabetes (45+ years), hypertension (45+ years) and stroke (65+ years)),[126] the premature development of CVD poses a serious threat to TCS' survival and HRQoL.

References

1. Altena R, Perik PJ, van Veldhuisen DJ*, et al.* (2009): **Cardiovascular toxicity caused by cancer treatment: strategies for early detection**. *Lancet Oncol* 10:391-9.

2. Ewer MS, Lenihan DJ (2008): **Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground?** *J Clin Oncol* 26:1201-3.

3. Lester SJ, Tajik AJ, Nishimura RA*, et al.* (2008): **Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later**. *J Am Coll Cardiol* 51:679-89.

4. Swain SM, Whaley FS, Ewer MS (2003): **Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials**. *Cancer* 97:2869-79.

5. Jensen BV, Skovsgaard T, Nielsen SL (2002): **Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients**. *Ann Oncol* 13:699-709.

6. Gnasso A, Carallo C, Irace C*, et al.* (1996): **Association between intima-media thickness and wall shear stress in common carotid arteries in healthy male subjects**. *Circulation* 94:3257-3262.

7. McEniery CM, Wallace S, Mackenzie IS*, et al.* (2006): **Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans**. *Hypertension* 48:602-8.

8. Philpott AC, Lonn E, Title LM*, et al.* (2009): **Comparison of new measures of vascular function to flow mediated dilatation as a measure of cardiovascular risk factors**. *Am J Cardiol* 103:1610-5.

9. Anderson TJ, Charbonneau F, Title LM*, et al.* (2011): **Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study**. *Circulation* 123:163-9.

10. Celermajer DS, Sorensen KE, Georgakopoulos D*, et al.* (1993): **Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults**. *Circulation* 88:2149-2155.

11. Ebrahim S, Papacosta O, Whincup P*, et al.* (1999): **Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study**. *Stroke* 30:841-50.

12. Sutton-Tyrrell K, Najjar SS, Boudreau RM*, et al.* (2005): **Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults**. *Circulation* 111:3384-90.

13. Thayer JF, Lane RD (2007): **The role of vagal function in the risk for cardiovascular disease and mortality**. *Biol Psychol* 74:224-42.

14. Carnethon MR, Jacobs DR, Jr., Sidney S*, et al.* (2003): **Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: the CARDIA study**. *Diabetes Care* 26:3035-41.

15. Cruickshank K, Riste L, Anderson SG*, et al.* (2002): **Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function?** *Circulation* 106:2085-90.

16. Heier MS, Nilsen T, Graver V*, et al.* (1991): **Raynaud's phenomenon after combination chemotherapy of testicular cancer, measured by laser Doppler flowmetry. A pilot study**. *Br J Cancer* 63:550-2.

17. Stehouwer CD, Henry RM, Dekker JM*, et al.* (2004): **Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: further evidence for a link between microalbuminuria and endothelial dysfunction--the Hoorn Study**. *Kidney Int Suppl* 66:S42-4.

18. Taniwaki H, Kawagishi T, Emoto M*, et al.* (1999): **Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes**. *Diabetes Care* 22:1851-1857.

19. Onufrak S, Abramson J, Vaccarino V (2007): **Adult-onset asthma is associated with increased carotid atherosclerosis among women in the Atherosclerosis Risk in Communities (ARIC) study**. *Atherosclerosis* 195:129-37.

20. Anderson TJ, Uehata A, Gerhard MD*, et al.* (1995): **Close relation of endothelial function in the human coronary and peripheral circulations**. *J Am Coll Cardiol* 26:1235-41.

21. Hodis HN, Mack WJ, LaBree L*, et al.* (1998): **The role of carotid arterial intima-media thickness in predicting clinical coronary events**. *Ann Intern Med* 128:262-9.

22. Lieberman EH, Gerhard MD, Uehata A*, et al.* (1996): **Flow-induced vasodilation of the human brachial artery is impaired in patients < 40 years of age with coronary artery disease**. *Am J Cardiol* 78:1210-1214.

23. Mattace-Raso FU, van der Cammen TJ, Hofman A*, et al.* (2006): **Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study**. *Circulation* 113:657-63.

24. Kobayashi K, Akishita M, Yu W*, et al.* (2004): **Interrelationship between non-invasive measurements of atherosclerosis: flow-mediated dilation of brachial artery, carotid intima-media thickness and pulse wave velocity**. *Atherosclerosis* 173:13-8.

25. Liao JK, Bettmann MA, Sandor T*, et al.* (1991): **Differential impairment of vasodilator responsiveness of peripheral resistance and conduit vessels in humans with atherosclerosis**. *Circ Res* 68:1027-34.

26. Lorenz MW, Markus HS, Bots ML*, et al.* (2007): **Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis**. *Circulation* 115:459-67.

27. Duprez DA, Cohn JN (2007): **Detection of early cardiovascular disease**, in Willerson JT, Wellens HJJ, Cohn JN, et al (eds): Cardiovascular Medicine, *Springer London*, pp 1615-1622.

28. Scott J (2004): **Pathophysiology and biochemistry of cardiovascular disease**. *Curr Opin Genet Dev* 14:271-9.

29. Aass N, Fossa SD, Aas M*, et al.* (1990): **Renal function related to different treatment modalities for malignant germ cell tumours**. *Br J Cancer* 62:842-6.

30. Altena R, de Haas EC, Nuver J*, et al.* (2009): **Evaluation of sub-acute changes in cardiac function after cisplatin-based combination chemotherapy for testicular cancer**. *Br J Cancer* 100:1861-6.

31. Altena R, Hummel YM, Nuver J*, et al.* (2011): **Longitudinal changes in cardiac function after cisplatin-based chemotherapy for testicular cancer**. *Ann Oncol* 22:2286-93.

32. Berger CC, Bokemeyer C, Schneider M*, et al.* (1995): **Secondary Raynaud's phenomenon and other late vascular complications following chemotherapy for testicular cancer**. *Eur J Cancer* 31A:2229-38.

33. Bissett D, Kunkeler L, Zwanenburg L*, et al.* (1990): **Long-term sequelae of treatment for testicular germ cell tumours**. *Br J Cancer* 62:655-9.

34. Bokemeyer C, Berger CC, Kuczyk MA*, et al.* (1996): **Evaluation of long-term toxicity after chemotherapy for testicular cancer**. *J Clin Oncol* 14:2923-32.

35. Brennemann W, Stoffel-Wagner B, Helmers A*, et al.* (1997): **Gonadal function of patients treated with cisplatin based chemotherapy for germ cell cancer**. *J Urol* 158:844-50.

36. Daugaard G, Rossing N, Rorth M (1988): **Effects of cisplatin on different measures of glomerular function in the human kidney with special emphasis on high-dose**. *Cancer Chemother Pharmacol* 21:163-7.

37. de Haas EC, Altena R, Boezen HM*, et al.* (2013): **Early development of the metabolic syndrome after chemotherapy for testicular cancer**. *Ann Oncol* 24:749-55.

38. Dieckmann KP, Gerl A, Witt J*, et al.* (2010): **Myocardial infarction and other major vascular events during chemotherapy for testicular cancer**. *Ann Oncol* 21:1607-11.

39. Fjeldborg P, Sorensen J, Helkjaer PE (1986): **The long-term effect of cisplatin on renal function**. *Cancer* 58:2214-7.

40. Fossa SD, Gilbert E, Dores GM*, et al.* (2007): **Noncancer causes of death in survivors of testicular cancer**. *J Natl Cancer Inst* 99:533-44.

41. Gietema JA, Meinardi MT, van der Graaf WTA*, et al.* (2001): **Syndrome X in testicular cancer survivors**. *The Lancet* 357:228-229.

42. Gietema JA, Sleijfer DT, Willemse PH*, et al.* (1992): **Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated nonseminomatous testicular cancer**. *Ann Intern Med* 116:709-15.

43. Groth S, Nielsen H, Sorensen JB*, et al.* (1986): **Acute and long-term nephrotoxicity of cis-platinum in man**. *Cancer Chemother Pharmacol* 17:191-6.

44. Hamilton CR, Bliss JM, Horwich A (1989): **The late effects of cis-platinum on renal function**. *Eur J Cancer Clin Oncol* 25:185-9.

45. Hansen SW, Groth S, Daugaard G*, et al.* (1988): **Long-term effects on renal function and blood pressure of treatment with cisplatin, vinblastine, and bleomycin in patients with germ cell cancer**. *J Clin Oncol* 6:1728-31.

46. Hansen SW, Olsen N (1989): **Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin for germ cell cancer: measurement of vasoconstrictor response to cold**. *J Clin Oncol* 7:940-2.

47. Haugnes HS, Aass N, Fossa SD*, et al.* (2007): **Components of the metabolic syndrome in long-term survivors of testicular cancer**. *Ann Oncol* 18:241-8.

48. Haugnes HS, Wethal T, Aass N*, et al.* (2010): **Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study**. *J Clin Oncol* 28:4649-57.

49. Huddart RA, Norman A, Moynihan C*, et al.* (2005): **Fertility, gonadal and sexual function in survivors of testicular cancer**. *Br J Cancer* 93:200-7.

50. Huddart RA, Norman A, Shahidi M*, et al.* (2003): **Cardiovascular disease as a long-term complication of treatment for testicular cancer**. *J Clin Oncol* 21:1513-23.

51. Lackner JE, Koller A, Schatzl G*, et al.* (2009): **Androgen deficiency symptoms in testicular cancer survivors are associated with sexual problems but not with serum testosterone or therapy**. *Urology* 74:825-9.

52. MacLeod PM, Tyrell CJ, Keeling DH (1988): **The effect of cisplatin on renal function in patients with testicular tumours**. *Clin Radiol* 39:190-2.

53. Meinardi MT, Gietema JA, van Veldhuisen DJ*, et al.* (2000): **Long-term chemotherapy-related cardiovascular morbidity**. *Cancer Treat Rev* 26:429-47.

54. Nichols CR, Roth BJ, Williams SD*, et al.* (1992): **No evidence of acute cardiovascular complications of chemotherapy for testicular cancer - an analysis of the Testicular-Cancer-Intergroup Study**. *J Clin Oncol* 10:760-765.

55. Nord C, Bjoro T, Ellingsen D*, et al.* (2003): **Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer**. *Eur Urol* 44:322-8.

56. Nuver J, Smit AJ, Sleijfer DT*, et al.* (2004): **Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer**. *Eur J Cancer* 40:701-6.

57. Nuver J, Smit AJ, van der Meer J*, et al.* (2005): **Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer**. *J Clin Oncol* 23:9130-7.

58. Oh JH, Baum DD, Pham S*, et al.* (2007): **Long-term complications of platinum-based chemotherapy in testicular cancer survivors**. *Med Oncol* 24:175-81.

59. Orre IJ, Murison R, Dahl AA*, et al.* (2009): **Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue**. *Brain Behav Immun* 23:868-74.

60. Raghavan D, Cox K, Childs A*, et al.* (1992): **Hypercholesterolemia after chemotherapy for testis cancer**. *J Clin Oncol* 10:1386-9.

61. Sagstuen H, Aass N, Fossa SD*, et al.* (2005): **Blood pressure and body mass index in long-term survivors of testicular cancer**. *J Clin Oncol* 23:4980-90.

62. Stefenelli T, Kuzmits R, Ulrich W*, et al.* (1988): **Acute vascular toxicity after combination chemotherapy with cisplatin, vinblastine, and bleomycin for testicular cancer**. *Eur Heart J* 9:552-6.

63. Strumberg D, Brugge S, Korn MW*, et al.* (2002): **Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer**. *Ann Oncol* 13:229-36.

64. Stuart NS, Woodroffe CM, Grundy R*, et al.* (1990): **Long-term toxicity of chemotherapy for testicular cancer--the cost of cure**. *Br J Cancer* 61:479-84.

65. van den Belt-Dusebout AW, de Wit R, Gietema JA*, et al.* (2007): **Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer**. *J Clin Oncol* 25:4370-8.

66. van den Belt-Dusebout AW, Nuver J, de Wit R*, et al.* (2006): **Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer**. *J Clin Oncol* 24:467-75.

67. van Schinkel LD, Willemse PM, van der Meer RW*, et al.* (2013): **Chemotherapy for testicular cancer induces acute alterations in diastolic heart function**. *Br J Cancer* 109:891-6.

68. Vaughn DJ, Palmer SC, Carver JR*, et al.* (2008): **Cardiovascular risk in long-term survivors of testicular cancer**. *Cancer* 112:1949-53.

69. Vogelzang NJ, Bosl GJ, Johnson K*, et al.* (1981): **Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer**. *Ann Intern Med* 95:288-92.

70. Wethal T, Haugnes HS, Kjekshus J*, et al.* (2010): **C-reactive protein; a potential marker of second cancer and cardiovascular disease in testicular cancer survivors?** *Eur J Cancer* 46:3425-33.

71. Willemse PM, Burggraaf J, Hamdy NA*, et al.* (2013): **Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors**. *Br J Cancer* 109:60-7.

72. Willemse PP, van der Meer RW, Burggraaf J*, et al.* (2014): **Abdominal visceral and subcutaneous fat increase, insulin resistance and hyperlipidemia in testicular cancer patients treated with cisplatin-based chemotherapy**. *Acta Oncol* 53:351-60.

73. Nuver J, De Haas EC, Van Zweeden M*, et al.* (2010): **Vascular damage in testicular cancer patients: a study on endothelial activation by bleomycin and cisplatin in vitro**. *Oncol Rep* 23:247-53.

74. Wiechno P, Demkow T, Kubiak K*, et al.* (2007): **The quality of life and hormonal disturbances in testicular cancer survivors in the cisplatin era**. *Eur Urol* 52:1448-54.

75. Petersen PM, Skakkebæk NE, Vistisen K*, et al.* (1999): **Semen quality and reproductive hormones before orchiectomy in men with testicular cancer**. *J Clin Oncol* 17:941.

76. Yeap BB (2009): **Testosterone and ill-health in aging men**. *Nat Clin Pract Endocrinol Metab* 5:113-121.

77. Corn BW, Trock BJ, Goodman RL (1990): **Irradiation-related ischemic heart disease**. *J Clin Oncol* 8:741-50.

78. Lederman GS, Sheldon TA, Chaffey JT*, et al.* (1987): **Cardiac disease after mediastinal irradiation for seminoma**. *Cancer* 60:772-6.

79. Mousavi N, Nohria A (2013): **Radiation-induced cardiovascular disease**. *Curr Treat Options Cardiovasc Med* 15:507-17.

80. Patterson H, Norman AR, Mitra SS*, et al.* (2001): **Combination carboplatin and radiotherapy in the management of stage II testicular seminoma: comparison with radiotherapy treatment alone**. *Radiother Oncol* 59:5-11.

81. Fossa SD, Aass N, Winderen M*, et al.* (2002): **Long-term renal function after treatment for malignant germ-cell tumours**. *Ann Oncol* 13:222-8.

82. Quarmby S, Kumar P, Kumar S (1999): **Radiation-induced normal tissue injury: role of adhesion molecules in leukocyte-endothelial cell interactions**. *Int J Cancer* 82:385-95.

83. Cassady JR (1995): **Clinical radiation nephropathy**. *Int J Radiat Oncol Biol Phys* 31:1249-56.

84. Dewit L, Anninga JK, Hoefnagel CA*, et al.* (1990): **Radiation injury in the human kidney: a prospective analysis using specific scintigraphic and biochemical endpoints**. *Int J Radiat Oncol Biol Phys* 19:977-983.

85. Kim TH, Somerville PJ, Freeman CR (1984): **Unilateral radiation nephropathy--the long-term significance**. *Int J Radiat Oncol Biol Phys* 10:2053-9.

86. Verheij M, Dewit LG, Valdes Olmos RA*, et al.* (1994): **Evidence for a renovascular component in hypertensive patients with late radiation nephropathy**. *Int J Radiat Oncol Biol Phys* 30:677-83.

87. Dorr RT (1992): **Bleomycin pharmacology: mechanism of action and resistance, and clinical pharmacokinetics**, Semin Oncol, pp 3-8.

88. Hecht SM (2000): **Bleomycin: new perspectives on the mechanism of action**. *J Nat Prod* 63:158-68.

89. Mabeta P, Pepper MS (2009): **A comparative study on the anti-angiogenic effects of DNA-damaging and cytoskeletal-disrupting agents**. *Angiogenesis* 12:81-90.

90. Adamson IY (1976): **Pulmonary toxicity of bleomycin**. *Environ Health Perspect* 16:119-26.

91. Meinardi MT, Gietema JA, van der Graaf WT*, et al.* (2000): **Cardiovascular morbidity in long-term survivors of metastatic testicular cancer**. *J Clin Oncol* 18:1725-32.

92. Toumbis-Ioannou E, Cohen PR (1994): **Chemotherapy-induced Raynaud's phenomenon**. *Cleve Clin J Med* 61:195-9.

93. Senkus E, Jassem J (2011): **Cardiovascular effects of systemic cancer treatment**. *Cancer Treat Rev* 37:300-11.

94. Fuertes MA, Castilla J, Alonso C*, et al.* (2003): **Cisplatin biochemical mechanism of action: from cytotoxicity to induction of cell death through interconnections between apoptotic and necrotic pathways**. *Curr Med Chem* 10:257-266.

95. Belotti D, Vergani V, Drudis T*, et al.* (1996): **The microtubule-affecting drug paclitaxel has antiangiogenic activity**. *Clin Cancer Res* 2:1843-1849.

96. Yoshikawa A, Saura R, Matsubara T*, et al.* (1997): **A mechanism of cisplatin action: antineoplastic effect through inhibition of neovascularization**. *Kobe J Med Sci* 43:109-120.

97. Doll DC, Ringenberg QS, Yarbro JW (1986): **Vascular toxicity associated with antineoplastic agents**. *J Clin Oncol* 4:1405-17.

98. Stoter G, Koopman A, Vendrik CP*, et al.* (1989): **Ten-year survival and late sequelae in testicular cancer patients treated with cisplatin, vinblastine, and bleomycin**. *J Clin Oncol* 7:1099-104.

99. Soultati A, Mountzios G, Avgerinou C*, et al.* (2012): **Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications**. *Cancer Treat Rev* 38:473-83.

100. Boer H, Proost JH, Nuver J*, et al.* (2015): **Long-term exposure to circulating platinum is associated with late effects of treatment in testicular cancer survivors**. *Ann Oncol* 26:2305-10.

101. Hjelle LV, Gundersen PO, Oldenburg J*, et al.* (2015): **Long-term platinum retention after platinum-based chemotherapy in testicular cancer survivors: a 20-year follow-up study**. *Anticancer Res* 35:1619-25.

102. de Vos FY, Nuver J, Willemse PH*, et al.* (2004): **Long-term survivors of ovarian malignancies after cisplatin-based chemotherapy; cardiovascular risk factors and signs of vascular damage**. *Eur J Cancer* 40:696-700.

103. Lechner D, Kollars M, Gleiss A*, et al.* (2007): **Chemotherapy-induced thrombin generation via procoagulant endothelial microparticles is independent of tissue factor activity**. *J Thromb Haemost* 5:2445-52.

104. Ito H, Okafuji T, Suzuki T (1995): **Vitamin-E prevents endothelial injury associated with cisplatin injection into the superior mesenteric-artery of rats**. *Heart and Vessels* 10:178-184.

105. Lubberts S, Boer H, Altena R*, et al.* (2016): **Vascular fingerprint and vascular damage markers associated with vascular events in testicular cancer patients during and after chemotherapy**. *Eur J Cancer* 63:180-8.

106. Falah M, Schiff D, Burns TM (2005): **Neuromuscular complications of cancer diagnosis and treatment**. *J Support Oncol* 3:271-82.

107. Armstrong T, Almadrones L, Gilbert MR (2005): **Chemotherapy-induced peripheral neuropathy**. *Oncol Nurs Forum* 32:305-11.

108. Boogerd W, ten Bokkel Huinink WW, Dalesio O*, et al.* (1990): **Cisplatin induced neuropathy: central, peripheral and autonomic nerve involvement**. *J Neurooncol* 9:255-63.

109. Dormann AJ, Grunewald T, Wigginghaus B*, et al.* (1998): **Gemcitabine-associated autonomic neuropathy**. *Lancet* 351:644.

110. Ekholm E, Rantanen V, Antila K*, et al.* (1997): **Paclitaxel changes sympathetic control of blood pressure**. *Eur J Cancer* 33:1419-24.

111. Ekholm EM, Salminen EK, Huikuri HV*, et al.* (2000): **Impairment of heart rate variability during paclitaxel therapy**. *Cancer* 88:2149-53.

112. Gomber S, Dewan P, Chhonker D (2010): **Vincristine induced neurotoxicity in cancer patients**. *Indian J Pediatr* 77:97-100.

113. Hansen SW (1990): **Autonomic neuropathy after treatment with cisplatin, vinblastine, and bleomycin for germ cell cancer**. *BMJ* 300:511-2.

114. Hrushesky WJ, Fader DJ, Berestka JS*, et al.* (1991): **Diminishment of respiratory sinus arrhythmia foreshadows doxorubicin-induced cardiomyopathy**. *Circulation* 84:697-707.

115. Viniegra M, Marchetti M, Losso M*, et al.* (1990): **Cardiovascular autonomic function in anthracycline-treated breast cancer patients**. *Cancer Chemother Pharmacol* 26:227-31.

116. Ewing DJ, Clarke BF (1986): **Autonomic neuropathy: its diagnosis and prognosis**. *Clin Endocrinol Metab* 15:855-88.

117. Nuver J, Smit AJ, Sleijfer DT*, et al.* (2005): **Left ventricular and cardiac autonomic function in survivors of testicular cancer**. *Eur J Clin Invest* 35:99-103.

118. Hirvonen HE, Salmi TT, Heinonen E*, et al.* (1989): **Vincristine treatment of acute lymphoblastic leukemia induces transient autonomic cardioneuropathy**. *Cancer* 64:801-5.

119. Turner ML, Boland OM, Parker AC*, et al.* (1993): **Subclinical autonomic dysfunction in patients with Hodgkin's disease and non-Hodgkin's lymphoma**. *Br J Haematol* 84:623-6.

120. Jerian SM, Sarosy GA, Link CJ, Jr.*, et al.* (1993): **Incapacitating autonomic neuropathy precipitated by taxol**. *Gynecol Oncol* 51:277-80.

121. Quasthoff S, Hartung HP (2002): **Chemotherapy-induced peripheral neuropathy**. *J Neurol* 249:9-17.

122. Shahani BT, Halperin JJ, Boulu P*, et al.* (1984): **Sympathetic skin response--a method of assessing unmyelinated axon dysfunction in peripheral neuropathies**. *J Neurol Neurosurg Psychiatry* 47:536-42.

123. Argyriou AA, Koutras A, Polychronopoulos P*, et al.* (2005): **The impact of paclitaxel or cisplatin-based chemotherapy on sympathetic skin response: a prospective study**. *Eur J Neurol* 12:858-61.

124. Adams SC, Schondorf R, Benoit J*, et al.* (2015): **Impact of cancer and chemotherapy on autonomic nervous system function and cardiovascular reactivity in young adults with cancer: a case-controlled feasibility study**. *BMC Cancer* 15:414.

125. Low PA (1993): **Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure**. *Mayo Clin Proc* 68:748-52.

126. Public Health Agency of Canada (2010): **The Chronic Disease Infobase website.**,

Appendix E: The Role of Aerobic Exercise Training in TC Survivorship

The Role of Aerobic Exercise Training in TC Survivorship

TCS are at high-risk of CVD directly related to the anti-cancer therapies they have received. In fact, CVD now completes as the leading cause of death in TCS.[1] Given the complex and interrelated nature of treatment-related injuries and risks in TCS, potential intervention strategies must be capable of simultaneously influencing multiple pathways of dysfunction. With well-documented multi-system benefits, aerobic exercise training is a strong candidate-therapy to prevent or control treatment-related cardiovascular impairments in TCS.

Potential Benefits of Aerobic Exercise on Cardiovascular Health in Oncology

Aerobic capacity (VO_{2peak}) is an established surrogate marker of CVD-specific and general mortality risk in healthy, CVD, and cancer populations.[2-5] In general, VO_{2peak} declines at an average of 10% per decade in healthy adults – an effect which has been reported to be independent of physical activity levels.[6] However, as described in two comprehensive reviews on the subject,[6,7] there are several important caveats accompanying this general finding which merit further discussion.

First, this general trend (i.e., 10% decrease per decade) is based on the combined findings of cross-sectional and prospective research studies with highly variable recruitment strategies, assessment methods, and comparison groups – often resulting in discrepant findings.[6,7] Despite these discrepancies, however, studies consistently show that average VO_{2peak} values in trained individuals are higher than in sedentary individuals of comparable age; and, given their higher initial VO_{2peak} values, the absolute loss of VO_{2peak} in trained populations throughout adulthood will be greater than in sedentary subjects.[6,7]

Second, central and peripheral factors contribute to age-related declines in VO_{2peak}, and these factors are variably influenced by exercise history and current training status.[6,7] Centrally,

age-related declines in VO_{2peak} are governed by the determinants of cardiac output. Among these, the declines in maximal HR are uninfluenced by exercise and are reported to account for at least 40% of the age-related decline in cardiac output; whereas, the age-related decline in maximal stroke volume may be mitigated by exercise. Peripherally, the age-related decline in VO_{2peak} is attributed, but not limited, to adverse changes in body composition (i.e., decreased lean body mass and increased adiposity), impaired O_2 delivery, and mitochondrial dysfunction;[6-10] and, evidence suggests that exercise may mitigate these changes.[7-11] Importantly, the characteristics of age-related declines in VO_{2peak} differ according to exercise history and training status.[6] In sedentary subjects the VO_{2peak} decline tends to be most dramatic between ages 20 to 40 years and is often associated with increasing sedentary behaviour and adiposity.[6,12] However, the VO_{2peak} decline in trained individuals is more gradual while exercise training is maintained, and the rapid decline in VO_{2peak} is primarily attributed detraining.[6,12]

Third, some evidence suggests that high-intensity exercise may reduce the rate of VO_{2peak} decline by upwards of 50% in younger and middle-age men; although, middle-age women and older men and women may not be similarly protected.[6] Importantly, although high-intensity exercise may be capable of delaying or reversing the age-related decline in VO_{2peak}, it is generally accepted that this type of training is difficult to sustain over prolonged periods (especially beyond a decade).[13] Therefore, only a select few individuals who maintain adequate exercise levels will be able to mitigate declines in VO_{2peak} into their eighth or ninth decade.

Although our understanding of the causes of age-related declines in VO_{2peak} remains incomplete, one universally accepted fact is that regular aerobic exercise is the most effective means of maintaining or improving it. Moreover, given the findings from large prospective cohort and cross-sectional studies (i.e., a 10% to 25% improvement in overall survival associated

with each 3.5 ml O_2/kg/min increment increase in VO_{2peak}), VO_{2peak} remains an important intervention target for healthy and clinical populations alike.[14]

To date, there are no published randomized controlled trials on assessing VO_{2peak}-mediated improvements in long-term cancer-specific and overall mortality. However, a recent systematic review of 27 observational studies reported significant, dose-sensitive, inverse relationships between physical activity levels and cancer-specific and general mortality outcomes in survivors of breast and colon cancers.[15] This observational evidence is further supported by a number of randomized controlled trials and systematic reviews which have demonstrated the potential for aerobic exercise interventions to improve the VO_{2peak} of cancer patients and survivors.[16-19]

In addition to improving VO_{2peak}, aerobic exercise training has established benefits in preventing and controlling multiple pathways of CVD development.[20] In their 2013 review, Scott, J. et al.[20] highlighted a number of risk factors common to cancer and CVD development including hypertension, metabolic dysregulation, hormonal dysregulation, oxidative stress, and inflammation. Importantly, in non-cancer populations, aerobic exercise training has established benefits in preventing and reversing these disease processes.[21-25] Drawing from this dense evidence base in non-cancer populations, we recently proposed the development of a research paradigm testing the effects of targeted therapeutic doses of aerobic exercise to treat cancer-related CVD across the CVD continuum in early stage breast cancer survivors[26] – a model which likely applies to other cancer patient and survivor groups (including TCS).

Anti-Atherosclerotic Properties of Aerobic Exercise

Established in non-cancer clinical CVD populations, aerobic exercise's therapeutic mechanisms of action are anti-atherogenic (i.e., improving blood-lipid profiles and insulin

sensitivity while decreasing adiposity, blood pressure, and inflammation), anti-thrombotic (i.e., decreasing platelet adhesiveness, fibrinogen, and blood viscosity while increasing fibrinolysis), anti-ischemic (i.e., improving endothelial function and coronary blood flow while decreasing myocardial demand) and anti-arrhythmic (i.e., increased parasympathetic tone and HR variability while reducing the ventricular fibrillation threshold) in nature.[21-23,27,28] In the cancer setting, the findings from recent meta-analyses and systematic reviews have reported aerobic exercise-related improvements in blood-lipid profiles, body composition, insulin-glucose axis function, and inflammatory markers.[29] There is also preliminary evidence that aerobic exercise can improve endothelial function and vascular structure,[30] reduce oxidative stress,[31] and prevent of treatment-related cardiac dysfunction in cancer patients and survivors.[32] However, to date, no study has investigated the impact of aerobic exercise on any of these cardiovascular outcomes in a homogeneous cohort of TCS.

Benefits of Aerobic Exercise on Vascular Health in Oncology

Vascular injury is increasingly recognized as an important precursor to, and unifying mechanism in, the development cardiovascular morbidity and mortality;[33-38] and, as such, may be an important therapeutic target in cancer-related CVD prevention. A recent review on the effects of aerobic exercise on mitigating endothelial dysfunction and vascular wall inflammation highlight several pathways of potential therapeutic benefit.[39] The proper functioning and bioavailability of nitric oxide, cellular adhesion molecules, and endothelial progenitor cells are integral to the maintenance of healthy coronary and peripheral vasculature. Any disturbance of these pathways may result in the vascular environment becoming pro-inflammatory, -thrombotic, and -atherosclerotic. Importantly, evidence suggests that aerobic exercise can control and reverse these pathological processes.[39] Regular aerobic exercise has been shown to increase the

bioavailability of nitric oxide,[40] enhance antioxidant defense mechanisms,[41] reduce the production of pro-inflammatory cytokines,[22,42] and enhance the endothelium's capacity to regenerate.[23] Aerobic exercise trials in healthy populations have demonstrated improvements in the vascular structure (e.g., carotid intima-media thickness[43,44]), vascular function (e.g., flow-mediated dilation[45-48]), and both vascular compliance[49] and stiffness.[50,51] Aerobic exercise has also been shown to improve vascular health in elderly individuals[40,46,48,49,52] and across multiple CVD states including persons with coronary artery disease,[25,47,50,53,54] type II diabetes,[55,56] hypertension,[55,57] metabolic syndrome,[23,58] and in preclinical models of atherosclerosis.[22] In the only published exercise trial targeting vascular health and endothelial function in cancer survivors to date, Järvelä et al.[30] reported exercise-related improvements in flow-mediated dilation at 40 seconds (males; $p<0.01$), peak flow-mediated dilation (males; $p=0.05$; $d=0.86$), and carotid intima-media thickness (males and females combined; $p=0.02$; $d=0.61$) in long-term survivors of acute lymphoblastic leukemia.

Benefits of Aerobic Exercise on Autonomic Health in Oncology

Aerobic exercise training has a profound and well-documented impact on decreasing resting and training HR, improving HR variability, and improving HRR from exercise through a combination of intrinsic and systemic mechanisms.[59-61] However, our current understanding of the mechanisms underlying the beneficial effects of regular aerobic exercise on autonomic function remains incomplete.

Cross-sectional studies investigating the association between regular aerobic exercise and resting HR and autonomic function have identified that, compared to matched sedentary controls, physically active middle-aged and older men,[62,63] physically active post-menopausal women,[64] and endurance-trained athletes[65-67] have higher resting levels of parasympathetic activity.

Moreover, longitudinal studies in younger,[68] middle-aged, and older individuals[69,70] consistently report greater levels of parasympathetic activity in more physically active individuals. Furthermore, training studies have demonstrated that aerobic exercise augments cardiac parasympathetic control and decreases sympathetic influence.[61,71-75] Although conflicting observational evidence exists,[76-80] most experimental research in this area concludes that increased parasympathetic function is responsible for the observed bradycardic adaptations to aerobic exercise training.[61,72,75,81-83] Moreover, compared to their untrained counterparts, trained individuals have reduced sympathetic drive/activity at any given exercise workload[84,85] and are able to recover faster from aerobic exercise.[86-88]

In the cancer setting, preliminary evidence suggests that aerobic exercise positively influences cardiovagal function (i.e., resting HR, HR variability, and HRR),[89,90] and that indices of cardiovagal function may be predictive of mortality.[91,92] Observational evidence in non-cancer populations consistently suggests that aerobic exercise improves autonomic function and that these improvements are associated with decreased CVD incidence, severity, and mortality risks. For example, pharmacological studies of affected animals[93-96] and large human trials[97-100] have demonstrated that the improvements in HR variability are associated with decreases the related morbidity and mortality risks. Moreover, human training studies have clearly demonstrated exercise's potential to improve HR variability post-myocardial infarction,[101-105] heart surgery,[106] and in those with congestive heart failure.[107-113] Several mechanisms explaining the observed protective effects of increased systemic and cardiac parasympathetic influence have been proposed [e.g., blunting peripheral inflammatory responses,[114,115] negative chronotropic effects (via the sino-atrial node),[61,116] and anti-arrhythmic effects on the atrial and ventricular muscles[59,117]], but the precise mechanisms through which behavioural and pharmaceutical

intervention strategies augmenting parasympathetic function can improve mortality outcomes in any population remain to be fully elucidated.

In review, pathologic autonomic perturbations, such as those observed in various cancer populations, disrupt its dynamic control mechanisms and are associated with increased risk/incidence of CVD-related morbidity and mortality. Pharmacologic- and aerobic exercise-based interventions of healthy and affected individuals have been shown to improve prognostic and functional patient outcomes, as well as decrease the related CVD morbidity and mortality risks. It is, therefore, plausible that aerobic exercise play a similar role in improving cancer- and treatment-related autonomic dysfunction and related CVD risks.

References

1. Fossa SD, Gilbert E, Dores GM*, et al.* (2007): **Noncancer causes of death in survivors of testicular cancer**. *J Natl Cancer Inst* 99:533-44.

2. Kavanagh T, Mertens DJ, Hamm LF*, et al.* (2002): **Prediction of long-term prognosis in 12,169 men referred for cardiac rehabilitation**. *Circulation* 106:666-71.

3. Jones LW, Watson D, Herndon JE, 2nd*, et al.* (2010): **Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer**. *Cancer* 116:4825-32.

4. Blair SN, Kohl HW, Paffenbarger RS*, et al.* (1989): **Physical fitness and all-cause mortality. A prospective study of healthy men and women.** *JAMA* 262:2395-401.

5. Jones LW, Courneya KS, Mackey JR*, et al.* (2012): **Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum**. *J Clin Oncol* 30:2530-7.

6. Hawkins S, Wiswell R (2003): **Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training**. *Sports Med* 33:877-88.

7. Betik AC, Hepple RT (2008): **Determinants of VO2 max decline with aging: an integrated perspective**. *Appl Physiol Nutr Metab* 33:130-140.

8. Amara CE, Koval JJ, Johnson PJ*, et al.* (2000): **Modelling the influence of fat-free mass and physical activity on the decline in maximal oxygen uptake with age in older humans**. *Exp Physiol* 85:877-86.

9. Talbot LA, Metter EJ, Fleg JL (2000): **Leisure-time physical activities and their relationship to cardiorespiratory fitness in healthy men and women 18-95 years old**. *Med Sci Sports Exerc* 32:417-425.

10. Toth MJ, Gardner AW, Ades PA*, et al.* (1994): **Contribution of body composition and physical activity to age-related decline in peak VO2 in men and women**. *J Appl Physiol* 77:647-52.

11. Joseph AM, Adhihetty PJ, Leeuwenburgh C (2016): **Beneficial effects of exercise on age-related mitochondrial dysfunction and oxidative stress in skeletal muscle**. *J Physiol* 594:5105-23.

12. Buskirk ER, Hodgson JL (1987): **Age and aerobic power: the rate of change in men and women**, Federation proceedings, pp 1824-1829.

13. Pollock ML, Mengelkoch LJ, Graves JE*, et al.* (1997): **Twenty-year follow-up of aerobic power and body composition of older track athletes**. *J Appl Physiol* 82:1508-16.

14. Kaminsky LA, Arena R, Beckie TM*, et al.* (2013): **The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association**. *Circulation* 127:652-62.

15. Ballard-Barbash R, Friedenreich CM, Courneya KS*, et al.* (2012): **Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review**. *J Natl Cancer Inst* 104:815-40.

16. Courneya KS, Jones LW, Peddle CJ*, et al.* (2008): **Effects of aerobic exercise training in anemic cancer patients receiving darbepoetin alfa: a randomized controlled trial**. *Oncologist* 13:1012-20.

17. Courneya KS, Segal RJ, Mackey JR*, et al.* (2007): **Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial**. *J Clin Oncol* 25:4396-404.

18. Courneya KS, Sellar CM, Stevinson C*, et al.* (2009): **Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients**. *J Clin Oncol* 27:4605-12.

19. Jones LW, Liang Y, Pituskin EN*, et al.* (2011): **Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis**. *Oncologist* 16:112-20.

20. Scott JM, Koelwyn GJ, Hornsby WE*, et al.* (2013): **Exercise therapy as treatment for cardiovascular and oncologic disease after a diagnosis of early-stage cancer**. *Semin Oncol* 40:218-28.

21. Green DJ (2009): **Exercise training as vascular medicine: direct impacts on the vasculature in humans**. *Exerc Sport Sci Rev* 37:196-202.

22. Kadoglou NP, Moustardas P, Kapelouzou A*, et al.* (2013): **The anti-inflammatory effects of exercise training promote atherosclerotic plaque stabilization in apolipoprotein E knockout mice with diabetic atherosclerosis**. *Eur J Histochem* 57:e3.

23. Sonnenschein K, Horvath T, Mueller M*, et al.* (2011): **Exercise training improves in vivo endothelial repair capacity of early endothelial progenitor cells in subjects with metabolic syndrome**. *Eur J Cardiovasc Prev Rehabil* 18:406-14.

24. Thompson PD, Buchner D, Pina IL*, et al.* (2003): **Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)**. *Circulation* 107:3109-16.

25. Wienbergen H, Hambrecht R (2013): **Physical exercise and its effects on coronary artery disease**. *Curr Opin Pharmacol* 13:218-25.

26. Scott JM, Adams SC, Koelwyn GJ*, et al.* (2016): **Cardiovascular late effects and exercise treatment in breast cancer: current evidence and future directions**. *Can J Cardiol* 32:881-90.

27. Lakoski SG, Eves ND, Douglas PS*, et al.* (2012): **Exercise rehabilitation in patients with cancer**. *Nat Rev Clin Oncol* 9:288-96.

28. Billman GE (2002): **Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention**. *J Appl Physiol* 92:446-54.

29. Courneya KS, Crawford JJ, Adams SC (2015): **Physical activity and exercise interventions in cancer survivors.**, in Holland JC, Breitbart WS, Jacobsen PB, et al (eds): Psychooncology (ed 3rd). New York, , *Oxford University Press.*

30. Jarvela LS, Niinikoski H, Heinonen OJ*, et al.* (2013): **Endothelial function in long-term survivors of childhood acute lymphoblastic leukemia: effects of a home-based exercise program**. *Pediatr Blood Cancer* 60:1546-51.

31. Allgayer H, Owen RW, Nair J*, et al.* (2008): **Short-term moderate exercise programs reduce oxidative DNA damage as determined by high-performance liquid chromatography-electrospray ionization-mass spectrometry in patients with colorectal carcinoma following primary treatment**. *Scand J Gastroenterol* 43:971-8.

32. Scott JM, Khakoo A, Mackey JR*, et al.* (2011): **Modulation of Anthracycline-Induced Cardiotoxicity by Aerobic Exercise in Breast Cancer: Current Evidence and Underlying Mechanisms**. *Circulation* 124:642-650.

33. Anderson TJ, Charbonneau F, Title LM*, et al.* (2011): **Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study**. *Circulation* 123:163-9.

34. Gomez D, Owens GK (2012): **Smooth muscle cell phenotypic switching in atherosclerosis**. *Cardiovasc Res* 95:156-64.

35. Kitta Y, Obata JE, Nakamura T*, et al.* (2009): **Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease**. *J Am Coll Cardiol* 53:323-30.

36. Libby P (2012): **Inflammation in atherosclerosis**. *Arterioscler Thromb Vasc Biol* 32:2045-51.

37. Shechter M, Matetzky S, Arad M*, et al.* (2009): **Vascular endothelial function predicts mortality risk in patients with advanced ischaemic chronic heart failure**. *Eur J Heart Fail* 11:588-93.

38. Weisbrod RM, Shiang T, Al Sayah L*, et al.* (2013): **Arterial stiffening precedes systolic hypertension in diet-induced obesity**. *Hypertension* 62:1105-10.

39. Ribeiro F, Alves AJ, Duarte JA*, et al.* (2010): **Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation?** *Int J Cardiol* 141:214-21.

40. Green DJ, Maiorana A, O'Driscoll G*, et al.* (2004): **Effect of exercise training on endothelium-derived nitric oxide function in humans**. *The Journal of Physiology* 561:1-25.

41. Rush JW, Denniss SG, Graham DA (2005): **Vascular nitric oxide and oxidative stress: determinants of endothelial adaptations to cardiovascular disease and to physical activity**. *Can J Appl Physiol* 30:442-74.

42. Hejazi SM, Rashidlamir A, Jebelli A*, et al.* (2013): **The effects of 8 weeks aerobic exercise on levels of homocysteine, HS-CRP serum and plasma fibrinogen in type II diabetic women**. *Life Sci*:430-435.

43. Tanaka H, Seals DR, Monahan KD*, et al.* (2002): **Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men**. *J Appl Physiol* 92:1458-64.

44. Dinenno FA, Tanaka H, Monahan KD*, et al.* (2001): **Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men**. *J Physiol* 534:287-95.

45. Kingwell BA, Sherrard B, Jennings GL*, et al.* (1997): **Four weeks of cycle training increases basal production of nitric oxide from the forearm**. *Am J Physiol* 272:H1070-7.

46. DeSouza CA, Shapiro LF, Clevenger CM*, et al.* (2000): **Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men**. *Circulation* 102:1351-7.

47. Currie KD, Dubberley JB, McKelvie RS*, et al.* (2013): **Low-volume, high-intensity interval training in patients with CAD**. *Med Sci Sports Exerc* 45:1436-42.

48. Pierce GL, Eskurza I, Walker AE*, et al.* (2011): **Sex-specific effects of habitual aerobic exercise on brachial artery flow-mediated dilation in middle-aged and older adults**. *Clin Sci* 120:13-23.

49. Tanaka H, Dinenno FA, Monahan KD*, et al.* (2000): **Aging, habitual exercise, and dynamic arterial compliance**. *Circulation* 102:1270-5.

50. Edwards DG, Schofield RS, Magyari PM*, et al.* (2004): **Effect of exercise training on central aortic pressure wave reflection in coronary artery disease**. *Am J Hypertens* 17:540-3.

51. Hayashi K, Sugawara J, Komine H*, et al.* (2005): **Effects of aerobic exercise training on the stiffness of central and peripheral arteries in middle-aged sedentary men**. *Jpn J Physiol* 55:235-9.

52. Rakobowchuk M, Tanguay S, Burgomaster KA*, et al.* (2008): **Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans**. *Am J Physiol Regul Integr Comp Physiol* 295:R236-42.

53. Currie KD, McKelvie RS, Macdonald MJ (2012): **Flow-mediated dilation is acutely improved after high-intensity interval exercise**. *Med Sci Sports Exerc* 44:2057-64.

54. Hambrecht R, Adams V, Erbs S*, et al.* (2003): **Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase**. *Circulation* 107:3152-8.

55. Madden KM, Lockhart C, Cuff D*, et al.* (2009): **Short-term aerobic exercise reduces arterial stiffness in older adults with type 2 diabetes, hypertension, and hypercholesterolemia**. *Diabetes Care* 32:1531-5.

56. Yokoyama H, Emoto M, Fujiwara S*, et al.* (2004): **Short-term aerobic exercise improves arterial stiffness in type 2 diabetes**. *Diabetes Res Clin Pract* 65:85-93.

57. Higashi Y, Yoshizumi M (2004): **Exercise and endothelial function: Role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients**. *Pharmacology & Therapeutics* 102:87-96.

58. Tjonna AE, Lee SJ, Rognmo O*, et al.* (2008): **Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study**. *Circulation* 118:346-54.

59. Lahiri MK, Kannankeril PJ, Goldberger JJ (2008): **Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications**. *J Am Coll Cardiol* 51:1725-33.

60. Pecanha T, Silva-Junior ND, Forjaz CL (2014): **Heart rate recovery: autonomic determinants, methods of assessment and association with mortality and cardiovascular diseases**. *Clin Physiol Funct Imaging* 34:327-39.

61. Billman GE, Cagnoli KL, Csepe T*, et al.* (2015): **Exercise training induced bradycardia: evidence for enhanced parasympathetic regulation without changes in" intrinsic" sinoatrial node function**. *J Appl Physiol* jap. 01111.2014-jap. 01111.2014.

62. De Meersman RE (1993): **Heart rate variability and aerobic fitness**. *Am Heart J* 125:726-31.

63. Seals DR, Chase PB (1989): **Influence of physical training on heart rate variability and baroreflex circulatory control**. *J Appl Physiol* 66:1886-95.

64. Davy KP, Miniclier NL, Taylor JA*, et al.* (1996): **Elevated heart rate variability in physically active postmenopausal women: a cardioprotective effect?** *Am J Physiol* 271:H455-60.

65. Barney JA, Ebert TJ, Groban L*, et al.* (1988): **Carotid baroreflex responsiveness in high-fit and sedentary young men**. *J Appl Physiol* 65:2190-4.

66. Dixon EM, Kamath MV, McCartney N*, et al.* (1992): **Neural regulation of heart rate variability in endurance athletes and sedentary controls**. *Cardiovasc Res* 26:713-9.

67. Goldsmith RL, Bigger JT, Jr., Steinman RC*, et al.* (1992): **Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men**. *J Am Coll Cardiol* 20:552-8.

68. De Meersman RE (1992): **Respiratory sinus arrhythmia alteration following training in endurance athletes**. *Eur J Appl Physiol Occup Physiol* 64:434-6.

69. Levy WC, Cerqueira MD, Harp GD*, et al.* (1998): **Effect of endurance exercise training on heart rate variability at rest in healthy young and older men**. *Am J Cardiol* 82:1236-1241.

70. Stein PK, Ehsani AA, Domitrovich PP*, et al.* (1999): **Effect of exercise training on heart rate variability in healthy older adults**. *Am Heart J* 138:567-76.

71. Billman GE (2009): **Cardiac autonomic neural remodeling and susceptibility to sudden cardiac death: effect of endurance exercise training**. *Am J Physiol Heart Circ Physiol* 297:H1171-93.

72. Carter JB, Banister EW, Blaber AP (2003): **Effect of endurance exercise on autonomic control of heart rate**. *Sports Med* 33:33-46.

73. Fu Q, Levine BD (2013): **Exercise and the autonomic nervous system**. *Handb Clin Neurol* 117:147-60.

74. Gregoire J, Tuck S, Hughson RL*, et al.* (1996): **Heart rate variability at rest and exercise: influence of age, gender, and physical training**. *Can J Appl Physiol* 21:455-470.

75. Zanesco A, Antunes E (2007): **Effects of exercise training on the cardiovascular system: pharmacological approaches**. *Pharmacol Ther* 114:307-17.

76. Bonaduce D, Petretta M, Cavallaro V*, et al.* (1998): **Intensive training and cardiac autonomic control in high level athletes**. *Med Sci Sports Exerc* 30:691-6.

77. Katona PG, McLean M, Dighton DH*, et al.* (1982): **Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest**. *J Appl Physiol* 52:1652-1657.

78. Lewis SF, Nylander E, Gad P*, et al.* (1980): **Non‐autonomic component in bradycardia of endurance trained men at rest and during exercise**. *Acta Physiologica Scandinavica* 109:297-305.

79. Smith ML, Hudson DL, Graitzer HM*, et al.* (1989): **Exercise training bradycardia: the role of autonomic balance**. *Med Sci Sports Exerc* 21:40-4.

80. Stein R, Medeiros CM, Rosito GA*, et al.* (2002): **Intrinsic sinus and atrioventricular node electrophysiologic adaptations in endurance athletes**. *J Am Coll Cardiol* 39:1033-8.

81. De Angelis K, Wichi RB, Jesus WR*, et al.* (2004): **Exercise training changes autonomic cardiovascular balance in mice**. *J Appl Physiol* 96:2174-8.

82. Ordway GA, Charles JB, Randall DC*, et al.* (1982): **Heart rate adaptation to exercise training in cardiac-denervated dogs**. *J Appl Physiol Respir Environ Exerc Physiol* 52:1586-90.

83. Shi X, Stevens GH, Foresman BH*, et al.* (1995): **Autonomic nervous system control of the heart: endurance exercise training**. *Med Sci Sports Exerc* 27:1406-13.

84. Hartley LH, Mason JW, Hogan RP*, et al.* (1972): **Multiple hormonal responses to graded exercise in relation to physical training**. *J Appl Physiol* 33:602-6.

85. Lehmann M, Schmid P, Keul J (1984): **Age- and exercise-related sympathetic activity in untrained volunteers, trained athletes and patients with impaired left-ventricular contractility**. *Eur Heart J* 5 Suppl E:1-7.

86. Hagberg JM, Hickson RC, Ehsani AA*, et al.* (1980): **Faster adjustment to and recovery from submaximal exercise in the trained state**. *J Appl Physiol Respir Environ Exerc Physiol* 48:218-24.

87. Hagberg JM, Hickson RC, McLane JA*, et al.* (1979): **Disappearance of norepinephrine from the circulation following strenuous exercise**. *J Appl Physiol Respir Environ Exerc Physiol* 47:1311-4.

88. Imai K, Sato H, Hori M*, et al.* (1994): **Vagally mediated heart-rate recovery after exercise is accelerated in athletes but alunted in aatients with chronic heart-failure**. *J Am Coll Cardiol* 24:1529-1535.

89. Hornsby WE, Douglas PS, West MJ*, et al.* (2014): **Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial**. *Acta Oncol* 53:65-74.

90. Niederer D, Vogt L, Gonzalez-Rivera J*, et al.* (2015): **Heart rate recovery and aerobic endurance capacity in cancer survivors: interdependence and exercise-induced improvements**. *Support Care Cancer* 23:3513-20.

91. Giese-Davis J, Wilhelm FH, Tamagawa R*, et al.* (2015): **Higher vagal activity as related to survival in patients with advanced breast cancer: an analysis of autonomic dysregulation**. *Psychosom Med* 77:346-55.

92. Guo Y, Koshy S, Hui D*, et al.* (2015): **Prognostic value of heart rate variability in patients with cancer**. *J Clin Neurophysiol* 32:516-20.

93. Hull SS, Jr., Vanoli E, Adamson PB*, et al.* (1994): **Exercise training confers anticipatory protection from sudden death during acute myocardial ischemia**. *Circulation* 89:548-52.

94. Schwartz PJ, Vanoli E, Strambabadiale M*, et al.* (1988): **Autonomic mechanisms and sudden-death - New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial-infarction**. *Circulation* 78:969-979.

95. Vanoli E, De Ferrari GM, Stramba-Badiale M*, et al.* (1991): **Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction**. *Circ Res* 68:1471-81.

96. Zuanetti G, De Ferrari GM, Priori SG*, et al.* (1987): **Protective effect of vagal stimulation on reperfusion arrhythmias in cats**. *Circ Res* 61:429-35.

97. Norwegian Multicenter Study Group (1981): **Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction**. *N Engl J Med* 304:801-807.

98. Hjalmarson A, Elmfeldt D, Herlitz J*, et al.* (1981): **Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial**. *Lancet* 2:823-7.

99. β-Blocker Heart Attack Trial Research Group (1982): **A randomized trial of propranolol in patients with acute myocardial infarction**. *JAMA* 247:1707-1714.

100. Packer M, Bristow MR, Cohn JN*, et al.* (1996): **The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group**. *N Engl J Med* 334:1349-55.

101. La Rovere MT, Mortara A, Sandrone G*, et al.* (1992): **Autonomic nervous system adaptations to short-term exercise training**. *Chest* 101:299S-303S.

102. Malfatto G, Facchini M, Bragato R*, et al.* (1996): **Short and long term effects of exercise training on the tonic autonomic modulation of heart rate variability after myocardial infarction**. *Eur Heart J* 17:532-8.

103. Malfatto G, Facchini M, Sala L*, et al.* (1998): **Effects of cardiac rehabilitation and beta-blocker therapy on heart rate variability after first acute myocardial infarction**. *Am J Cardiol* 81:834-40.

104. Oya M, Itoh H, Kato K*, et al.* (1999): **Effects of exercise training on the recovery of the autonomic nervous system and exercise capacity after acute myocardial infarction**. *Jpn Circ J* 63:843-8.

105. Schwartz PJ, La Rovere MT, Vanoli E (1992): **Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification**. *Circulation* 85:I77-91.

106. Iellamo F, Legramante JM, Massaro M*, et al.* (2000): **Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: a randomized, controlled study**. *Circulation* 102:2588-92.

107. Adamopoulos S, Ponikowski P, Cerquetani E*, et al.* (1995): **Circadian pattern of heart rate variability in chronic heart failure patients. Effects of physical training**. *Eur Heart J* 16:1380-6.

108. Belardinelli R, Georgiou D, Cianci G*, et al.* (1999): **Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome**. *Circulation* 99:1173-82.

109. Coats AJ, Adamopoulos S, Radaelli A*, et al.* (1992): **Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function**. *Circulation* 85:2119-31.

110. European Heart Failure Training Group (1998): **Experience from controlled trials of physical training in chronic heart failure. Protocol and patient factors in effectiveness in the improvement in exercise tolerance.** *Eur Heart J* 19:466-75.

111. Keteyian SJ, Brawner CA, Schairer JR*, et al.* (1999): **Effects of exercise training on chronotropic incompetence in patients with heart failure**. *Am Heart J* 138:233-40.

112. Kiilavuori K, Naveri H, Leinonen H*, et al.* (1999): **The effect of physical training on hormonal status and exertional hormonal response in patients with chronic congestive heart failure**. *Eur Heart J* 20:456-64.

113. Kiilavuori K, Toivonen L, Naveri H*, et al.* (1995): **Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability**. *Eur Heart J* 16:490-5.

114. Tracey KJ (2009): **Reflex control of immunity**. *Nat Rev Immunol* 9:418-28.

115. Thayer JF, Lane RD (2007): **The role of vagal function in the risk for cardiovascular disease and mortality**. *Biol Psychol* 74:224-42.

116. Fox K, Borer JS, Camm AJ*, et al.* (2007): **Resting heart rate in cardiovascular disease**. *J Am Coll Cardiol* 50:823-30.

117. Peltola M, Tulppo MP, Kiviniemi A*, et al.* (2008): **Respiratory sinus arrhythmia as a predictor of sudden cardiac death after myocardial infarction**. *Ann Med* 40:376-382.

Appendix F: Exercise Prescription Considerations for TCS

Exercise Prescription Considerations for TCS

To date, there have been no published accounts of aerobic exercise interventions in a homogeneous cohort of TCS. Given the benefits described throughout this dissertation, aerobic exercise may prove to be a critical preventative and restorative therapeutic exposure targeting the specific contributors to cardiovascular injury, CRF, and poor HRQoL in TCS. Compared to other high-CVD-risk and CVD populations, available evidence suggests TCS present with CVD at a younger age.[1-3] By virtue of their youth, TCS are not as likely to have undergone natural age-related deconditioning and, therefore, may be more capable of performing higher intensities of exercise which have been shown to be associated with greater benefits in non-cancer[4-6] and cancer[7] populations (including TCS[8]). Furthermore, TCS may be more likely than older cancer survivor groups to be in a pre-retirement life-stage, and, therefore, may be less able to participate in high-volume/time consuming aerobic exercise interventions. This is supported by a report that TCS are likely to cite 'competing demands' as major barriers to exercise participation.[9] With these considerations in mind, high-intensity and time efficient aerobic exercise interventions may best align themselves with the unique life circumstance of TCS.

Continuous versus Interval Training

A recent cross-sectional survey, involving 5106 healthy men and women aged 21-90, demonstrated that higher exercise intensity had a stronger, positive association with improvements in all-cause and coronary heart disease mortality rates, compared to those performing greater durations of exercise.[10] Furthermore, comparisons of traditional MCT to HIIT have demonstrated comparable or greater improvements in $VO_{2peak,}$[11] arterial compliance,[12] metabolic/lipid profiles,[13-15] flow-mediated dilation,[11-14,16,17] cardiac remodeling,[14] sarcoplasmic

calcium release,[14,17] and antioxidant defense.[14] Importantly, Rognmo et al.[18] reported a comparably low-risk of adverse cardiovascular events related to HIIT and MCT in the rehabilitation of 4846 patients with coronary heart disease. Moreover, Bartlett et al.[19] reported that HIIT was more enjoyable than MCT which may have important participant adherence implications.

Table F1: Reported interval training parameters

Trial	Intervention Length	Training Modalities	Work-to-rest Ratio (W:R)	Training Intensity	Session Frequency	Session Length
Burgomaster et al. (2008)	6 weeks	Cycling	1:7	W: Max R: <50 rpm @ 30 watts	3 days/week	30 min/day (4 - 6 Windgates)
Currie et al. (2013)	12 weeks	Cycling	1:1	W: 89% PPO* R: 10% PPO	3 days/week	30 min/day (10 interval cycles)
Rakobowchuk et al. (2008)	6 weeks	Cycling	1:7	W: Max R: <50 rpm @ 30 watts	3 days/week	30 min/day (4 - 6 Windgates)
Tjonna et al. (2008)	16 weeks	Uphill walking/ running	4:3	W: 90% H_{fmax}* R: 70% H_{fmax}	3 days/week	40 min/day
Trombold et al. (2013)	3 x 3-day treatments	Cycling	1:1	W: 90% VO_{2peak} R: 25% VO_{2peak}	N/A	40-45 min/day
Wisloff et al. (2007)	12 weeks	Uphill walking/ running	4:3	W: 90-95% HR_{peak}* R: 50-75% HR_{peak}	3 days/week	38 min/day

* speed and workloads adjusted for improvements in conditioning
W: work interval; R: rest interval; rpm: revolutions per minute; PPO: peak power output; H_{fmax}: maximal heart frequency; VO_{2peak}: peak oxygen uptake; HR_{peak}: peak heart rate

Reported Interval Training Parameters

HIIT prescriptions are infinitely variable given the multiple, alterable testing parameters. Although few studies have directly compared HIIT to MCT, the characteristics of six trials

which have demonstrated that HIIT causes comparable or superior benefits to MCT are summarized in **Table F1**. In brief, the interventions ran between three days and 16 weeks, included both cycling and treadmill-based exercise, had highly variable work-to-rest ratios, required participants trained between 89% and 110% of maximal capacity (determined at baseline), with session frequencies of three days per week and durations between 30 and 45 minutes per session.

Summary

Overall this evidence suggests that HIIT is a time efficient and enjoyable modality of aerobic exercise training which is *at least* as effective and *likely more* effective than MCT at improving cardiovascular health outcomes.

References

1. Abouassaly R, Fossa SD, Giwercman A*, et al.* (2011): **Sequelae of treatment in long-term survivors of testis cancer**. *Eur Urol* 60:516-26.

2. Feldman DR, Schaffer WL, Steingart RM (2012): **Late Cardiovascular Toxicity Following Chemotherapy for Germ Cell Tumors**. *Journal of the National Comprehensive Cancer Network* 10:537-544.

3. Mulrooney DA, Blaes AH, Duprez D (2012): **Vascular injury in cancer survivors**. *J Cardiovasc Transl Res* 5:287-95.

4. Hawkins S, Wiswell R (2003): **Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training**. *Sports Med* 33:877-88.

5. Kessler HS, Sisson SB, Short KR (2012): **The potential for high-intensity interval training to reduce cardiometabolic disease risk**. *Sports Med* 42:489-509.

6. Weston KS, Wisloff U, Coombes JS (2014): **High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis**. *Br J Sports Med* 48:1227-34.

7. Devin JL, Sax AT, Hughes GI*, et al.* (2016): **The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial**. *J Cancer Surviv* 10:467-79.

8. Fung C, Sesso HD, Williams AM*, et al.* (2017): **Multi-institutional assessment of adverse health outcomes among north american testicular cancer survivors after modern cisplatin-based chemotherapy**. *J Clin Oncol* 35:1211-1222.

9. Reilley MJ, Jacobs LA, Vaughn DJ*, et al.* (2014): **Health behaviors among testicular cancer survivors**. *J Community Support Oncol* 12:121-8.

10. Schnohr P, Marott JL, Jensen JS*, et al.* (2012): **Intensity versus duration of cycling, impact on all-cause and coronary heart disease mortality: the Copenhagen City Heart Study**. *Eur J Prev Cardiol* 19:73-80.

11. Currie KD, Dubberley JB, McKelvie RS*, et al.* (2013): **Low-volume, high-intensity interval training in patients with CAD**. *Med Sci Sports Exerc* 45:1436-42.

12. Rakobowchuk M, Tanguay S, Burgomaster KA*, et al.* (2008): **Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans**. *Am J Physiol Regul Integr Comp Physiol* 295:R236-42.

13. Burgomaster KA, Howarth KR, Phillips SM*, et al.* (2008): **Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans**. *J Physiol* 586:151-60.

14. Wisloff U, Stoylen A, Loennechen JP*, et al.* (2007): **Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study**. *Circulation* 115:3086-94.

15. Trombold JR, Christmas KM, Machin DR*, et al.* (2013): **Acute high-intensity endurance exercise is more effective than moderate-intensity exercise for attenuation of postprandial triglyceride elevation**. *J Appl Physiol* 114:792-800.

16. Currie KD, McKelvie RS, Macdonald MJ (2012): **Flow-mediated dilation is acutely improved after high-intensity interval exercise**. *Med Sci Sports Exerc* 44:2057-64.

17. Tjonna AE, Lee SJ, Rognmo O*, et al.* (2008): **Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study**. *Circulation* 118:346-54.

18. Rognmo O, Moholdt T, Bakken H*, et al.* (2012): **Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients**. *Circulation* 126:1436-40.

19. Bartlett JD, Close GL, MacLaren DP*, et al.* (2011): **High-intensity interval running is perceived to be more enjoyable than moderate-intensity continuous exercise: implications for exercise adherence**. *J Sports Sci* 29:547-53.

Appendix G: HIITTS Trial Cover Letter

Cross Cancer Institute
11560 University Avenue, Edmonton,
Alberta, Canada, T6G 1Z2
Tel: 780.432.8770

Dear Sir,

My name is Kerry Courneya and I am a Professor and Canada Research Chair at the University of Alberta. I am also a Scientific Staff member of the Cross Cancer Institute in Edmonton. As part of my responsibilities, I conduct research on the health of cancer survivors. The Alberta Cancer Registry is contacting you on my behalf to see if you might be interested in participating in an exercise intervention study that requires the voluntary participation of testicular cancer survivors. The study has been approved by the Alberta Health Services and Health Research Ethics Board of Alberta – Cancer Committee and the University of Alberta Health Research Ethics Board, and has met rigorous requirements for ethical approval. My collaborators for this study include Dr. Scott North, a medical oncologist at the Cross Cancer Institute; and Dr. Adrian Fairey, a urologic surgical-oncologist at the Alberta Urology Institute.

Research has shown that some testicular cancer survivors, especially those who were treated with chemotherapy, are at higher risk of developing cardiovascular disease. Those who underwent surgery only, without needing further cancer treatments, may have a slightly higher risk of cardiovascular disease than the average healthy male. Importantly, regular aerobic exercise (e.g. walking, running, cycling) is known to prevent and treat cardiovascular disease in non- cancer populations. High-intensity interval training (i.e. which involves exercising hard for short periods of time and slowing down to recover in-between) is especially good at improving cardiovascular health in people living with various cardiovascular risks and diseases. However, due to the unique causes of cardiovascular damage in testicular cancer survivors, we do not know if this type of aerobic exercise can have similar cardiovascular benefits. To address this issue, we are conducting a clinical trial on the effects of high intensity interval training in testicular cancer survivors, and we would like to invite you to participate in the study.

If you decide to participate in this study, you will be asked to attend 2 testing sessions 3 months apart at Alberta Health Services and University of Alberta facilities. Each visit will require between 2 to 3 hours and include assessments of your cardiovascular fitness, vascular function, a blood draw, and questionnaires.

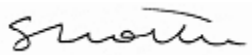
We would then assign you by chance to either participate in the high intensity interval training program (i.e., the intervention group) or to continue with your usual exercise levels (i.e., the control group). If you are assigned to the intervention group, we would ask you to attend supervised high-intensity aerobic interval training exercise sessions 3 days a week for 12 weeks. These short-duration and high-intensity exercise sessions only require you to work hard for 16 minutes of the total 35 minutes. Furthermore, this type of aerobic exercise training is known to be very well-tolerated in middle-age and older individuals with various cardiovascular diseases and with little-to-no previous exercise experience. If you are assigned to the control group, we would offer you a shorter version of the intervention program after you completed the final assessments (i.e., 8 training sessions over a 4 week period).

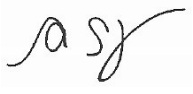
The program will take place at the Behavioural Medicine Fitness Centre at the University of Alberta. This is a fully equipped fitness facility dedicated for research purposes only, and available to you free of charge for the 12-week program. Your personal exercise trainer and supervised exercise program are also free. We will also pay for your parking at the Behavioural Medicine Fitness Centre when you come for your testing and training sessions.

Your participation in this study is completely voluntary. Any information that you provide will be held in strict confidence. It is only through voluntary participation in research projects that we increase our knowledge about developing physical activity programs to improve quality of life and cardiovascular health in testicular cancer survivors. We hope that you find the time to assist us. If you are interested in participating in this study or need any questions answered before making up your mind, please contact my Research Coordinator, Scott Adams, at (780) 492-8246 or e- mail hitts@ualberta.ca for more information.

Thank you for considering our study.

Sincerely,





Kerry S. Courneya, PhD
Professor & Canada Research Chair
in PA & Cancer

Scott North, MD
Medical Oncologist Cross Cancer
Institute

Adrian Fairey, MD
Surgical Uro-Oncologist Alberta
Urology Institute

Appendix H: Alberta Cancer Registry Cover Letter

Dear Sir:

From time to time on behalf of researchers, the Alberta Cancer Registry contacts individuals who may be eligible for research studies. This letter is to introduce you to a research study being undertaken by an affiliate of the Alberta Health Services. These types of studies ***must*** be approved by the Alberta Cancer Research Ethics Committee. Information on new cancer cases and cancer-related deaths is recorded in the Alberta Cancer Registry. The Alberta Health Services is mandated by the Regional Health Authorities Act, please read the enclosed letter for further information describing the Registry.

We are enclosing information from a research study that has been recently approved by the Ethics Board and which may be of interest to you. Please note, this is a random sample generated by the computer and your name was selected, however, depending upon your diagnosis, this study may not apply to you. We have not disclosed any of your personal information to the researchers and are simply contacting you on their behalf to provide you with an opportunity to participate in a research study. Your participation in this or any research study is absolutely voluntary. Enclosed is some information from the researchers describing the study in order to help you make an informed choice about whether or not you would like to participate. If you are interested in finding out more about the study, please follow the enclosed instructions. If you are not interested in participating, simply ignore the materials that we have sent you or return the unanswered questionnaire in the envelope provided by the researchers.

The Alberta Cancer Registry is very supportive of research studies conducted with its registry, as voluntary participation in research projects helps to improve our knowledge about issues that are important to cancer patients and survivors. We hope that you find time to read the enclosed materials closely and participate in the study if you feel it is of interest to you.

If you have further questions regarding the Alberta Cancer Registry, please call me at (780) 432-8781 or email me at cindy.nikiforuk@albertahealthservices.ca.

Sincerely,

Cindy Nikiforuk

Cindy Nikiforuk, CHIM
Director, Alberta Cancer Registry
Cancer Measurement Outcomes & Evaluation
Cancer Care, Alberta Health Services
Cross Cancer Institute

Appendix I: Participant Screening Sheet

PARTICIPANT SCREENING CHECKLIST

Recruit. Priority:
- □ High (1)
- □ Medium (2)
- □ Low (3)

Contact Date: ____/____/____ (YY / MM / DD) **First Name**: _____ **Last Name**: _____

Phone Number: _____ **Date of Birth**: _____/_____/_____ (YY / MM / DD)

1. Are you a currently a smoker? Y / N *Details*: _____

2. Are you a former smoker? Y / N *Details*: _____

3. Prediagnosis Cardiovascular Disease:

3a. Heart attack? Y / N **3b.** High-cholesterol? Y / N **3c.** Obesity? Y / N

3d. Diabetes? Y / N **3e.** Hypertension? Y / N

Details: _____

4. Cancer History:

4a. Date of diagnosis? _____/_____/_____ (YY / MM / DD) **4b.** Cancer type? Seminoma or Non-seminoma

4c. Was this the only time you have been diagnosed with cancer? Y / N

Details: _____

4d. Disease stage at diagnosis? I / II / III / IV

5. Treatment Exposure (Primary):

5a. Surgery? Y / N **5b.** _____/_____/_____ (YY / MM / DD) **5c.** Type of surgery? Unilateral / Bilateral

5d. Lymph nodes affected? Y / N *Details*: _____

5e. Radiotherapy? Y / N **5f.** Completed: _____/_____/_____ (YY / MM / DD) **5g.** # sessions _____

5h. Area affected? Abdomen / Abdomen + Pelvis / Other (*Details*: _____)

5i. Chemotherapy? Y / N **5j.** Completed: _____/_____/_____ (YY / MM / DD) **5k.** Type: _____ **5l.** # cycles: ___

6. Treatment Exposure (Secondary):

6a. Surgery? Y / N **6b.** _____/_____/_____ (YY / MM / DD) **6c.** Type of surgery? Unilateral / Bilateral

6d. Lymph nodes affected? Y / N *Details*: _____

6e. Radiotherapy? Y / N **6f.** Completed: _____/_____/_____ (YY / MM / DD) **6g.** # sessions _____

6h. Area affected? Abdomen / Abdomen + Pelvis / Other (*Details*: _____)

6i. Chemotherapy? Y / N **6j.** Completed: _____/_____/_____ (YY / MM / DD) **6k.** Type: _____ **6l.** # cycles: ___

7. Current Physical Activity:

7a. Are you currently physically active? Y / N **7b.** 1-2 hrs/wk 3-5 hrs/wk 5+ hrs/wk

7c. What type of activities or exercises do you participate in?

7ci. **Details:** _____
Intensity: Low / Med / High **Duration:** _____ *(mins)* **Frequency:** _____ *#/wk*

7cii. **Details:** _____
Intensity: Low / Med / High **Duration:** _____ *(mins)* **Frequency:** _____ *#/wk*

7ciii. **Details:** _____
Intensity: Low / Med / High **Duration:** _____ *(mins)* **Frequency:** _____ *#/wk*

7civ. **Details:** _____
Intensity: Low / Med / High **Duration:** _____ *(mins)* **Frequency:** _____ *#/wk*

7cv. **Details:** _____
Intensity: Low / Med / High **Duration:** _____ *(mins)* **Frequency:** _____ *#/wk*

7cvi. **Details:** _____
Intensity: Low / Med / High **Duration:** _____ *(mins)* **Frequency:** _____ *#/wk*

7cvii. **Details:** _____
Intensity: Low / Med / High **Duration:** _____ *(mins)* **Frequency:** _____ *#/wk*

High intensity exercise: heavy sweating + heavy breathing
Moderate intensity exercise: light-moderate sweating + moderate breathing ***(maintain conversation)***

Examples:

- Running
- Hockey
- Ultimate Frisbee
- Soccer
- Rowing
- Cycling or spin class
- Swimming
- Racquetball / Squash
- Aerobic fitness classes
- Basketball

8. MET hrs/wk: ____

9. Meeting PA guidelines? Y / N

10. Are you planning on taking a summer vacation? Y / N

Details: _____

Remember to return and complete Par-Q+

Appendix J: Informed Consent

Cross Cancer Institute
11560 University Avenue,
Edmonton, Alberta, Canada,
T6G 1Z2
Tel: 780.432.8770

A study to test the effects of high-intensity aerobic interval exercise on the cardiovascular health of testicular cancer survivors.

CONSENT FORM

This form is part of the process of informed consent. It is designed to explain this research study and what will happen to you if you choose to be in this study.

If you would like to know more about something mentioned in this consent form, or have any questions at any time regarding this research study, please be sure to contact the Primary Investigator - Dr. Kerry Courneya at (780) 492-1031, or the Research Coordinator - Scott Adams at (780) 492-8246. Read this consent form carefully to make sure you understand all the information it provides. You will get a copy of this consent form to keep. You do not have to take part in this study and your care does not depend on whether or not you take part.

Your participation in this study is entirely voluntary. Please take your time to make your decision. It is recommended that you discuss with your friends and/or family about whether to participate in this study.

"WHY IS THIS STUDY BEING DONE?"

You are being asked to take part in this study because you had testicular cancer. Testicular cancer survival has improved as new types and combinations of cancer therapies have developed (i.e., surgery, radiation and chemotherapy). Nevertheless, our cardiovascular system (i.e., our heart, lungs and blood vessels) may be damaged by several of these therapies. Research has shown that testicular cancer survivors are one of several cancer survivor groups known to be at slightly higher risk of such cardiovascular complications. Some testicular cancer survivors are at higher risk than others, depending on the intensity of cancer treatments given, among other factors. Importantly, regular aerobic exercise (e.g., walking, running, cycling) is known to prevent and treat cardiovascular disease in non-cancer populations. High-intensity interval training (i.e., which involves exercising hard for short periods of time and slowing down to recover in-between) is especially good at improving cardiovascular health in people living with various cardiovascular risks and diseases. However, due to the unique causes of cardiovascular injury in testicular cancer survivors, we do not know if this type of aerobic exercise can have similar cardiovascular benefits.

"WHAT DO WE HOPE TO LEARN?"

We hope to learn if this specific type of aerobic exercise can improve the cardiovascular health of testicular cancer survivors. If successful, we hope to extend these findings to prevent the development of cancer-related cardiovascular disease in testicular cancer survivors.
More specifically, the purpose of this study is to examine the impact of 12 weeks of high-intensity aerobic interval training on the general and cardiovascular health of testicular cancer survivors. The primary outcome is a treadmill-based assessment of maximum aerobic exercise capacity. Secondary outcomes include measures of blood vessel structure and function, nervous system function, and self-report measures of general health and post-treatment cancer-related symptoms.

This is a Phase II study which is designed to determine the effects of performing high-intensity aerobic interval exercises, three days a week for 12 weeks, on the cardiovascular health of testicular cancer survivors.

"WHAT IS INVOLVED IN THIS STUDY?"

In this study you will be assigned to either the high-intensity aerobic interval exercise group or the "wait list" control group (described in the following section). Your assignment will be "randomized" which means the treatment that you are assigned will be determined by chance. It is like flipping a coin. The randomization is done by a computer. Neither you nor the researcher will choose which group you will be assigned to. You will have an equal chance of being assigned to either group.

Following your initial (baseline) assessments, you will be randomly assigned to 1 of the 2 groups: (1) 3 days a week of high-intensity aerobic interval exercise training, or (2) usual care* (no supervised exercise training).

***IMPORTANT:** If you are assigned to the usual care group, we will offer you a one month high-intensity aerobic interval exercise training program after the final study assessment.

"HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?"

Overall we hope to recruit 70 testicular cancer survivors from Edmonton, Alberta.

"WHAT WILL MY PARTICIPATION INVLOLVE?"

If you take part in this study, you will have the following tests and be asked to complete the following intervention:

Complete three assessments, one at the beginning (#1), another after 12 weeks (#2), and a final evaluation an additional 12 weeks after that (#3). Assessments #1 & 2 are the longest and require approximately 3.5 hours to complete. Assessment #3 just requires you to complete a questionnaire (approximately 30 minutes to complete).

Assessments #1 & 2 involve an aerobic exercise test, a resting nervous system test, and four resting blood vessel tests. All aspects of the assessments will be conducted by the Research Coordinator, who has been trained and licensed to perform all of the techniques.

The aerobic exercise tests will take place at the Cross Cancer Institute or the Behavioural Medicine Fitness Centre (University of Alberta campus) and will consist of walking (maybe jogging) on a treadmill until you are very tired.

The nervous system and blood vessel tests will take place at the Physical Activity and Diabetes Laboratory (University of Alberta) and will consist of recording your resting heart rate, blood pressure and measuring your blood vessel thickness and movements using non-invasive recording devices placed on the skin (i.e., ultrasound and tonometry probes). You will be required to fast (you may drink water only) and avoid exercise for a period of ≥8 hours prior to each test.

Self-administered questionnaires that ask about your current health status, physical activity, quality of life, fatigue, perceived stress, depression, sleeping patterns and sexual function will be completed either on-site or at home and will take approximately 30 minutes to complete.

Prior to assessments #1 & 2, you will be asked to visit a Dynalife Laboratory clinic location to have a small sample of blood drawn to measure various biomarkers. You will be required to fast (you may drink water only) and avoid exercise for a period of ≥8 hours prior to each blood sample.

Type of Assessment	Baseline	12 Week Follow-up	24 week Follow-up
Aerobic fitness test	x	x	
Nervous system test	x	x	
Blood vessel tests	x	x	
Blood collection	x	x	
Questionnaires	x	x	x

Following your initial (baseline) assessments, you will be randomly assigned to either the high-intensity aerobic interval exercise training or usual care group.

High-Intensity Aerobic Interval Exercise Training Group: If you are randomized to this exercise program, you will be asked to perform three exercise sessions per week consisting of 35 minutes of aerobic exercise at a vigorous intensity on a treadmill. You will also be asked to maintain your current light- to moderate-intensity exercise but avoid performing any additional high-intensity aerobic exercise.

Usual Care Group: If you are randomized to this group, you will be asked to maintain your current light- to moderate-intensity exercise but avoid performing any high-intensity aerobic exercise. Once you have finished assessment #3, you will have the opportunity to receive one month of twice-weekly, supervised high-intensity aerobic interval exercise training sessions.

For all those who are randomized to the exercise group, or any of the usual care participants who choose to participate in the wait-list exercise program, you will be given a customized and

supervised exercise program. All exercise will take place at the Behavioural Medicine Fitness Centre (University of Alberta campus) for 3 sessions per week. Exercise training sessions are available any time between 7 am and 7 pm, Monday to Friday, and 9 am to 12 pm Saturday.

Each exercise training session will last up to 60 minutes (including warm-up, cool-down, as well as pre- and post-exercise measurements). Trained staff will supervise all exercise training sessions.

"HOW LONG WILL I BE INVOLVED IN THE STUDY?"

You may be in this study for seven to eight months depending on your group and whether or not you choose to take part in the bonus month of aerobic exercise training (usual care group only).

"WHAT ARE THE SIDE EFFECTS?"

There are a few risks associated with participating in this research. It is possible that some people will experience muscle soreness and fatigue following the fitness testing. This type of response is normal, and generally poses no threat to health. Do not take any over the counter medications without speaking to your doctor first. If the soreness persists more than five days, or might be associated with a muscle or joint injury, participants should see a physician. Some of the side effects of chemotherapy could be made worse with exercise (e.g., fatigue, cardiac problems), but no research has shown this to be the case. These risks will be reduced as much as possible by the attention and careful instruction of research staff and by the fact that your exercise testing will be conducted by certified fitness appraisers and that you are no longer receiving active cancer treatment.

There is some risk associated with the aerobic fitness test. Maximal effort exercise is sometimes associated with health risk. During and immediately after the tests, it is possible to experience symptoms such as abnormal blood pressure, fainting, light-headedness, muscle cramps or strain, nausea, and in very rare cases (1 per 20,000 in testing facilities) heart rhythm disturbances or heart attack. While serious risk to healthy participants is highly unlikely, such risks must be acknowledged, and participants must willingly assume the risks associated with very hard exercise.

There are no known risks associated with either of the nervous system tests. One of the blood vessel tests may cause numbness, tingling or discomfort (similar to your foot falling asleep) as it requires complete blood flow restriction to your lower arm for a period of five minutes. It is highly unlikely that you will experience any long term effects due to the brief blood flow restriction.

Finally, blood collection may cause minor discomfort and bruising but this is normal and only temporary. There is a slight risk of infection at the needle site. In order to avoid this risk, all blood tests will be conducted by qualified medical staff.

If you have any side effects, either those on the list or others, or if you want more information you should call your doctor, or the Principal Investigator or Research Coordinator in charge of the study. Their telephone numbers are on page 6 of this form.

Unique Side Effects/Special Precaution

With this level of exercise testing and training, you may experience sore muscles, joint problems, an injury related to the exercise or some cardiac side effects.

"WHAT ARE MY RESPONSIBILITIES?"

You must be willing to attend all scheduled study visits and undergo all of the procedures described above. It is very important that you inform the study doctor, Principal Investigator or Research Coordinator of any side effects or health problems that you may be experiencing. Additionally, you must be willing to fill out the questionnaires that are part of the study protocol.

"WHAT ARE MY ALTERNATIVES?"

You may choose not to participate in this study and obtain a fitness appraisal and supervised exercise program from a private organization that would include some of the tests and the aerobic exercise intervention being completed in this study.

"ARE THERE ANY BENEFITS TO PARTICIPATING IN THIS STUDY?"

The benefits to you for participating in this research may include improvements to your health and fitness. The information you provide may help us understand whether this type of aerobic exercise can improve the cardiovascular health of testicular cancer survivors.

We understand that there is a significant time commitment to the study, but this is necessary for the successful completion of the research.

"CAN I WITHDRAW FROM THIS STUDY?"

Taking part in this study is voluntary; you may withdraw from the study at any time if you wish to do so. If you decide to stop participating in the study, we encourage you to talk to our staff first. Simply inform the researcher of your wish. Should you decide to withdraw from the study at any time, information collected on you up until that point would still be utilized in this study unless you request to remove the information. The information collected in this study will be used for research and teaching purposes, and to help develop guidelines for helping improve the quality of life and health for people with cancer.

"ARE THERE COSTS TO ME FOR TAKING PART IN THIS STUDY?"

There are no financial costs to you for participating in this study. The fitness assessments, nervous system assessment, blood vessel assessments, quality of life assessments, and exercise program are free. We will also pay for your parking at the Behavioural Medicine Fitness Centre

when you come for your testing and exercise training sessions. Your personal exercise trainer is also free.

"WHAT ARE MY RIGHTS AS A PARTICIPANT?"

It is important to note that nothing said in this consent form alters your legal rights to recover damages. If you suffer an injury as a result of participating in this research, compensation will not be provided. However, you retain all your legal rights to pursue other possible avenues of compensation (e.g. legal action).

"WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?"

Identifiable health information will be collected during this study. This information may be used by the researchers who are carrying out this study, and may be disclosed to others as described below. Any research proposal to use information that identifies you for a purpose other than this study must be approved in advance by the Health Research Ethics Board of Alberta – Cancer Committee.

Direct access to your identifiable health information collected for this study will be restricted to the researchers who are directly involved in this study except in the following circumstances:

Your identifiable health information may need to be inspected or copied from time to time for quality assurance (to make sure the information being used in the study is accurate) and for data analysis (to do statistical analysis that will not identify you). The following organizations may do this inspection:

Health Canada, the Canadian regulatory body.
Health Research Ethics Board of Alberta – Cancer Committee

Any disclosure of your identifiable health information will be in accordance with the Alberta Health Information Act. As well, any person from the organizations looking at your records on-site at the Cross Cancer Institute will follow the relevant **Alberta Health Services and Health Research Ethics Board of Alberta – Cancer Committee** policies and procedures that control these actions. Any disclosure of your identifiable health information to another individual or organization not listed here will need the approval of the Health Research Ethics Board of Alberta – Cancer Committee.

Your identifiable health information collected as part of this study, which includes responses to the questionnaires, will be kept confidential. We will be retaining the anonymous data file for a period of 5 years after the completion of the research project. The data will be stored in the Behavioural Medicine Laboratory. This laboratory is secure. If a secondary analysis is planned using the data, appropriate ethical approval will be obtained.

The researchers who are directly involved in your study may share information about you with other researchers, but you will not be identified in that shared information except by a number.

The key that indicates what number you have been assigned will be kept secure by the researchers directly involved with your study and will not be released.

Although absolute confidentiality can never be guaranteed, the Alberta Health Services will make every effort to keep your identifiable health information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information in accordance with the Alberta Health Information Act and other regulatory requirements.

"WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?"

For information about your disease you may contact your oncologist or the Primary Medical Advisor Scott North at (780) 432-8762. For information about research related injury/illness, you may contact the Principal Investigator Dr. Kerry Courneya at (780) 492-1031, the Research Coordinator Scott Adams at (780) 492-8246.

If you feel, at any time, that you have not been informed to your satisfaction about the risks, benefits, or alternatives of this study, or that you have been encouraged to continue in this study after you wanted to withdraw, you can call the Patient Representative at (780) 432-8585.

UNDERSTANDING OF PARTICIPANTS

I can refuse to take part or withdraw from this study at any time without jeopardizing my health care. If I continue to take part in the study, I will be kept informed of any important new developments and information learned after the time I gave my original consent.

I also give consent for the Principal Investigator and the Alberta Health Services (the Custodian) to disclose identifiable health information, as per the Alberta Health Information Act, to the organizations mentioned on the previous page.

I have read and understood all of the information in this consent form. I have asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review and discussion. My consent has not been forced or influenced in any way. I consent to participate in this research study. Upon signing this form I will receive a signed copy of the consent.

(PRINT NAMES CLEARLY)

_____ _____ _____
Name of Patient Signature of Patient Date

_____ _____ _____
Name of Person Obtaining Consent Signature of Person Date
Obtaining Consent

Patient Study Number or Hospital Number: _____

Was the patient assisted during the consent process in one of the ways listed below?
□ Yes □ No

If yes, please check the relevant box and complete the signature space below:

□ The consent form was read to the patient, and the person signing below attests that the study was accurately explained to, and apparently understood by the patient.

□ The person signing below acted as a translator for the patient during the consent process.

_____ _____
Signature of person assisting Date
In the consent discussion

Please note: More information regarding the assistance provided during the consent process should be noted in the medical record for the patient if applicable.

Appendix K: Pretest Instructions

HITTS TRIAL TESTING & TRAINING LOCATIONS

Parking Lot Meeting Place:

- Parking Lot behind the Jubilee Auditorium (30 minutes before your test)

Exercise Testing Meeting Place:

- Research Translation Facility – BML Testing Centre

Exercise Intervention Location:

- Research Translation Facility – BML Fitness Centre

Vascular Testing Meeting Place:

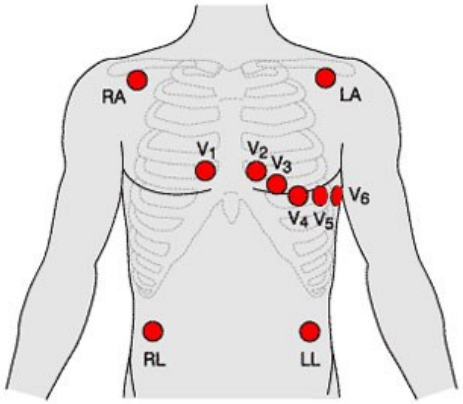
- Van Vliet Complex

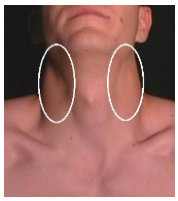
HITTS Trial Contact Information:

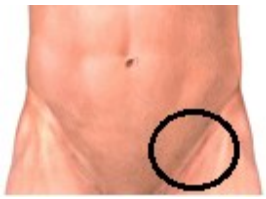
- Scott Adams – Study Coordinator
  - BML Office Phone: 780-492-8246
  - BML Testing & Fitness Centre Phone: 780-492-5404
  - **Email Address**: hitts@ualberta.ca
  - Cell Phone: 587-589-1607 ← use this number to reach us on testing days

HITTS TRIAL PRETEST INFORMATION

Electrode Placement Sites







Test-specific Sites

Electrode Placement for Vascular Test

- RA + LA + V5 only

Electrode Placement for Exercise Test

- All sites (V1-V6, RA, RL, LA, LL)

IMPORTANT

- The electrodes must be placed directly on the skin.
- You may choose to trim body hair yourself OR we will spot-shave the necessary sites.

MEASUREMENT SITES

- Most measurements will be taken at the neck.
- One measurement taken at the left upper arm.
- The last measurement will be taken where the femoral artery crosses into the leg.

THINGS TO REMEMBER

Vascular Testing:

- Please respect all pre-test instructions (*see below*)
- Bring loose-fitting t-shirt and shorts

Exercise Testing:

- Please respect all pre-test instructions (*see below*)
- Bring running shoes, t-shirt, shorts & water bottle

TEST DESCRIPTIONS

Vascular Testing:

- 15 minutes for administration, instrumentation & set up
- 30 minutes of quiet pre-test rest
- 45-60 minutes of testing
- The measurements are VERY sensitive. Therefore, talking is not permitted during tests (*you may ask questions between the tests*).
- You will be lying down comfortably throughout

Exercise Testing:

- 15 minutes for administration, instrumentation & set-up
- 10 minutes for resting measures
- 30 minutes of testing (*including warm-up and cool-down*)

HITTS TRIAL PRETEST INSTRUCTIONS

Morning Tests (7:00 – 11:00 a.m. start):

- Previous 12-hours
  - No food, drink, caffeine, alcohol, vitamins and medication.
    - You may drink water only.
  - No exercise.
- Day of test
  - No food, drink, caffeine, alcohol, vitamins and medication.
    - You may drink water only.
  - No exercise.
  - Absolutely **no smoking** the day of the test.

Afternoon Tests (12:00 – 4:00 p.m. start):

- Previous 12-hours
  - No caffeine, alcohol, vitamins and medication.
  - No exercise.
- Day of test (within 8 hours)
  - You may eat a **light meal** no sooner than **8 hours before** your test
    - You can have some toast or a bagel with jam and some fruit no closer than 8 hours before your test, but **you must avoid all sources of fat** (e.g., butter, margarine, oils, dairy products, etc.).
  - You may drink water, but no other food or drink.
  - Absolutely **no smoking** the day of the test.

Evening Tests (5:00 – 8:00 p.m. start):

- Previous 12-hours
  - No caffeine, alcohol, vitamins and medication.
  - No exercise.
- Day of test (within 8 hours)
  - You may eat a regular breakfast (MUST be low fat)
  - You may eat a **light meal** no sooner than **8 hours before** your test
    - You can have some toast or a bagel with jam and some fruit no closer than 8 hours before your test, but **you must avoid all sources of fat** (e.g., butter, margarine, oils, dairy products, etc.).
  - You may drink water throughout the day, but no other food or drink!
  - Absolutely **no smoking** the day of the test.

Appendix L: Intervention Tracking Sheet

Behavioural Medicine Laboratory
University of Alberta

Intervention Tracking Sheet

STUDY ID: _____

Participant Name: _____

Start Date (YY/MM/DD): ____ / ____ / ____

BLOCK I (Weeks 1-4)

Session Number	Date (YY/MM/DD)	Resting HR (bpm)	Resting BP (mmHg)	Full Session	Target Work HR (bpm)	Final Work HR (bpm)	Target Rec. HR (bpm)	Final Rec. HR (bpm)
1.1				Y / N				
1.2				Y / N				
1.3				Y / N				
2.1				Y / N				
2.2				Y / N				
2.3				Y / N				
3.1				Y / N				
3.2				Y / N				
3.3				Y / N				
4.1				Y / N				
4.2				Y / N				
4.3				Y / N				

BLOCK I – Session Heart Rates

Session Number	Period Heart Rates							Notes/Adjustments
	Work 1	Rec. 1	Work 2	Rec. 2	Work 3	Rec. 3	Work 4	
1.1								
1.2								
1.3								
2.1								
2.2								
2.3								
3.1								
3.2								
3.3								
4.1								
4.2								
4.3								

Supplemental Notes

Intervention Tracking Sheet

STUDY ID: _____

Participant Name: _____

Start Date (YY/MM/DD): ____ / ____ / ____

BLOCK II (Weeks 5-8)

Session Number	Date (YY/MM/DD)	Resting HR (bpm)	Resting BP (mmHg)	Full Session	Target Work HR (bpm)	Final Work HR (bpm)	Target Rec. HR (bpm)	Final Rec. HR (bpm)
5.1				Y / N				
5.2				Y / N				
5.3				Y / N				
6.1				Y / N				
6.2				Y / N				
6.3				Y / N				
7.1				Y / N				
7.2				Y / N				
7.3				Y / N				
8.1				Y / N				
8.2				Y / N				
8.3				Y / N				

BLOCK II – Session Heart Rates

Session Number	Period Heart Rates							Notes/Adjustments
	Work 1	Rec. 1	Work 2	Rec. 2	Work 3	Rec. 3	Work 4	
5.1								
5.2								
5.3								
6.1								
6.2								
6.3								
7.1								
7.2								
7.3								
8.1								
8.2								
8.3								

Supplemental Notes

Behavioural Medicine Laboratory
University of Alberta

Intervention Tracking Sheet

STUDY ID: _____

Participant Name: _____

Start Date (YY/MM/DD):
____ / ____ / ____

BLOCK III (Weeks 9-12)

Session Number	Date (YY/MM/DD)	Resting HR (bpm)	Resting BP (mmHg)	Full Session	Target Work HR (bpm)	Final Work HR (bpm)	Target Rec. HR (bpm)	Final Rec. HR (bpm)
9.1				Y / N				
9.2				Y / N				
9.3				Y / N				
10.1				Y / N				
10.2				Y / N				
10.3				Y / N				
11.1				Y / N				
11.2				Y / N				
11.3				Y / N				
12.1				Y / N				
12.2				Y / N				
12.3				Y / N				

BLOCK III – Session Heart Rates

Session Number	Period Heart Rates							Notes/Adjustments
	Work 1	Rec. 1	Work 2	Rec. 2	Work 3	Rec. 3	Work 4	
9.1								
9.2								
9.3								
10.1								
10.2								
10.3								
11.1								
11.2								
11.3								
12.1								
12.2								
12.3								

Supplemental Notes

Make-Up Sessions

Session Number	Date (YY/MM/DD)	Resting HR (bpm)	Resting BP (mmHg)	Full Session	Target HR (bpm)	Work HR Avg. (bpm)	Rec. HR Avg. (bpm)	Notes/Adjustments
E.1				Y / N				
E.2				Y / N				
E.3				Y / N				
E.4				Y / N				

Make-Up Session Heart Rates

Session Number	Period Heart Rates							Notes/Adjustments
	Work 1	Rec. 1	Work 2	Rec. 2	Work 3	Rec. 3	Work 4	
E.1								
E.2								
E.3								
E.4								

Supplemental Notes

Appendix M: Baseline Self-Report Questionnaire

Cross Cancer Institute
11560 University Avenue, Edmonton,
Alberta, Canada, T6G 1Z2
Tel: 780.432.8770

Identification #_____

Date: _____

A study to test the effects of high-intensity aerobic interval exercise on the cardiovascular health of testicular cancer survivors.

Baseline Questionnaire

Investigators: Scott C. Adams, MSc[1]; Margie Davenport, PhD[1]; Darren DeLorey, PhD[1]; Adrian Fairey, MD[1,2]; Scott North, MD[1,3]; Kerry Courneya, PhD[1].

[1] – University of Alberta; [2] – Alberta Urology Institute; [3] – Cross Cancer Institute

Instructions

Thank you for agreeing to participate in this study. In this questionnaire, we are going to ask you a series of questions about yourself. Many of the questions ask you about your physical and mental health, and some may be viewed as personal. It is important to answer as many of these questions as possible, however, if you feel uncomfortable answering certain questions please leave them blank. All responses are completely confidential and will never be used in any way that could link them to you. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for each. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30-45 minutes of your time to complete. If you have any questions about completing the questionnaire, please contact our Research Coordinator at (780) 492-8246 or hitts@ualberta.ca.

This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking a single answer. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is:

1	2	3	4	5
Excellent	Very good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?

1	2	3	4	5
Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse than one year ago	Much worse now than one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	**Vigorous Activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b.	**Moderate Activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c.	Lifting or carrying groceries	1	2	3
d.	Climbing **several** flights of stairs	1	2	3
e.	Climbing **one** flight of stairs	1	2	3
f.	Bending, kneeling or stooping	1	2	3
g.	Walking more than a mile	1	2	3
h.	Walking several hundred yards	1	2	3
i.	Walking one hundred yards	1	2	3
j.	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Were **limited** in the **kind** of work or other activities	1	2	3	4	5
d.	Had **difficulty** performing the work or other activities (e.g., it took extra effort)	1	2	3	4	5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Did work or other activities **less carefully than usual**	1	2	3	4	5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

7. How much bodily pain have you had during the past 4 weeks?

1	2	3	4	5	6
None	Very mild	Mild	Moderate	Severe	Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of life?	1	2	3	4	5
b.	Have you been very nervous?	1	2	3	4	5
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d.	Have you felt calm and peaceful?	1	2	3	4	5
e.	Did you have a lot of energy?	1	2	3	4	5
f.	Have you felt downhearted and depressed?	1	2	3	4	5
g.	Did you feel worn out?	1	2	3	4	5
h.	Have you been happy?	1	2	3	4	5
i.	Did you feel tired?	1	2	3	4	5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

1	2	3	4	5
All of the time	Most of the time	Some of the time	A little of the time	None of the time

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

FATIGUE SYMPTOMS

During the PAST WEEK:

		Not at all	Little bit	Some-what	Quite a bit	Very much
1.	I feel fatigued	0	1	2	3	4
2.	I feel weak all over	0	1	2	3	4
3.	I feel listless ("washed out")	0	1	2	3	4
4.	I feel tired	0	1	2	3	4
5.	I have trouble starting things because I am tired	0	1	2	3	4
6.	I have trouble finishing things because I am tired	0	1	2	3	4
7.	I have energy	0	1	2	3	4
8.	I am able to do my usual activities	0	1	2	3	4
9.	I need to sleep during the day	0	1	2	3	4
10.	I am too tired to eat	0	1	2	3	4
11.	I need help doing my usual activities	0	1	2	3	4
12.	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13.	I have to limit my social activity because I am tired	0	1	2	3	4

The questions in this scale ask you about your feelings and thoughts during the last month. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each one fairly quickly. For each question, please choose from the following alternatives:

In the last month, how often have you…

		Never	Almost never	Some-times	Fairly often	Very often
1.	been upset because of something that happened unexpectedly?	0	1	2	3	4
2.	felt that you were unable to control the important things in your life?	0	1	2	3	4
3.	felt nervous and stressed?	0	1	2	3	4
4.	dealt successfully with irritating life hassles?	0	1	2	3	4
5.	felt that you were effectively coping with important changes that were occurring in your life?	0	1	2	3	4
6.	felt confident about your ability to handle your personal problems?	0	1	2	3	4
7.	felt that things were going your way?	0	1	2	3	4
8.	found that you could not cope with all the things that you had to do?	0	1	2	3	4
9.	been able to control irritations in your life?	0	1	2	3	4
10.	felt that you were on top of things?	0	1	2	3	4
11.	been angered because of things that happened that were outside of your control?	0	1	2	3	4
12.	found yourself thinking about things that you have to accomplish?	0	1	2	3	4
13.	been able to control the way you spend your time?	0	1	2	3	4
14.	felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

The following questions concern the general perceptions that you currently have about yourself. Please circle the number that best reflects your current view of yourself using the following scale as a guide for your responses.

		Strongly disagree	Disagree	Agree	Strongly agree
1.	On the whole I am satisfied with myself.	1	2	3	4
2.	At times I think that I am no good at all.	1	2	3	4
3.	I feel that I have a number of good qualities.	1	2	3	4
4.	I am able to do things as well as most other people.	1	2	3	4
5.	I feel I do not have much to be proud of.	1	2	3	4
6.	I certainly feel useless at times.	1	2	3	4
7.	I feel that I am a person of worth, at least on an equal plane with others.	1	2	3	4
8.	I wish I could have more respect for myself.	1	2	3	4
9.	All in all, I am inclined to feel that I am a failure.	1	2	3	4
10.	I take a positive attitude toward myself.	1	2	3	4

Below is a list of statements concerning how you might have felt or behaved in the past week. Please use the following scale to indicate how often you felt or behaved in these ways in the past week.

0	1	2	3
Rarely or none of the time (< 1 day)	Some of the time (1-2 days)	Much of the time (3-4 days)	Most or all of the time (5-7 days)

During the PAST WEEK:

1.	I felt depressed.	0	1	2	3
2.	I felt that everything I did was an effort.	0	1	2	3
3.	My sleep was restless.	0	1	2	3
4.	I was happy.	0	1	2	3
5.	I felt lonely.	0	1	2	3
6.	People were unfriendly.	0	1	2	3
7.	I enjoyed life.	0	1	2	3
8.	I felt sad.	0	1	2	3
9.	I felt that people disliked me.	0	1	2	3
10.	I could not get "going".	0	1	2	3

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number that best indicates how you have felt during the past week. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that best describes how you felt.

During the PAST WEEK:

	Not at all	Somewhat	Moderately so	Very much so
1. I felt calm	1	2	3	4
2. I was tense	1	2	3	4
3. I felt at ease	1	2	3	4
4. I worried over possible misfortunes	1	2	3	4
5. I felt frightened	1	2	3	4
6. I felt self-confident	1	2	3	4
7. I was jittery	1	2	3	4
8. I was relaxed	1	2	3	4
9. I was worried	1	2	3	4
10. I felt steady	1	2	3	4

The following questions relate to your usual sleep habits during the past month. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

---

1. During the past month, when have you usually gone to bed at night?

USUAL BED TIME _____

2. During the past month, how long has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

HOURS OF SLEEP PER NIGHT _____

5. During the past month, how would you rate your sleep quality overall?

_____ Very good _____ Fairly good _____ Fairly bad _____ Very bad

6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month _____ | Less than once a week _____ | Once or twice a week _____ | Three or more times a week _____

7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____ | Less than once a week _____ | Once or twice a week _____ | Three or more times a week _____

8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____ Only a very slight problem _____

Somewhat of a problem _____ A very big problem _____

For this next question, we would like you to recall the amount of exercise you have done IN THE PAST MONTH.

When answering these questions please:

- only count exercise sessions that lasted 10 minutes or longer in duration.
- only count exercise that was done during free time (i.e., not occupation or housework).
- note that the main difference between the first three categories is the intensity of the endurance (aerobic) exercise and the fourth category is for strength (resistance) exercise.
- please write the average frequency on the first line and the average duration on the second.
- if you did not do any exercise in one of the categories, please write in "0".

Considering a typical week (7 days) how many times on the average did you do the following kinds of exercise IN THE PAST MONTH?

		Times Per Week	Average Duration
a.	VIGOROUS/STRENUOUS EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g. running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling)	_____	_____
b.	MODERATE EXERCISE (NOT EXHAUSTING LIGHT PERSPIRATION) (e.g. fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing)	_____	_____
c.	LIGHT/MILD EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g. easy walking, yoga, bowling, lawn bowling, shuffleboard)	_____	_____
d.	RESISTANCE/STRENGTH EXERCISE (e.g. lifting weights, push ups, sit ups, therabands)	_____	_____

The next set of questions on this page relate to how you feel about the high-intensity aerobic interval exercise protocol used in this study.

> *As a reminder, this protocol involves walking/running on a treadmill while performing alternating bouts of four 4-minute vigorous work periods (i.e., at 75-95% intensity) and three 3-minute lower intensity recovery periods (e.g. <50%) – for a total of 25 minutes.*

For the following questions, please circle the number that most closely represents how you feel about the protocol described above.

---

1. How beneficial do you think it will be for you to perform this high-intensity aerobic interval protocol?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

2. How enjoyable do you think it will be to perform this high-intensity aerobic interval protocol?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

3. How supportive do you think your family/friends will be of you performing this high-intensity aerobic interval protocol?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

4. How motivated are you to perform this high-intensity aerobic interval protocol?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

5. How difficult will it be for you to perform this high-intensity aerobic interval protocol?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

For the following questions (a-l), we are interested in knowing about any benefits or harm you feel may result from performing high-intensity aerobic interval exercise. Please use the following scale to guide your responses.

1	2	3	4	5	6	7
Very much worse	Somewhat worse	Slightly worse	No change	Slightly improved	Somewhat improved	Very much improved

---

What effect, if any, will performing <u>high-intensity aerobic interval exercise</u> have on each of the following for you?

a.	physical functioning	1	2	3	4	5	6	7
b.	overall quality of life	1	2	3	4	5	6	7
c.	cardiovascular endurance	1	2	3	4	5	6	7
d.	muscular strength	1	2	3	4	5	6	7
e.	fatigue	1	2	3	4	5	6	7
f.	sleep quality	1	2	3	4	5	6	7
g.	depressed feelings	1	2	3	4	5	6	7
h.	anxious feelings	1	2	3	4	5	6	7
i.	self-esteem	1	2	3	4	5	6	7
j.	stress	1	2	3	4	5	6	7
k.	body weight or shape	1	2	3	4	5	6	7
l.	illness or injury	1	2	3	4	5	6	7

Any other positive or negative effects you may experience?_____

For the following questions (a-l), we are also interested in knowing what, if any, barriers you feel would make it difficult for you to perform high-intensity aerobic interval exercise. Please use the scale below to guide your responses.

1	2	3	4	5	6	7
Not at all		Somewhat		A fair bit		Very much

How much of a barrier will each of the following factors be for you in trying to perform <u>high-intensity aerobic interval exercise</u>?

a.	bad weather	1	2	3	4	5	6	7
b.	feeling tired or fatigued	1	2	3	4	5	6	7
c.	symptoms and side effects of treatments	1	2	3	4	5	6	7
d.	other medical/health problems	1	2	3	4	5	6	7
e.	too busy and had limited time	1	2	3	4	5	6	7
f.	pain or soreness	1	2	3	4	5	6	7
g.	feeling sick/not feeling well	1	2	3	4	5	6	7
h.	nausea/vomiting	1	2	3	4	5	6	7
i.	urinary incontinence	1	2	3	4	5	6	7
j.	medical appointments	1	2	3	4	5	6	7
k.	lack of motivation	1	2	3	4	5	6	7
l.	travelling to the fitness centre	1	2	3	4	5	6	7

Any other barriers you may experience? _____

This next part of the questionnaire is needed to help understand the medical profile for those participating in the study. For this reason it is very important information. All information is held in strict confidence. Please answer the questions to the best of your knowledge.

---

1. When were you diagnosed with testicular cancer (month/year)?

_____

2. Did your cancer involve the lymph nodes (please check)?

_____ Yes _____ No _____ Unsure

3. Was your cancer described as "localized" (confined to the testicle) or "metastasized" (spread to other parts of the body)?

_____ Localized _____ Metastasized _____ Unsure

4. If your cancer was described as metastasized, where else in your body was it? (check all that apply)

_____ Lung _____ Lymph nodes _____ Brain _____ Liver

_____ Bone _____ Other (Please specify:_____) _____ Unsure

5a. Did your treatment include surgical removal of a testicle (please check)?

_____ Yes _____ No

5b. If yes, was it one or both testicles?

_____ One _____ Two

6a. Did your treatment include radiation therapy (please check)?

_____ Yes _____ No

6b. If yes, how many treatments did you receive and to which area(s) of your body (please fill in below)?

Number of treatments: _____

Area(s) of the body treated: _____

7a. Did your treatment include chemotherapy therapy (please check)?

_____ Yes _____ No

7b. If yes, what kind of chemotherapy did you receive? (check all that apply)

_____ Cisplatin _____ Bleomycin _____ Etoposide _____ Paclitaxel

_____ Ifosfamide _____ Vinblastine _____ Other *(Please List)*: _____

_____

8. What is the current status of your cancer treatments?

_____ I am not currently receiving any treatments.

_____ I am currently still receiving cancer treatments.

If currently on treatment, what treatment? _____

9. Have you ever had a recurrence of your testicular cancer? _____ Yes _____ No

10. What is the current status of your testicular cancer?

_____ the doctors have told me that the cancer is gone from my body.

_____ the doctors have told me that I still have some cancer in my body.

This part of the questionnaire is needed to help understand the characteristics of the people participating in the study. For this reason it is very important information. All information is held in strict confidence and its presentation to the public will be group data only.

---

1. Age: _____

2. Current Marital Status:

Never Married	_____	Married	_____	Common Law	_____
Separated	_____	Widowed	_____	Divorced	_____

3. Education (Please check highest level attained):

Some High School	_____	Completed High School	_____	Some University/College	_____
Completed Univ/Coll	_____	Some Graduate School	_____	Completed Grad School	_____

4. Annual Family Income:

< $20,000	_____	$20-39,999	_____	$40-59,999	_____
$60-79,999	_____	$80-99,999	_____	> $100,000	_____

5. Current Employment Status:

Disability	_____	Retired	_____	Part Time	_____
Full Time	_____	Sick Leave	_____		

6. What is your primary ethnic origin or race (please circle)?

White Black Hispanic Asian Aboriginal Other _____

7. Which of the following best describes your current smoking status?

Never Smoked _____ Ex-Smoker _____ Current Smoker _____

8. Has a doctor or nurse ever told you that you had any of the following conditions? (check all that apply):

High blood pressure	____ No	____ Yes		High cholesterol	____ No	____ Yes	
Heart attack	____ No	____ Yes		Stroke	____ No	____ Yes	
Emphysema	____ No	____ Yes		Chronic bronchitis	____ No	____ Yes	
Diabetes	____ No	____ Yes		Other cancer	____ No	____ Yes	
Angina (chest pains)	____ No	____ Yes		Arthritis	____ No	____ Yes	

Any other long term health condition? _____

9. In the past month, was your ability to exercise limited by a health condition, injury, or disability?

1	2	3	4	5
Not at all	A little	Somewhat	Quite a lot	Completely

10. Are you currently taking any medications for health problems? (e.g., for anxiety, depression, blood pressure, constipation, pain, to help with sleep, etc.).

What is the medication?	What is it for? (e.g., blood pressure, anxiety)
1. _____	_____
2. _____	_____
3. _____	_____

Others? _____

Anything else you would like to tell us? On this final page, please feel free to make any comments concerning your testicular cancer, the tests, the questionnaire, the exercise program, or anything else you think may be helpful to us. All comments are welcome.

Thank you very much for participating in this research. Please bring the completed questionnaire to your fitness testing appointment at the Behavioural Medicine Fitness Centre.

Appendix N: Postintervention Self-Report Questionnaire – Usual Care Group

Cross Cancer Institute
11560 University Avenue, Edmonton,
Alberta, Canada, T6G 1Z2
Tel: 780.432.8770

Identification #_____

Date: _____

A study to test the effects of high-intensity aerobic interval exercise on the cardiovascular health of testicular cancer survivors.

Follow-Up Questionnaire

Investigators: Scott C. Adams, MSc[1]; Margie Davenport, PhD[1]; Darren DeLorey, PhD[1]; Adrian Fairey, MD[1,2]; Scott North, MD[1,3]; Kerry Courneya, PhD[1].

[1] – University of Alberta; [2] – Alberta Urology Institute; [3] – Cross Cancer Institute

Instructions

Thank you for your continued participation in this study. Now that you have completed the 12 week follow-up period, we are going to ask you many of the same questions as in the first questionnaire. However, it is important to answer these questions based on what you are thinking and feeling right now and not on how you answered the questions last time. This will give us important information about how your thoughts and feelings have changed. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for all the questions if possible. However, if you feel uncomfortable answering certain questions please leave them blank. All responses are completely confidential and will never be used in any way that could link them to you. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for each. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30-45 minutes of your time to complete. If you have any questions about completing the questionnaire, please contact Scott Adams (Research Coordinator) at (780) 492-8246 or hitts@ualberta.ca.

This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking a single answer. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is:

1	2	3	4	5
Excellent	Very good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?

1	2	3	4	5
Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse than one year ago	Much worse now than one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	**Vigorous Activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b.	**Moderate Activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c.	Lifting or carrying groceries	1	2	3
d.	Climbing **several** flights of stairs	1	2	3
e.	Climbing **one** flight of stairs	1	2	3
f.	Bending, kneeling or stooping	1	2	3
g.	Walking more than a mile	1	2	3
h.	Walking several hundred yards	1	2	3
i.	Walking one hundred yards	1	2	3
j.	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Were **limited** in the **kind** of work or other activities	1	2	3	4	5
d.	Had **difficulty** performing the work or other activities (e.g., it took extra effort)	1	2	3	4	5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Did work or other activities **less carefully than usual**	1	2	3	4	5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

7. How much bodily pain have you had during the past 4 weeks?

1	2	3	4	5	6
None	Very mild	Mild	Moderate	Severe	Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of life?	1	2	3	4	5
b.	Have you been very nervous?	1	2	3	4	5
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d.	Have you felt calm and peaceful?	1	2	3	4	5
e.	Did you have a lot of energy?	1	2	3	4	5
f.	Have you felt downhearted and depressed?	1	2	3	4	5
g.	Did you feel worn out?	1	2	3	4	5
h.	Have you been happy?	1	2	3	4	5
i.	Did you feel tired?	1	2	3	4	5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

1	2	3	4	5
All of the time	Most of the time	Some of the time	A little of the time	None of the time

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

FATIGUE SYMPTOMS

During the PAST WEEK:

		Not at all	Little bit	Some-what	Quite a bit	Very much
1.	I feel fatigued	0	1	2	3	4
2.	I feel weak all over	0	1	2	3	4
3.	I feel listless ("washed out")	0	1	2	3	4
4.	I feel tired	0	1	2	3	4
5.	I have trouble starting things because I am tired	0	1	2	3	4
6.	I have trouble finishing things because I am tired	0	1	2	3	4
7.	I have energy	0	1	2	3	4
8.	I am able to do my usual activities	0	1	2	3	4
9.	I need to sleep during the day	0	1	2	3	4
10.	I am too tired to eat	0	1	2	3	4
11.	I need help doing my usual activities	0	1	2	3	4
12.	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13.	I have to limit my social activity because I am tired	0	1	2	3	4

The questions in this scale ask you about your feelings and thoughts during the last month. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each one fairly quickly. For each question, please choose from the following alternatives:

In the last month, how often have you…

		Never	Almost never	Some-times	Fairly often	Very often
1.	been upset because of something that happened unexpectedly?	0	1	2	3	4
2.	felt that you were unable to control the important things in your life?	0	1	2	3	4
3.	felt nervous and stressed?	0	1	2	3	4
4.	dealt successfully with irritating life hassles?	0	1	2	3	4
5.	felt that you were effectively coping with important changes that were occurring in your life?	0	1	2	3	4
6.	felt confident about your ability to handle your personal problems?	0	1	2	3	4
7.	felt that things were going your way?	0	1	2	3	4
8.	found that you could not cope with all the things that you had to do?	0	1	2	3	4
9.	been able to control irritations in your life?	0	1	2	3	4
10.	felt that you were on top of things?	0	1	2	3	4
11.	been angered because of things that happened that were outside of your control?	0	1	2	3	4
12.	found yourself thinking about things that you have to accomplish?	0	1	2	3	4
13.	been able to control the way you spend your time?	0	1	2	3	4
14.	felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

The following questions concern the general perceptions that you currently have about yourself. Please circle the number that best reflects your current view of yourself using the following scale as a guide for your responses.

		Strongly disagree	Disagree	Agree	Strongly agree
1.	On the whole I am satisfied with myself.	1	2	3	4
2.	At times I think that I am no good at all.	1	2	3	4
3.	I feel that I have a number of good qualities.	1	2	3	4
4.	I am able to do things as well as most other people.	1	2	3	4
5.	I feel I do not have much to be proud of.	1	2	3	4
6.	I certainly feel useless at times.	1	2	3	4
7.	I feel that I am a person of worth, at least on an equal plane with others.	1	2	3	4
8.	I wish I could have more respect for myself.	1	2	3	4
9.	All in all, I am inclined to feel that I am a failure.	1	2	3	4
10.	I take a positive attitude toward myself.	1	2	3	4

Below is a list of statements concerning how you might have felt or behaved in the past week. Please use the following scale to indicate how often you felt or behaved in these ways in the past week.

0	1	2	3
Rarely or none of the time (< 1 day)	Some of the time (1-2 days)	Much of the time (3-4 days)	Most or all of the time (5-7 days)

During the PAST WEEK:

1.	I felt depressed.	0	1	2	3
2.	I felt that everything I did was an effort.	0	1	2	3
3.	My sleep was restless.	0	1	2	3
4.	I was happy.	0	1	2	3
5.	I felt lonely.	0	1	2	3
6.	People were unfriendly.	0	1	2	3
7.	I enjoyed life.	0	1	2	3
8.	I felt sad.	0	1	2	3
9.	I felt that people disliked me.	0	1	2	3
10.	I could not get "going".	0	1	2	3

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number that best indicates how you have felt during the past week. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that best describes how you felt.

During the PAST WEEK:

	Not at all	Somewhat	Moderately so	Very much so
1. I felt calm	1	2	3	4
2. I was tense	1	2	3	4
3. I felt at ease	1	2	3	4
4. I worried over possible misfortunes	1	2	3	4
5. I felt frightened	1	2	3	4
6. I felt self-confident	1	2	3	4
7. I was jittery	1	2	3	4
8. I was relaxed	1	2	3	4
9. I was worried	1	2	3	4
10. I felt steady	1	2	3	4

The following questions relate to your usual sleep habits during the past month. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

1. During the past month, when have you usually gone to bed at night?

USUAL BED TIME _____

2. During the past month, how long has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

HOURS OF SLEEP PER NIGHT _____

5. During the past month, how would you rate your sleep quality overall?

_____ Very good _____ Fairly good _____ Fairly bad _____ Very bad

6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____ Only a very slight problem _____

Somewhat of a problem _____ A very big problem _____

For this next question, we would like you to recall the amount of exercise you have done during the past 12 weeks.

When answering these questions please:

- only count exercise sessions that lasted 10 minutes or longer in duration.
- only count exercise that was done during free time (i.e., not occupation or housework).
- note that the main difference between the first three categories is the intensity of the endurance (aerobic) exercise and the fourth category is for strength (resistance) exercise.
- please write the average frequency on the first line and the average duration on the second.
- if you did not do any exercise in one of the categories, please write in "0".

Considering a typical week (7 days) how many times on the average did you do the following kinds of exercise during the past 12 weeks?

		Times Per Week	Average Duration
a.	VIGOROUS/STRENUOUS EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g. running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling)	_____	_____
b.	MODERATE EXERCISE (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g. fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing)	_____	_____
c.	LIGHT/MILD EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g. easy walking, yoga, bowling, lawn bowling, shuffleboard)	_____	_____
d.	RESISTANCE EXERCISE (e.g. lifting weights, push ups, sit ups, therabands)	_____	_____

The next set of questions on this page relate to how you felt about taking part in this study. Please answer each one as honestly as possible using the following scale:

1	2	3	4	5	6	7
Not at all		Somewhat		A fair bit		Very much

---

1. How much of a burden was it for you to complete each of the following assessments in this study?

a.	the treadmill fitness test	1	2	3	4	5	6	7
b.	the blood vessel imaging tests	1	2	3	4	5	6	7
c.	the questionnaires	1	2	3	4	5	6	7

---

2. With hindsight, how do you feel about participating in this study?

a.	rewarding	1	2	3	4	5	6	7
b.	a waste of my time	1	2	3	4	5	6	7
c.	useful for research helping others	1	2	3	4	5	6	7
d.	useful for me personally	1	2	3	4	5	6	7
e.	something that I would recommend to other testicular cancer survivors	1	2	3	4	5	6	7

---

3. Thinking back, how did you feel when you found out that you were randomly assigned to the control group?

1	2	3	4	5	6	7
Extremely disappointed	Quite disappointed	Slightly disappointed	Neutral	Slightly pleased	Quite pleased	Extremely pleased

---

The following questions ask you to rate how you feel about exercising over the next six months. Please pay careful attention to the words and descriptors for each scale and circle the number that best represents how you feel.

---

1. How beneficial do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

2. How enjoyable do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

3. How supportive do you think your family/friends will be if you try to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

4. How motivated are you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

5. How difficult do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

6. Do you have a specific plan for where, when, and how you are going to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

Anything else you would like to tell us? On this final page, please feel free to make any comments concerning your testicular cancer, the tests, the questionnaire, the exercise program, or anything else you think may be helpful to us. All comments are welcome.

Thank you very much for participating in this research. Please bring the completed questionnaire to your fitness testing appointment at the Behavioural Medicine Fitness Centre.

Appendix O: Postintervention Self-Report Questionnaire – HIIT Group

Cross Cancer Institute
11560 University Avenue, Edmonton,
Alberta, Canada, T6G 1Z2
Tel: 780.432.8770

Identification #_____

Date: _____

A study to test the effects of high-intensity aerobic interval exercise on the cardiovascular health of testicular cancer survivors.

Follow-Up Questionnaire

Investigators: Scott C. Adams, MSc[1]; Margie Davenport, PhD[1]; Darren DeLorey, PhD[1]; Adrian Fairey, MD[1,2]; Scott North, MD[1,3]; Kerry Courneya, PhD[1].

[1] – University of Alberta; [2] – Alberta Urology Institute; [3] – Cross Cancer Institute

Instructions

Thank you for your continued participation in this study. Now that you have completed the exercise intervention, we are going to ask you many of the same questions as in the first questionnaire. However, it is important to answer these questions based on what you are thinking and feeling right now and not on how you answered the questions last time. This will give us important information about how your thoughts and feelings have changed. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for all the questions if possible. However, if you feel uncomfortable answering certain questions please leave them blank. All responses are completely confidential and will never be used in any way that could link them to you. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for each. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30-45 minutes of your time to complete. If you have any questions about completing the questionnaire, please contact Scott Adams (Research Coordinator) at (780) 492-8246 or hitts@ualberta.ca.

This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking a single answer. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is:

1	2	3	4	5
Excellent	Very good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?

1	2	3	4	5
Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse than one year ago	Much worse now than one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	**Vigorous Activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b.	**Moderate Activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c.	Lifting or carrying groceries	1	2	3
d.	Climbing **several** flights of stairs	1	2	3
e.	Climbing **one** flight of stairs	1	2	3
f.	Bending, kneeling or stooping	1	2	3
g.	Walking more than a mile	1	2	3
h.	Walking several hundred yards	1	2	3
i.	Walking one hundred yards	1	2	3
j.	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Were **limited** in the **kind** of work or other activities	1	2	3	4	5
d.	Had **difficulty** performing the work or other activities (e.g., it took extra effort)	1	2	3	4	5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Did work or other activities **less carefully than usual**	1	2	3	4	5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

7. How much bodily pain have you had during the past 4 weeks?

1	2	3	4	5	6
None	Very mild	Mild	Moderate	Severe	Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of life?	1	2	3	4	5
b.	Have you been very nervous?	1	2	3	4	5
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d.	Have you felt calm and peaceful?	1	2	3	4	5
e.	Did you have a lot of energy?	1	2	3	4	5
f.	Have you felt downhearted and depressed?	1	2	3	4	5
g.	Did you feel worn out?	1	2	3	4	5
h.	Have you been happy?	1	2	3	4	5
i.	Did you feel tired?	1	2	3	4	5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

1	2	3	4	5
All of the time	Most of the time	Some of the time	A little of the time	None of the time

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

FATIGUE SYMPTOMS

During the PAST WEEK:

		Not at all	Little bit	Some-what	Quite a bit	Very much
1.	I feel fatigued	0	1	2	3	4
2.	I feel weak all over	0	1	2	3	4
3.	I feel listless ("washed out")	0	1	2	3	4
4.	I feel tired	0	1	2	3	4
5.	I have trouble starting things because I am tired	0	1	2	3	4
6.	I have trouble finishing things because I am tired	0	1	2	3	4
7.	I have energy	0	1	2	3	4
8.	I am able to do my usual activities	0	1	2	3	4
9.	I need to sleep during the day	0	1	2	3	4
10.	I am too tired to eat	0	1	2	3	4
11.	I need help doing my usual activities	0	1	2	3	4
12.	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13.	I have to limit my social activity because I am tired	0	1	2	3	4

The questions in this scale ask you about your feelings and thoughts during the last month. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each one fairly quickly. For each question, please choose from the following alternatives:

In the last month, how often have you…

		Never	Almost never	Some-times	Fairly often	Very often
1.	been upset because of something that happened unexpectedly?	0	1	2	3	4
2.	felt that you were unable to control the important things in your life?	0	1	2	3	4
3.	felt nervous and stressed?	0	1	2	3	4
4.	dealt successfully with irritating life hassles?	0	1	2	3	4
5.	felt that you were effectively coping with important changes that were occurring in your life?	0	1	2	3	4
6.	felt confident about your ability to handle your personal problems?	0	1	2	3	4
7.	felt that things were going your way?	0	1	2	3	4
8.	found that you could not cope with all the things that you had to do?	0	1	2	3	4
9.	been able to control irritations in your life?	0	1	2	3	4
10.	felt that you were on top of things?	0	1	2	3	4
11.	been angered because of things that happened that were outside of your control?	0	1	2	3	4
12.	found yourself thinking about things that you have to accomplish?	0	1	2	3	4
13.	been able to control the way you spend your time?	0	1	2	3	4
14.	felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

The following questions concern the general perceptions that you currently have about yourself. Please circle the number that best reflects your current view of yourself using the following scale as a guide for your responses.

		Strongly disagree	Disagree	Agree	Strongly agree
1.	On the whole I am satisfied with myself.	1	2	3	4
2.	At times I think that I am no good at all.	1	2	3	4
3.	I feel that I have a number of good qualities.	1	2	3	4
4.	I am able to do things as well as most other people.	1	2	3	4
5.	I feel I do not have much to be proud of.	1	2	3	4
6.	I certainly feel useless at times.	1	2	3	4
7.	I feel that I am a person of worth, at least on an equal plane with others.	1	2	3	4
8.	I wish I could have more respect for myself.	1	2	3	4
9.	All in all, I am inclined to feel that I am a failure.	1	2	3	4
10.	I take a positive attitude toward myself.	1	2	3	4

Below is a list of statements concerning how you might have felt or behaved in the past week. Please use the following scale to indicate how often you felt or behaved in these ways in the past week.

0	1	2	3
Rarely or none of the time (< 1 day)	Some of the time (1-2 days)	Much of the time (3-4 days)	Most or all of the time (5-7 days)

During the PAST WEEK:

1.	I felt depressed.	0	1	2	3
2.	I felt that everything I did was an effort.	0	1	2	3
3.	My sleep was restless.	0	1	2	3
4.	I was happy.	0	1	2	3
5.	I felt lonely.	0	1	2	3
6.	People were unfriendly.	0	1	2	3
7.	I enjoyed life.	0	1	2	3
8.	I felt sad.	0	1	2	3
9.	I felt that people disliked me.	0	1	2	3
10.	I could not get "going".	0	1	2	3

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number that best indicates how you have felt during the past week. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that best describes how you felt.

During the PAST WEEK:

	Not at all	Somewhat	Moderately so	Very much so
1. I felt calm	1	2	3	4
2. I was tense	1	2	3	4
3. I felt at ease	1	2	3	4
4. I worried over possible misfortunes	1	2	3	4
5. I felt frightened	1	2	3	4
6. I felt self-confident	1	2	3	4
7. I was jittery	1	2	3	4
8. I was relaxed	1	2	3	4
9. I was worried	1	2	3	4
10. I felt steady	1	2	3	4

The following questions relate to your usual sleep habits during the past month. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

---

1. During the past month, when have you usually gone to bed at night?

USUAL BED TIME _____

2. During the past month, how long has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the
number of hours you spend in bed.)

HOURS OF SLEEP PER NIGHT _____

5. During the past month, how would you rate your sleep quality overall?

_____ Very good _____ Fairly good _____ Fairly bad _____ Very bad

6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____ Only a very slight problem _____

Somewhat of a problem _____ A very big problem _____

For this next question, we would like you to recall the amount of exercise you have done during the past 12 weeks that was not part of the exercise program you did for this study. This means any exercise you did that was in addition to what you did for this study.

When answering these questions please:

- only count exercise sessions that lasted 10 minutes or longer in duration.
- only count exercise that was done during free time (i.e., not occupation or housework).
- note that the main difference between the first three categories is the intensity of the endurance (aerobic) exercise and the fourth category is for strength (resistance) exercise.
- please write the average frequency on the first line and the average duration on the second.
- if you did not do any exercise in one of the categories, please write in "0".

Considering a typical week (7 days) how many times on the average did you do the following kinds of exercise during the past 12 weeks that was not part of the exercise program?

		Times Per Week	Average Duration
a.	VIGOROUS/STRENUOUS EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g. running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling)	_____	_____
b.	MODERATE EXERCISE (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g. fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing)	_____	_____
c.	LIGHT/MILD EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g. easy walking, yoga, bowling, lawn bowling, shuffleboard)	_____	_____
d.	RESISTANCE EXERCISE (e.g. lifting weights, push ups, sit ups, therabands)	_____	_____

The next set of questions on this page relate to how you felt about taking part in this study. Please answer each one as honestly as possible using the following scale:

1	2	3	4	5	6	7
Not at all		Somewhat		A fair bit		Very much

---

1. How much of a burden was it for you to complete each of the following assessments in this study?

a.	the treadmill fitness test	1	2	3	4	5	6	7
b.	the blood vessel imaging tests	1	2	3	4	5	6	7
c.	the questionnaires	1	2	3	4	5	6	7
d.	the supervised training sessions	1	2	3	4	5	6	7

---

2. With hindsight, how do you feel about participating in this study?

a.	rewarding	1	2	3	4	5	6	7
b.	a waste of my time	1	2	3	4	5	6	7
c.	useful for research helping others	1	2	3	4	5	6	7
d.	useful for me personally	1	2	3	4	5	6	7
e.	something that I would recommend to other testicular cancer survivors	1	2	3	4	5	6	7

---

3. Thinking back, how did you feel when you found out that you were randomly assigned to the exercise group?

1	2	3	4	5	6	7
Extremely disappointed	Quite disappointed	Slightly disappointed	Neutral	Slightly pleased	Quite pleased	Extremely pleased

The following questions ask you to relate how you felt about doing the high-intensity aerobic interval exercise program over the past 12 weeks. Please pay careful attention to the words and descriptions for each scale and circle the number that best represents how you felt.

1. How beneficial was the aerobic interval training program?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

2. How enjoyable was the aerobic interval training program?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

3. How supportive were your family/friends of the aerobic interval training program?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

4. How motivated were you to do the aerobic interval training program?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

5. How difficult was it to do the aerobic interval training program?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

We are interested in knowing about any benefits or harms you feel resulted from participating in the aerobic training program. Please use the following scale to guide your responses.

1	2	3	4	5	6	7
Very much worse	Somewhat worse	Slightly worse	No change	Slightly improved	Somewhat improved	Very much improved

What affect, if any, did the aerobic training program have on each of the following for you?

a.	physical functioning	1	2	3	4	5	6	7
b.	overall quality of life	1	2	3	4	5	6	7
c.	cardiovascular endurance	1	2	3	4	5	6	7
d.	muscular strength	1	2	3	4	5	6	7
e.	fatigue	1	2	3	4	5	6	7
f.	sleep quality	1	2	3	4	5	6	7
g.	depressed feelings	1	2	3	4	5	6	7
h.	anxious feelings	1	2	3	4	5	6	7
i.	self-esteem	1	2	3	4	5	6	7
j.	stress	1	2	3	4	5	6	7
k.	body weight or shape	1	2	3	4	5	6	7
l.	illness or injury	1	2	3	4	5	6	7

Any other positive or negative effects you experienced?_____

We are also interested in knowing what, if any, barriers you felt made it difficult for you to do the exercise program. Please use the scale below to guide your responses.

1	2	3	4	5	6	7
Not at all		Somewhat		A fair bit		Very much

How much of a barrier was each of the following factors for you in trying to do the aerobic training program?

a.	bad weather	1	2	3	4	5	6	7
b.	feeling tired or fatigued	1	2	3	4	5	6	7
c.	symptoms and side effects of treatments	1	2	3	4	5	6	7
d.	other medical/health problems	1	2	3	4	5	6	7
e.	too busy and had limited time	1	2	3	4	5	6	7
f.	pain or soreness	1	2	3	4	5	6	7
g.	feeling sick/not feeling well	1	2	3	4	5	6	7
h.	nausea/vomiting	1	2	3	4	5	6	7
i.	urinary incontinence	1	2	3	4	5	6	7
j.	medical appointments	1	2	3	4	5	6	7
k.	lack of motivation	1	2	3	4	5	6	7
l.	travelling to the fitness centre	1	2	3	4	5	6	7

Any other barriers you experienced? _____

The following questions ask you to rate how you feel about exercising over the next six months on your own now that the supervised program is over. Please pay careful attention to the words and descriptors for each scale and circle the number that best represents how you feel.

---

1. How beneficial do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

2. How enjoyable do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

3. How supportive do you think your family/friends will be if you try to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

4. How motivated are you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

5. How difficult do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

6. Do you have a specific plan for where, when, and how you are going to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

Anything else you would like to tell us? On this final page, please feel free to make any comments concerning your testicular cancer, the tests, the questionnaire, the exercise program, or anything else you think may be helpful to us. All comments are welcome.

Any suggestions on how to improve the aerobic training program?

Thank you very much for participating in this research. Please bring the completed questionnaire to your fitness testing appointment at the Behavioural Medicine Fitness Centre.

Appendix P: 3-Month Follow-Up Self-Report Questionnaire – Combined

Cross Cancer Institute
11560 University Avenue, Edmonton,
Alberta, Canada, T6G 1Z2
Tel: 780.432.8770

Identification #_____

Date: _____

A study to test the effects of high-intensity aerobic interval exercise on the cardiovascular health of testicular cancer survivors.

3-Month Follow-Up Questionnaire

Investigators: Scott C. Adams, MSc[1]; Margie Davenport, PhD[1]; Darren DeLorey, PhD[1]; Adrian Fairey, MD[1,2]; Scott North, MD[1,3]; Kerry Courneya, PhD[1].

[1] – University of Alberta; [2] – Alberta Urology Institute; [3] – Cross Cancer Institute

Instructions

Thank you for your continued participation in this study. Now that you are 3 months post intervention, we are going to ask you many of the same questions as in the first two questionnaires. However, it is important to answer these questions based on what you are thinking and feeling right now and not on how you answered the questions last time. This will give us important information about how your thoughts and feelings have changed. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for all the questions if possible. However, if you feel uncomfortable answering certain questions please leave them blank. All responses are completely confidential and will never be used in any way that could link them to you. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for each. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30-45 minutes of your time to complete. If you have any questions about completing the questionnaire, please contact Scott Adams (Research Coordinator) at (780) 492-8246 or hitts@ualberta.ca.

This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking a single answer. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is:

1	2	3	4	5
Excellent	Very good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?

1	2	3	4	5
Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse than one year ago	Much worse now than one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	**Vigorous Activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b.	**Moderate Activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c.	Lifting or carrying groceries	1	2	3
d.	Climbing **several** flights of stairs	1	2	3
e.	Climbing **one** flight of stairs	1	2	3
f.	Bending, kneeling or stooping	1	2	3
g.	Walking more than a mile	1	2	3
h.	Walking several hundred yards	1	2	3
i.	Walking one hundred yards	1	2	3
j.	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Were **limited** in the **kind** of work or other activities	1	2	3	4	5
d.	Had **difficulty** performing the work or other activities (e.g., it took extra effort)	1	2	3	4	5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the **amount of time** you spent on work or other activities	1	2	3	4	5
b.	**Accomplished less** than you would like	1	2	3	4	5
c.	Did work or other activities **less carefully than usual**	1	2	3	4	5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

7. How much bodily pain have you had during the past 4 weeks?

1	2	3	4	5	6
None	Very mild	Mild	Moderate	Severe	Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

1	2	3	4	5
Not at all	Slightly	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of life?	1	2	3	4	5
b.	Have you been very nervous?	1	2	3	4	5
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d.	Have you felt calm and peaceful?	1	2	3	4	5
e.	Did you have a lot of energy?	1	2	3	4	5
f.	Have you felt downhearted and depressed?	1	2	3	4	5
g.	Did you feel worn out?	1	2	3	4	5
h.	Have you been happy?	1	2	3	4	5
i.	Did you feel tired?	1	2	3	4	5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

1	2	3	4	5
All of the time	Most of the time	Some of the time	A little of the time	None of the time

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

FATIGUE SYMPTOMS

During the PAST WEEK:

		Not at all	Little bit	Some-what	Quite a bit	Very much
1.	I feel fatigued	0	1	2	3	4
2.	I feel weak all over	0	1	2	3	4
3.	I feel listless ("washed out")	0	1	2	3	4
4.	I feel tired	0	1	2	3	4
5.	I have trouble starting things because I am tired	0	1	2	3	4
6.	I have trouble finishing things because I am tired	0	1	2	3	4
7.	I have energy	0	1	2	3	4
8.	I am able to do my usual activities	0	1	2	3	4
9.	I need to sleep during the day	0	1	2	3	4
10.	I am too tired to eat	0	1	2	3	4
11.	I need help doing my usual activities	0	1	2	3	4
12.	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13.	I have to limit my social activity because I am tired	0	1	2	3	4

The questions in this scale ask you about your feelings and thoughts during the last month. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each one fairly quickly. For each question, please choose from the following alternatives:

In the last month, how often have you…

		Never	Almost never	Some-times	Fairly often	Very often
1.	been upset because of something that happened unexpectedly?	0	1	2	3	4
2.	felt that you were unable to control the important things in your life?	0	1	2	3	4
3.	felt nervous and stressed?	0	1	2	3	4
4.	dealt successfully with irritating life hassles?	0	1	2	3	4
5.	felt that you were effectively coping with important changes that were occurring in your life?	0	1	2	3	4
6.	felt confident about your ability to handle your personal problems?	0	1	2	3	4
7.	felt that things were going your way?	0	1	2	3	4
8.	found that you could not cope with all the things that you had to do?	0	1	2	3	4
9.	been able to control irritations in your life?	0	1	2	3	4
10.	felt that you were on top of things?	0	1	2	3	4
11.	been angered because of things that happened that were outside of your control?	0	1	2	3	4
12.	found yourself thinking about things that you have to accomplish?	0	1	2	3	4
13.	been able to control the way you spend your time?	0	1	2	3	4
14.	felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

The following questions concern the general perceptions that you currently have about yourself. Please circle the number that best reflects your current view of yourself using the following scale as a guide for your responses.

		Strongly disagree	Disagree	Agree	Strongly agree
1.	On the whole I am satisfied with myself.	1	2	3	4
2.	At times I think that I am no good at all.	1	2	3	4
3.	I feel that I have a number of good qualities.	1	2	3	4
4.	I am able to do things as well as most other people.	1	2	3	4
5.	I feel I do not have much to be proud of.	1	2	3	4
6.	I certainly feel useless at times.	1	2	3	4
7.	I feel that I am a person of worth, at least on an equal plane with others.	1	2	3	4
8.	I wish I could have more respect for myself.	1	2	3	4
9.	All in all, I am inclined to feel that I am a failure.	1	2	3	4
10.	I take a positive attitude toward myself.	1	2	3	4

Below is a list of statements concerning how you might have felt or behaved in the past week. Please use the following scale to indicate how often you felt or behaved in these ways in the past week.

0	1	2	3
Rarely or none of the time (< 1 day)	Some of the time (1-2 days)	Much of the time (3-4 days)	Most or all of the time (5-7 days)

During the PAST WEEK:

1.	I felt depressed.	0	1	2	3
2.	I felt that everything I did was an effort.	0	1	2	3
3.	My sleep was restless.	0	1	2	3
4.	I was happy.	0	1	2	3
5.	I felt lonely.	0	1	2	3
6.	People were unfriendly.	0	1	2	3
7.	I enjoyed life.	0	1	2	3
8.	I felt sad.	0	1	2	3
9.	I felt that people disliked me.	0	1	2	3
10.	I could not get "going".	0	1	2	3

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number that best indicates how you have felt during the past week. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that best describes how you felt.

During the PAST WEEK:

		Not at all	Somewhat	Moderately so	Very much so
1.	I felt calm	1	2	3	4
2.	I was tense	1	2	3	4
3.	I felt at ease	1	2	3	4
4.	I worried over possible misfortunes	1	2	3	4
5.	I felt frightened	1	2	3	4
6.	I felt self-confident	1	2	3	4
7.	I was jittery	1	2	3	4
8.	I was relaxed	1	2	3	4
9.	I was worried	1	2	3	4
10.	I felt steady	1	2	3	4

The following questions relate to your usual sleep habits during the past month. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

---

1. During the past month, when have you usually gone to bed at night?

USUAL BED TIME _____

2. During the past month, how long has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the
number of hours you spend in bed.)

HOURS OF SLEEP PER NIGHT _____

5. During the past month, how would you rate your sleep quality overall?

_____ Very good _____ Fairly good _____ Fairly bad _____ Very bad

6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month _____ | Less than once a week _____ | Once or twice a week _____ | Three or more times a week _____

7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____ | Less than once a week _____ | Once or twice a week _____ | Three or more times a week _____

8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____ Only a very slight problem _____

Somewhat of a problem _____ A very big problem _____

For this next question, we would like you to recall the amount of exercise you have done during the past month.

When answering these questions please:

- only count exercise sessions that lasted 10 minutes or longer in duration.
- only count exercise that was done during free time (i.e., not occupation or housework).
- note that the main difference between the first three categories is the intensity of the endurance (aerobic) exercise and the fourth category is for strength (resistance) exercise.
- please write the average frequency on the first line and the average duration on the second.
- if you did not do any exercise in one of the categories, please write in "0".

Considering a typical week (7 days) how many times on the average did you do the following kinds of exercise during the past month?

		Times Per Week	Average Duration
a.	VIGOROUS/STRENUOUS EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g. running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling)	_____	_____
b.	MODERATE EXERCISE (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g. fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing)	_____	_____
c.	LIGHT/MILD EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g. easy walking, yoga, bowling, lawn bowling, shuffleboard)	_____	_____
d.	RESISTANCE EXERCISE (e.g. lifting weights, push ups, sit ups, therabands)	_____	_____

The following questions ask you to relate how you felt about performing aerobic exercise over the past three months. Please pay careful attention to the words and descriptions for each scale and circle the number that best represents how you felt.

---

1. How beneficial was it to perform aerobic exercise?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

2. How enjoyable was it to perform aerobic exercise?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

3. How supportive were your family/friends of you performing aerobic exercise?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

4. How motivated were you to perform aerobic exercise?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

5. How difficult was it for you to perform aerobic exercise?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

We are interested in knowing about any benefits or harms you feel resulted from participating in aerobic exercise over the past three months. Please use the following scale to guide your responses.

1	2	3	4	5	6	7
Very much worse	Somewhat worse	Slightly worse	No change	Slightly improved	Somewhat improved	Very much improved

What affect, if any, did the aerobic exercise have on each of the following for you?

a.	physical functioning	1	2	3	4	5	6	7
b.	overall quality of life	1	2	3	4	5	6	7
c.	cardiovascular endurance	1	2	3	4	5	6	7
d.	muscular strength	1	2	3	4	5	6	7
e.	fatigue	1	2	3	4	5	6	7
f.	sleep quality	1	2	3	4	5	6	7
g.	depressed feelings	1	2	3	4	5	6	7
h.	anxious feelings	1	2	3	4	5	6	7
i.	self-esteem	1	2	3	4	5	6	7
j.	stress	1	2	3	4	5	6	7
k.	body weight or shape	1	2	3	4	5	6	7
l.	illness or injury	1	2	3	4	5	6	7

Any other positive or negative effects you experienced?_____

We are also interested in knowing what, if any, barriers you felt made it difficult for you to perform aerobic exercise. Please use the scale below to guide your responses.

1	2	3	4	5	6	7
Not at all		Somewhat		A fair bit		Very much

How much of a barrier was each of the following factors for you in trying to do aerobic exercise?

a.	bad weather	1	2	3	4	5	6	7
b.	feeling tired or fatigued	1	2	3	4	5	6	7
c.	symptoms and side effects of treatments	1	2	3	4	5	6	7
d.	other medical/health problems	1	2	3	4	5	6	7
e.	too busy and had limited time	1	2	3	4	5	6	7
f.	pain or soreness	1	2	3	4	5	6	7
g.	feeling sick/not feeling well	1	2	3	4	5	6	7
h.	nausea/vomiting	1	2	3	4	5	6	7
i.	urinary incontinence	1	2	3	4	5	6	7
j.	medical appointments	1	2	3	4	5	6	7
k.	lack of motivation	1	2	3	4	5	6	7
l.	travelling to the fitness centre	1	2	3	4	5	6	7

Any other barriers you experienced? _____

The following questions ask you to rate how you feel about exercising over the next six months on your own now that the supervised program is over. Please pay careful attention to the words and descriptors for each scale and circle the number that best represents how you feel.

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1. How beneficial do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

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2. How enjoyable do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

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3. How supportive do you think your family/friends will be if you try to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

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4. How motivated are you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

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5. How difficult do you think it will be for you to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

---

6. Do you have a specific plan for where, when, and how you are going to train aerobically over the next six months?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

Anything else you would like to tell us? On this final page, please feel free to make any comments concerning your testicular cancer, the tests, the questionnaire, the exercise program, or anything else you think may be helpful to us. All comments are welcome.

Any suggestions on how to improve the aerobic training program?

Thank you very much for participating in this research. Please bring the completed questionnaire to your fitness testing appointment at the Behavioural Medicine Fitness Centre.