REVIEW / SYNTHÈSE

Evidence-based risk assessment and recommendations for physical activity clearance: cancer[1]

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Abstract: Physical activity is becoming increasingly acknowledged as an integral component of in the multidisciplinary management of cancer patients. Intensive inquiry in this area is likely to increase further over the next decade; however, cancer-specific, evidence-based risk assessment and recommendations for physical activity are not available. A systematic literature review was performed of all studies conducting an exercise training intervention and (or) any form of objective exercise test among adults diagnosed with cancer. Studies were assessed according to evaluation criteria developed by a panel of experts. A total of 118 studies involving 5529 patients were deemed eligible. Overall, the results suggest that exercise training and maximal and submaximal exercise testing are relatively safe procedures with a total nonlife-threatening adverse event rate of <2%. There was only 1 exercise training-related death. However, the quality of exercise testing methodology and data reporting is less than optimal. Thus, whether the low incidence of events reflects the true safety of exercise training and exercise testing in cancer patients or less than optimal methodology and (or) data reporting remains to be determined. Evidence-based absolute and relative contraindications to physical activity and exercise training and testing are provided as well as probing decision-trees to optimize the adoption and safety of physical activity in persons diagnosed with cancer.

Key words: exercise training, exercise testing, PAR-Q, PARmed-X, safety, clinical decision-trees.

Résumé : L'activité physique devient de plus en plus reconnue comme partie intégrante de la prise en charge multidisciplinaire des patients atteints de cancer. La demande intensive de renseignements dans ce domaine risque de s'accroître davantage au cours de la prochaine décennie; toutefois, il n'existe pas d'évaluation des risques ni de recommandations fondées sur des données probantes concernant l'activité physique chez les patients atteints de cancer en particulier. Un examen systématique de la documentation portant sur toutes les études qui ont effectué une intervention liée à l'entraînement physique ou à toute forme d'épreuve d'effort objective chez des adultes qui ont reçu un diagnostic de cancer a été réalisé. Les études ont été évaluées selon des critères d'évaluation élaborés par un groupe d'experts. Un nombre total de 118 études portant sur 5529 patients ont été jugées admissibles. Dans l'ensemble, les résultats donnent à penser que l'entraînement physique et les épreuves d'effort maximales et sous-maximales constituent des interventions relativement sans danger, montrant un taux total d'événements indésirables ne menaçant pas le pronostic vital inférieur à 2 %. On ne rapporte qu'un seul décès lié à l'entraînement physique. Toutefois, la qualité de la méthodologie des épreuves d'effort et de la communication des données n'est pas optimale. Par conséquent, il reste à déterminer si l'incidence faible des événements reflète vraiment l'aspect sécuritaire de l'entraînement physique et des épreuves d'effort chez les patients atteints de cancer ou plutôt le manque de qualité quant à la méthodologie et à la communication des données. Des contre indications absolues et relatives fondées sur des données probantes de l'activité physique, de l'entraînement physique et de l'épreuve d'effort sont présentées ainsi que des arbres d'exploration et de décision pour optimiser l'adoption et la sécurité de l'activité physique chez les personnes ayant reçu un diagnostic de cancer.

Mots-clés : entraînement physique, épreuves d'effort, PAR-Q, PARmed-X, sécurité, arbres de décision cliniques.

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Introduction

Cancer is among the main causes of morbidity and mortality in North America. Improvements in early detection and surgical techniques together with more effective locoregional and systemic therapies has led to significant survival gains for individuals diagnosed with cancer, with approximately 66% of all patients expected to live 5 years after diagnosis (Edwards et al. 2005; Jemal et al. 2008). Concomitantly, there has also been a substantial enhancement in longevity among the general population. Recent estimates indicate that more than 13 million people are alive in North America today with a history of cancer (Edwards et al. 2005; Jemal et al. 2008).

The use of conventional and novel therapies is associated with a diverse range of debilitating physiologic (e.g., physical deconditioning, weight gain, cardiac and pulmonary dysfunction, etc.) and psychosocial (e.g., fatigue, nausea, depression, anxiety, etc.) symptoms that can have profound implications on quality of life. The negative impact of surgery is dependent on the tumor location (site) and extent of resection. For example, among patients with non-small cell lung cancer, resection of the lung parenchyma reduces ventilatory capacity and reserve. Prospective studies have reported an average reduction in peak oxygen consumption of 28% and 13% for pneumonectomy and lobectomy, respectively, up to 2 years following resection (Bolliger et al. 1996; Nezu et al. 1998; Pelletier et al. 1990). In comparison, the negative side-effects of surgeries performed in other cancer sites (e.g., breast) have received less attention. Nevertheless, cancer operations are not benign and despite the adoption of more sophisticated surgical approaches, some procedures are associated with functional limitations and pain, which can negatively impact activities of daily living (Rietman et al. 2004, 2003, 2006). The adoption of a more sedentary lifestyle would be expected to further negatively impact quality of life (QOL) (Clark et al. 2008; Humpel and Iverson 2007; Richardson et al. 2008; Valenti et al. 2008; Vallance et al. 2008).

Given improving prognosis, long-term therapy-associated toxicity and its affect on overall QOL is becoming recognized as an outcome of major importance in the multidisciplinary management of cancer patients. To this end, physical activity and exercise training interventions are becoming increasingly acknowledged as an integral component of multidisciplinary management of cancer patients. In recent years, groups have started to examine the efficacy of physical activity and exercise training as an adjunct, supportive care intervention before, during, or following cancer therapy. Several recent reviews have reported that physical activity is safe and feasible for cancer patients and associated with significant improvements in cardiorespiratory fitness, fatigue, and overall QOL (Jones et al. 2011; Speck et al. 2010). Intensive inquiry in this area is likely to increase further over the next decade; therefore, cancer-specific, evidence-based risk assessment and recommendations for physical activity are required (Schmitz et al. 2010). The development of such guidelines is critical to maximize both patient safety and the beneficial outcomes of physical activity in this population.

The following section was written by the consensus panel that guided the overall revision of the PA clearance process. This information is reprinted in each of the systematic review papers so that these reviews can stand alone from the paper describing the overall consensus process (Jamnik et al. 2011).

Physical activity (PA) participation is recommended and beneficial for all asymptomatic persons and for persons with chronic diseases (Warburton et al. 2006, 2007). However, the PA participation of persons with certain chronic disease conditions or constraints may need to be restricted. The Physical Activity Readiness Questionnaire (PAR-Q) is a screening tool completed by persons who plan to undergo a fitness assessment or to become "much more physically active"; for example, when initiating PA participation that is beyond a person's habitual daily activity level or when beginning a structured PA–exercise program. Screening is also recommended when a person is joining a health club, commencing a training program with a fitness professional, or joining a sports team. If a person provides a positive response to any question on the PAR-Q, then that person is directed to consult with a physician for clearance to engage in either unrestricted or restricted PA.

The Physical Activity Readiness Medical Evaluation (PARmed-X) is a screening tool developed for use by physicians to assist them in addressing medical concerns regarding PA participation that were identified by the PAR-Q. Recent feedback from PA participants, fitness professionals, and physicians has brought to light substantial limitations to the utility and effectiveness of PA participation screening by the PAR-Q and PARmed-X. In short, the exercise clearance process is not working as intended and at times is a barrier to PA participation for those persons who may be most in need of increased PA. The aim of the present project is for experts in each chronic disease, together with an expert panel, to revise and increase the effectiveness of the PAR-Q and PARmed-X screening process using an evidence-based consensus approach that adheres to the established Appraisal of Guidelines for Research and Evaluation (AGREE).

An important objective of this project is to provide evidence-based support for the direct role of university-educated and qualified exercise professionals in the exercise clearance process. An example of a qualified exercise professional is the Canadian Society for Exercise Physiology Certified Exercise Physiologist (CSEP-CEP). The CSEP-CEP is the highest nationally recognized certification in the health and fitness industry. It recognizes the qualifications of those persons who possess advanced formal academic preparation and practical experience in health-related and performance-related PA–exercise science fitness applications for both non-clinical and clinical populations.

The AGREE instrument was developed by a group of researchers from 13 countries to provide a systematic framework for assessing the quality and impact on medical care of clinical practice guidelines (CPGs) (AGREE Collaboration 2001, 2003). The AGREE collaboration published the rigorous development process and associated reliability and validity data of the AGREE instrument based on a large-scale study focussing primarily on CPGs (AGREE Collaboration 2001, 2003). The AGREE instrument is now a commonly used tool for assessing CPGs and other health management guidelines (Lau 2007). The AGREE guidelines were applied in the present project to assess the formulation of risk stratification and PA participation clearance recommendations for each of the critical chronic diseases. One of the authors of

this project (J.M.) is an AGREE instrument expert, and she was responsible for evaluating the compliance of the overall process to the AGREE guidelines.

In addition to adhering to the AGREE process, the Level of Evidence (1 = randomized control trials (RCTs); 2 = RCTs with limitations or observational trials with overwhelming evidence; 3 = observational studies; 4 = anecdotal evidence) supporting each PA participation clearance recommendation and the Grade (A = strong; B = intermediate; C = weak) of the PA participation clearance recommendation was assigned by applying the standardized Level and Grade of Evidence detailed in the consensus document (Warburton et al. 2011). In this series of articles, each chronic disease condition was considered in reference to a continuum of risk from lower risk to intermediate (moderate) and higher risk categories. Particular attention was paid to the short-term (acute) risks of PA–exercise vs. the long-term (chronic) benefits on the chronic disease. Physical activity participation may transiently increase the risk acutely while leading to physiological and psychological adaptations that markedly reduce the long-term risk. Adverse events (AEs) were considered as any adverse change in health status or a "side effect" that resulted in relation to PA–exercise participation.

The objectives of this paper are to provide (*i*) a comprehensive overview of absolute and relative contraindications to physical activity based on published trials and cancer etiology and therapy, (*ii*) a critical review of the appropriateness of the PAR-Q and PARmed-X for physical activity risk assessment in cancer patients, (*iii*) evidence-based absolute and relative contradindications to physical activity participation as well as feasible decision trees to facilitate clinical decision-making, and (*iv*) articulate the role of the qualified exercise professionals.

Methods

A comprehensive literature review using PubMed, MEDLINE, Sport Discus, and Cochrane Controlled Trials Register (1966 through February 2008) was conducted using the following MeSH terms and text words: physical activity, exercise, cardiorespiratory fitness, exercise capacity, cardiopulmonary fitness, functional capacity, exercise test, exercise training, exercise behaviour, oncology, cancer, and neoplasms. Relevant reference lists were also hand-searched. Studies conducting an exercise training intervention and (or) any form of objective exercise test among adults diagnosed with cancer were deemed eligible. Studies with a participant mean age below 18 years (studies among children and adolescents with cancer were excluded), were non-English, review article only, physical activity or exercise behaviour was the dependent variable (i.e., physical activity promotion studies), assessed the effects of exercise in combination with other nonexercise interventions (e.g., stress management, dietary counseling, etc.), assessed the effects of complementary forms of exercise training (e.g., tai chi, yoga, etc.), and assessed cardiorespiratory fitness – functional capacity using indirect and (or) subjective instruments (e.g., self-reported physical activity behaviour) were excluded.

Studies were assessed according to evaluation criteria developed by the author (Table 1). In terms of AEs, studies were evaluated as follows: (*i*) the number of studies reporting an AE, (*ii*) those evaluating AEs but none were observed, and (*iii*) those not evaluating or reporting AEs. Two independent reviewers, guided by the author, identified potential studies and evaluated study eligibility based on criteria described in Table 1. These reviewers also independently performed data extraction using standardized data abstraction forms.

Table 1. Exercise oncology evaluation criteria.

Study characteristics
Year of publication
Country of publication
Study design (randomized controlled design, prospective pre–post designs
No. of subjects
Sex breakdown
Mean age and age range
Cancer population – site (e.g., breast, lung, prostate, colorectal, etc.)
Study setting (e.g., before surgery, after surgery during treatment, etc.)
Cancer treatment (e.g., chemotherapy, radiation, chemoradiation, etc.)
Stage of disease (e.g., early, advanced, etc.)
Study methodology
Reason for patient exclusion (e.g., recurrent cancer, uncontrolled heart disease, etc.)
Patient inclusion – exclusion determination (e.g., physician clearance, prescreening exercise tool, etc.)
Type of functional test (e.g., cardiopulmonary exercise test, stress test, walk test, etc.)
Functional test modality (e.g., treadmill, ergometer, etc.)
Safety monitoring (e.g., physician monitored, ECG, etc.)
Exercise intervention (if applicable)
Exercise intervention prescription (e.g., frequency, intensity, duration, modality, etc.)
Safety monitoring during exercise intervention (e.g., physician monitored, ECG, etc.)
Conduct of exercise training (e.g., supervised vs. unsupervised)
Exercise intervention outcomes–results
Cardiopulmonary outcomes (e.g., cardiorespiratory fitness, blood pressure, body weight, etc.)
Psychosocial outcomes (e.g., quality of life, fatigue, depression, etc.)
Type of psychosocial assessment tool
Adherence to the exercise intervention
Study attrition
Intention-to-treat analyses conducted
Adverse events
Type and frequency of adverse events reported during functional capacity testing
Type and frequency of adverse events reported during exercise intervention

Descriptive statistics are presented to describe the study characteristics. Inferential statistics were not used to evaluate study outcomes. To establish physical activity prescription recommendations for patients diagnosed with cancer, the effects of exercise training on select physiologic (i.e., cardiorespiratory fitness (defined as peak oxygen consumption, exercise duration, or walk distance)) and psychosocial outcomes (i.e., QOL, fatigue, and depression) of identified intervention studies was conducted. Given the heterogeneity in

study methodology, data are expressed as a percentage to enable between study comparisons.

Results

A total of 852 potential citations were identified. After initial review, 152 were deemed potentially eligible. On secondary review, 118 met inclusion criteria. The most common reasons for exclusion were no objective measure of cardiorespiratory fitness, review article only, participant mean age <18 years, nonindependent studies (i.e., multiple publications from same study), and physical activity – exercise behaviour was the dependent outcome (i.e., exercise promotion study).

Study characteristics

The overall study characteristics are provided in Table 2. A total of 118 studies were included involving a total of 5529 adult patients. Overall, the mean age of study participants was 53 ± 11 years and 56% of study participants were female. Forty-four percent of study designs were RCTs while 25% were cross-sectional in nature. Across all study designs, the majority included patients with operable disease (77%). Breast, mixed, and lung cancer patients were the target populations for 36%, 34%, and 20% of studies, respectively. The majority of studies were conducted after surgical resection either following (41%) or during (24%) adjuvant therapy. Of those studies conducted during adjuvant therapy, 49% were performed during chemotherapy while 21% were conducted during multimodal therapies.

Study methodology characteristics and exercise-related AEs

Pre-exercise training, testing screening criteria, and exercise testing methodology are presented in Table 3. Concerning study inclusion and exclusion criteria, 41% of studies reported no patient exclusion criteria. Of those reporting exclusion criteria, the most widely reported exclusion criteria were uncontrolled heart disease (38%), uncontrolled hypertension (16%), physically active (16%), and cognitive or psychiatric illness (15%). Other common criteria were pulmonary dysfunction (13%), presence of persistent or recurrent cancer (13%), and extensive skeletal or visceral metastases (11%).

Forty-five percent of studies reported no pre-exercise training or exercise testing screening procedures while 34% reported physician–oncologist clearance prior to study entry. Of note, use of the PAR-Q or PARmed-X was reported in only 6% of studies. Maximal cardiopulmonary exercise testing with gas exchange assessment was reported by 42% while submaximal exercise testing was reported by 45%. During testing, 37% reported continuous heart rate monitoring while physician and ECG monitoring was reported by 28% and 24%, respectively. Finally, 39% did not report any physiologic monitoring during exercise testing.

Overall, a total of 101 AEs were reported from 16 studies (16 out of 118 = 14.0%); 88 AEs during exercise testing and 13 AEs during exercise training. No studies reporting evaluating AEs but did not report an AE, while 102 studies did not either report or state that AEs were evaluated (102 out of 118 = 86%). The total AE rate was 6.3% (number of AEs / number of studies stating AEs were evaluated) (Table 4). In order of magnitude, the most common AEs during exercise testing were ST segment changes (n = 32), blunted heart rate or blood pressure responses (n = 13), pain (n = 11), ischemia (n = 11), and general abnormalities (n = 11). No fatal events were reported during exercise testing. One fatal event was reported during exercise training. Other

Table 2. Study Characteristics (n = 118).

	No. (%)
Year of publication	
1980–1989	10 (18)
1990–1999	28 (24)
>2000	80 (68)
Number of subjects per study	
Overall mean±SD	64±61
0–20	23 (19)
21–50	40 (34)
>50	55 (47)
Age (y)	
Overall mean±SD	53±11
18–50	45 (38)
>50–60	27 (23)
>60	46 (39)
Sex	
Male	2245 (44)
Female	2903 (56)
Cancer population–site	
Breast	42 (36)
Mixed	40 (34)
NSCLC–SCLC–bronchogenic	24 (20)
NHL–Hodgkin's	4 (3)
Prostate	4 (3)
Colorectal	2 (2)
Testicular	1 (1)
Study setting	
Before surgery	16 (14)
After surgery, during treatment	28 (24)
After surgery, after treatment	48 (41)
Mixed (before and after surgery)	9 (8)
Pre-BMT	2 (2)
Other	15 (13)
Cancer treatment	
Chemotherapy	21 (49)
Radiation	7 (16)
Chemotherapy plus radiation	4 (9)
Endocrine therapy	2 (5)
Multimodal therapies	9 (21)
Disease stage	
Early-stage – operable disease	91 (77)
Advanced stage – inoperable disease	8 (7)
Post-BMT	10 (9)
Pre-BMT	3 (2)
Mixed (early and advanced disease)	6 (5)
Study design	
Randomized controlled trial	52 (44)
Cross-sectional	29 (25)
Prospective, interventional	21 (18)
Prospective, noninterventional	16 (14)

Note: NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Table 3. Pre-exercise training, testing screening criteria, and exercise testing methodology of studies (n = 118).

	No. (%)
Reason for patient exclusion*	
Uncontrolled heart disease	45 (38)
Uncontrolled hypertension	19 (16)
Physically active	19 (16)
Cognitive dysfunction	18 (15)
Pulmonary dysfunction	15 (13)
Presence of persistent or recurrent cancer	13 (11)
Extensive skeletal or visceral metastases	13 (11)
Left ventricular ejection fraction <50%	10 (8)
Orthopedic problems	9 (8)
Undergoing therapy	7 (6)
Other	6 (5)
Estimated life expectancy <6 mo	5 (4)
Type 2 diabetes	5 (4)
Other or prior malignancy	4 (3)
Pregnant	3 (2)
KPS<70%	3 (2)
No exclusion criteria listed	48 (41)
Study prescreening procedures*	
Physician–oncologist clearance	40 (34)
Negative exercise test	6 (5)
Prescreening exercise tool (i.e., PAR-Q or PARmed-X)	7 (6)
American Thoracic Society guidelines	4 (3)
Not stated	53 (45)
Type of exercise test	
Maximal, cardiopulmonary exercise test	49 (42)
Maximal, without expired gas exchange assessment	16 (14)
Submaximal, age-predicted heart rate test	19 (16)
Submaximal, 6 or 12-min walk test	15 (13)
Submaximal, other	5 (4)
Not stated	14 (12)
Exercise test modality	
Cycle ergometer	48 (41)
Treadmill	33 (28)
Walk test	19 (16)
Other	4 (3)
Missing	14 (12)
Exercise test monitoring*	
Physician-monitored	28 (24)
ECG	33 (28)
Blood pressure	24 (20)
Continuous heart rate	44 (37)
Rate of perceived exertion	9 (8)
Arterial saturation (SaO_2)	16 (14)
Not stated	46 (39)

*Studies could report more than 1 criterion.

common events during exercise training included lymphedema (n = 3) and nephrotoxicity (n = 2). Of the 17 studies reporting an AE, 7 (44%) were conducted among patients with mixed cancer diagnoses, 4 (25%) in breast cancer, 2 (12.5%) in non-small cell lung cancer, 2 (12.5%) in small cell lung cancer., and 1 (6%) in adult childhood cancer survivors.

To further elucidate the absolute and relative contraindications to exercise in adult cancer patients, the characteristics between studies reporting AEs and those that did not were compared (data not presented). There were several differences in terms of patient exclusion criteria, pre-exercise screening procedures, and exercise test monitoring. Concerning patient exclusion eligibility, 13% of studies reporting an adverse event stated no exclusion criteria in comparison with 45% of studies not reporting an event. In addition, uncontrolled heart disease, cognitive–psychiatric illness, and uncontrolled hypertension were exclusion criteria in 59%, 30%, and 29% of studies reporting an adverse event, respectively. The corresponding numbers for studies not reporting AEs were 35%, 14%, and 13%, respectively.

Table 4. Adverse events (AEs) in clinical oncology exercise research studies (n = 16).

Event	No.
Total no. of AEs	101 (6.3%) (101 patient events / 16 number of studies stating AEs were evaluated)
Types of AEs during exercise testing (n = 88)	
ST segment changes	32
Blunted blood pressure – heart rate response	13
Pain	11
Ischemia	11
General abnormality	11
Hypotension	5
Premature exercise termination	2
Bundle branch block	1
Hip pain	1
Dizziness	1
Types of AEs during exercise training (n = 13)	
Death	1
Lymphedema	3
Nephrotoxicity	2
Infection	1
Hypotension	1
Nausea	1
Gynecologic problems	1
Influenza	1
Foot fracture	1
Bronchitis	1

Concerning pre-exercise screening procedures, physician–oncologist clearance was reported in 65% of studies reporting an adverse event compared with 30% of those not reporting an event. Similarly, only 12% of studies reporting an adverse event did not use any prescreening procedures compared with 51% of studies not reporting an adverse event. Finally, those reporting an adverse event were, in general, more likely to report the use of exercise test-monitoring procedures (e.g., physician or ECG monitored) compared with those who did not. There were no other differences in any study- or patient-related characteristics.

Discussion

Evidence-based review of absolute and relative contraindications to exercise training and exercise testing in persons with cancer

Results of this evidence-based systematic review suggest that both exercise training and maximal and submaximal exercise testing are relatively safe procedures. The American Thoracic Society–American College of Chest Physicians (ATS–ACCP) report that the risk of death and life threaten-

ing complications during exercise testing is 2 to 5 per 100 000 tests (ATS–ACCP 2003). Thus, maximal, and particularly submaximal exercise testing, is a relatively safe procedure for all individuals. Of note, 1 study was responsible for 47% of all AEs reported among exercise testing studies included in this review. This study, conducted by Jones et al. (2007*e*) examined the feasibility and safety of exercise testing among patients with advanced (inoperable) non-small cell lung cancer or metastatic breast cancer. Using a cross-sectional design, a total of 85 patients, 46 non-small lung cancer patients, and 39 metastatic breast cancer patients, all patients presented metastases at 1 or more sites, had received prior chemotherapy, and had a diverse range of comorbid conditions. Each patient performed a maximal cardiopulmonary exercise test with gas exchange analysis on a cycle ergometer. Each test was physician monitored with continuous ECG and SaO_2 assessment as well as exercise blood pressure monitoring. Overall, 3 positive stress tests were observed while detailed ECG analysis indicated that 26% and 43.6% of patients with non-small cell lung cancer and breast cancer, respectively, developed asymptomatic ST segment changes during exercise. In addition, 2 patients experienced a nonlife-threatening, non-ECG-related event during exercise testing. Furthermore, at rest, approximately 30% of these patients presented with at least 1 ECG abnormality (Jones et al. 2007*e*).

Clearly, the findings of Jones et al. (2007*e*) are in contrast to the overall results of this systematic review which indicated a low incidence of AEs among clinical oncology physical activity studies. These contrasting findings may be partially explained by differences in exercise testing methodology and (or) participant characteristics. First, in the study by Jones et al. (2007*e*) rigorous exercise testing methodology (i.e., appropriately monitored maximal cardiopulmonary exercise testing) was adopted as recommended for clinical populations. The results of this systematic review, in general, indicate that exercise testing methodology is less than optimal with <30% reporting appropriate exercise test monitoring. Relatedly, the purpose of the Jones et al. (2007*e*) study was to investigate the safety of maximal exercise testing and detailed ECG analysis was conducted that revealed a number of abnormalities at rest and peak exercise. It is currently not clear whether studies identified in this systematic review conducted similar extensive ECG analysis. Second, Jones et al. (2007*e*) investigated the safety of maximal exercise testing in cancer patients with advanced (inoperable) disease, whereas the vast majority of studies included in this systematic review were conducted among cancer patients with early-stage (operable) disease. The risk of a physical activity-related AE is likely distinct between these 2 groups. Given that advanced cancer patients are likely to be heavily pre-treated with cytotoxic agents, have poor cardiorespiratory fitness, and present with significant comorbid disease, the risk of a physical activity-related AE may be elevated. Evidence to support this contention is currently limited and large-scale evaluations that comprehensively investigate the safety of exercise testing and training in oncology populations are required.

A total of only 13 AEs were reported from 11 studies that conducted an exercise training intervention among persons diagnosed with cancer. The most common exercise-related AE was lymphedema. Although 1 exercise-related death was reported, the majority of events were relatively non-serious (e.g., infection, influenza, etc.) and temporal in nature suggesting that standardized guidelines are required to assess whether observed events are related to exercise participation as well as appropriate grading of events (i.e., serious vs. non-serious). Although only a paucity of intervention studies reported an AE (in the exercise intervention group), even fewer reported AEs in subjects randomized to the control (nonexercising) group. Without report of AEs in the control group, it cannot be determined whether the reported incidence of AEs is truly associated with the addition of exercise participation or are simply a reflection of normal living. Again, future studies should strive to report AEs in all experimental groups when conducting a randomized trial of exercise in persons diagnosed with cancer.

Detailed analysis revealed several interesting methodological differences between studies reporting an AE and those that did not. In general, the overall results of the systematic analysis reporting an AE were more likely to employ strict patient eligibility criteria and pre-exercise screening procedures than studies not reporting an AE. This finding appears counterintuitive, since one might expect a lower number of events in studies employing stricter eligibility–screening criteria. However, the opposite may be true. Studies employing more rigorous eligibility and screening are likely of higher quality and more likely to monitor and report AEs. Further, these studies were also more likely to report the use of appropriate exercise test monitoring procedures and thus more likely to identify that an AE has occurred. Notwithstanding these findings, there were surprisingly few clear differences in cancer-related outcomes (e.g., cancer diagnosis, stage, therapy) between study groups. However, the small number of studies reporting an AE is likely a major contributing factor to this finding.

Although supporting evidence is currently lacking, a cancer diagnosis and the use of conventional and novel therapies may increase the risk of physical activity-related complications. The hypothesized increased risk associated with a cancer diagnosis is probably highly dependent on the type of cancer and the stage of disease. For example, primary gliomas are highly angiogenic which can lead to increase risk of prothrombotic events (Lebelt et al. 2008; Reardon et al. 2008). Other tumors (e.g., colon, lung, and pancreatic cancer), on the other hand, stimulate a proinflammatory cascade leading to muscle cachexia and anorexia (Fearon 2008; Fortunati et al. 2007; Johnson et al. 2008; MacDonald 2007; McKay et al. 2008). Finally, the location of the tumor can also impact the exercise response and thus the risk of complication. Tumor burden in the lungs is expected to negatively impact pulmonary mechanics and reduce pulmonary reserve leading to exercise intolerance and potentially the exacerbation of other comorbid conditions (Jones et al. 2007*d*). The severity of these conditions is ultimately dependent on the stage of disease. The adverse effects of tumor burden may be less important among patients with operable disease, since tumors have likely been surgically resected at the time when physical activity interventions are initiated (i.e., postsurgery). However, patients with inoperable disease have varying degrees of tumor burden (depending on the metastatic spread), thus the systemic effects of the tumor characteristics on exer-

cise function is an important consideration beyond location and normal tissue invasion.

The potential increased risk of exercise complications associated with cancer surgery is dependent on the tumor location (site) and extent of resection. For example, prospective studies have reported an average reduction in peak oxygen consumption of 28% and 13% for pneumonectomy and lobectomy, respectively, up to 2 years following resection among patients with operable lung cancer (Bolliger et al. 1996; Nezu et al. 1998; Pelletier et al. 1990). Further, regardless of the extent or location of surgery, many, if not all cancer procedures are associated with an increased risk of bleeding, infection, inflammation, functional limitations, and a reduction in activities of daily living. Radiotherapy is a common form of locoregional therapy used in approximately 50% of all cancer diagnoses. Although modern planning techniques have reduced the amount of normal tissue damage, some incidental damage is unavoidable. Of importance, in a prospective study of patients receiving modern computed tomography-based radiotherapy for left sided breast cancer between 1998 and 2005, subclinical abnormalities in myocardial perfusion were noted in >50% of patients (Das et al. 2005; Evans et al. 2006; Prosnitz et al. 2005, 2007). These perfusion defects persisted for up to 6 years post-radiation therapy (RT) and are associated with subtle changes in wall motion. In addition, RT can affect other aspects of the heart including the myocardium, pericardium, valves, and coronary vessels (Das et al. 2005; Evans et al. 2006; Prosnitz et al. 2005, 2007). RT can also cause lung damage (Allen et al. 2005; Evans et al. 2007; Mao et al. 2007*a*, 2007*b*; Miller et al. 2005). Symptomatic shortness of breath can occur in up to 5% of patients who receive local and regional (i.e., nodal) irradiation along with systemic chemotherapy. Subclinical injury, detected by either imaging or pulmonary function tests, occurs in up to 20%–50% of patients (Allen et al. 2005; Evans et al. 2007; Mao et al. 2007*a*, 2007*b*; Miller et al. 2005). Whether these abnormalities increase the risk of exercise-related events is currently not known.

Each of the many chemotherapeutic agents used in cancer management are associated with unique, significantly acute, and long-term cardiovascular side-effects that may have implications for the safety of physical activity among cancer populations (Floyd et al. 2005; Jones et al. 2007*a*; Yeh et al. 2004). For example, anthracycline-containing regimens (i.e., doxorubicin, epirubicin) are associated with dose-dependent, cumulative, progressive cardiac dysfunction manifest as decreased left ventricular ejection fraction, and ultimately, symptomatic heart failure (Erselcan et al. 2000; Gennari et al. 1999; Gianni et al. 2007, 2001; Outomuro et al. 2007; Perez et al. 2004; Takemura and Fujiwara 2007). Platinum-based regimens cause reductions in FEV_1 (Esteban et al. 2008; Maas et al. 2003), whereas a number of chemotherapeutics cause anemia, endothelial dysfunction (Jones et al. 2007*b*, 2007*c*), autonomic dysfunction (Miller et al. 2008; Nuver et al. 2005; Zachariae et al. 2007), tachycardia (Jones et al. 2007*b*, 2007*c*), and hypotension (Floyd et al. 2005). Further, the cardiovascular effects of many chemotherapeutic agents are currently unknown. Hormone therapy, used predominantly among patients with breast or prostate cancer, is associated with a broad range of adverse effects that are particularly relevant in exercise settings including type 2 diabetes, osteoporosis, muscle weakness, and possibly even cardiac dysfunction (Kurebayashi 2008; Singer et al. 2008). New classes of drugs, small molecule inhibitors (e.g., trastuzumab, bevacizumab, etc.), that target tyrosine kinase receptors, are already known to be associated with several cardiovascular complications, including arterial thromboembolic events, proteinuria, cardiac dysfunction, and most commonly, hypertension (Bengala et al. 2006; Chu et al. 2007; Floyd et al. 2005; Kerkelä et al. 2006; Yeh et al. 2004). Finally, use of many cancer therapies are associated with unfavorable health behaviour changes (i.e., physical inactivity and weight gain) that can exacerbate the direct adverse effects of conventional therapy (Irwin et al. 2004, 2005, 2007).

Taken together, the sequential and often concurrent impact of therapy adversely affects the integrative ability of the heart, lungs, vasculature, and circulation to deliver oxygen to the metabolically active skeletal muscles, which in turn reduces a patient's ability to tolerate exercise and possibly increases the risk of an adverse event (Jones et al. 2007*a*). Adequately powered, well-controlled, and methodologically rigorous studies that systematically investigate exercise-related AEs in persons diagnosed with cancer are required.

Appropriateness of PAR-Q and PARmed-X for pre-exercise screening in oncology

Out of 118 studies identified in this systematic review, only 7 (6%) reported using the PAR-Q or PARmed-X as a pre-physical activity risk assessment tool. Moreover, as described, <15% of studies identified in this systematic review reported an exercise-related adverse event although a minority reported appropriate exercise test methodology and monitoring. As such, based on the current literature, it is not possible to provide an evidence-based recommendation on the appropriateness of the existing PAR-Q or PARmed-X for pre-exercise screening in persons diagnosed with cancer.

Evidence-based absolute and relative contraindications to exercise and clinical decision trees

Conclusion no. 1: Based on current evidence, the risk-to-benefit ratio favors the recommendation of physical activity for all cancer patients.

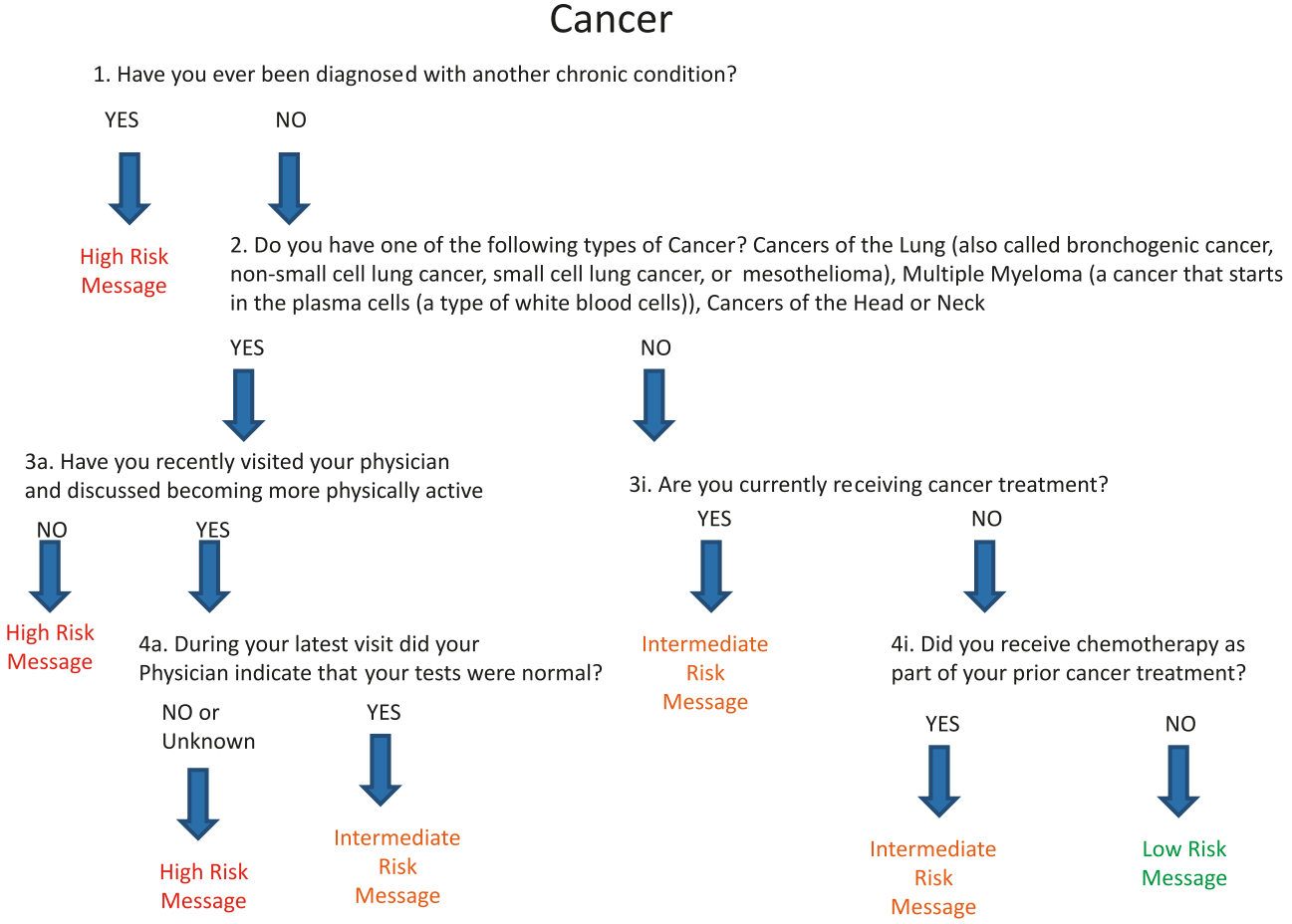
Recommendation no. 1: The demonstrated benefits of exercise training on select physiologic and psychosocial outcomes, the promising observational data of the relationship between regular physical activity and cancer recurrence and overall survival, combined with the low incidence of events, suggest that the risk-to-benefit ratio favors the recommendation of physical activity for all cancer patients (Level 2, Grade B).

Conclusion no. 2: There is no evidence to support any absolute or relative contraindications to physical activity in adults diagnosed with cancer. Despite this, an informed evaluation of potential contraindications and subsequent clinical decision trees is provided based on best available knowledge and clinical experience.

Recommendation no. 2: The ATS–ACCP absolute and relative contraindications appear appropriate for general physical activity in cancer patients but should be modified to include the absolute contraindications of presence of extensive skeletal or visceral metastases and anemia (Level 2, Grade B).

Although these absolute and contraindications are useful,

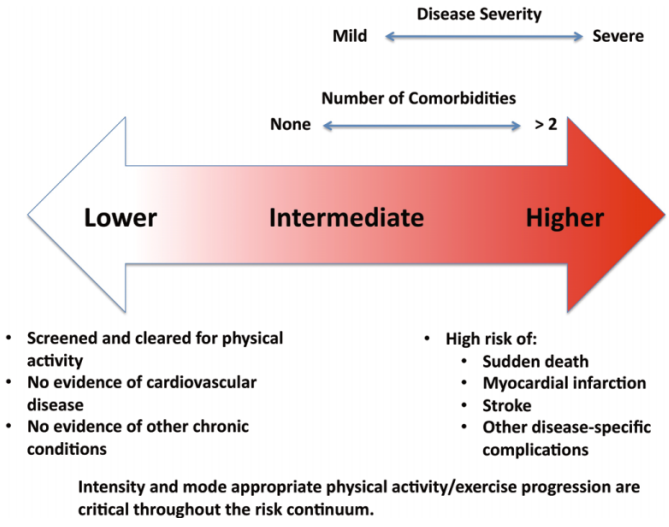
Fig. 1. Stage 1: Initial screening – oncology-specific PAR-Q – PARmed-X. Stage 2: Pre-exercise screening for a patient with a current or prior cancer diagnosis. Stage 3: Pre-exercise screening for a patient with a current or prior cancer diagnosis. Stage 4: Pre-exercise screening for patient with a current or prior cancer diagnosis. Stage 5: Pre-exercise screening for a patient with a current or prior cancer diagnosis.



oncology-specific clinical decision trees that can assist the qualified exercise professional, allied health professional, or physician in determining the level of pre-physical activity risk assessment are critical to optimize the safety of physical activity. Concurrently, such risk assessment guidelines must not unduly limit physical activity participation among cancer patients. Patients at high risk of an exercise-related event will very likely be captured by existing questions on the PAR-Q, thus there is no compelling evidence to modify this instrument for oncology patients. The exception is for patients with comorbidities such as CVD or CVD risk factors.

The PARmed-X is an exercise-specific checklist used by a physician with patients who have had positive responses to the PAR-Q. Currently, a diagnosis of cancer is not a specifically stated condition limiting exercise in the PARmed-X in its present form. Despite limited evidence, given that persons with cancer are typically older, present with a broad range of comorbid conditions, and receive a diverse range of loco-regional and systemic cytotoxic therapies, there is a strong case to include cancer as a precautionary category although cancer patients may experience a range of other conditions that can be captured by the existing categories (i.e., special prescriptive conditions). A clinical decision tree with appropriate probing questions to facilitate pre-physical activity risk assessment and exercise prescription guidelines is provided in Fig. 1. Operationalization of the risk stratification continuum is provided in Fig. 2.

Fig. 2. The disease risk continuum.



Conclusion no. 3: A prior cancer diagnosis does not mandate a PARmed-X referral to a physician or other allied health professional; however, the client can be referred to a

qualified exercise professional following an initial positive response to the PAR-Q (i.e., conformation of a prior cancer diagnosis) for secondary screening.

Recommendation no. 3: At the secondary qualified exercise professional screening, the primary question should focus on the type of cancer diagnosis and type of cancer therapy. Information on the type of cancer is of direct relevance to the risk of exercise-related events as well as the recommended exercise prescription (Level 3, Grade B).

Initial use of the PAR-Q should be undertaken when a client (i.e., person with cancer) opts to do any of the following: (*i*) undergo a fitness assessment, (*ii*) join a health club or sports team, (*iii*) work with a personal trainer, or (*iv*) decide to become much more physically active than current levels (i.e., above their habitual (daily) physical activity level or adopting a structured physical activity or exercise program). At the initial consultation, the PAR-Q should be administered by the qualified exercise professional. As stated, a diagnosis of cancer is not 1 of the 7 major screening questions in the PAR-Q; however, clients will likely, although not certainly, report a prior diagnosis of cancer when asked about other reasons that may limit physical activity participation.

It is not possible to screen or provide cancer-specific recommendations for all known cancer types; however, diagnoses of certain forms of cancer may be immediately informative. For example, patients with lung cancer or bronchogenic carcinoma may be at particularly high risk of an adverse given that the pathophysiology of the disease as well as the degree of concomitant comorbid disease associated with the typical smoking history (Jones et al. 2007*d*, 2007*e*). Other specific diagnoses include multiple myeloma, a disease associated with severe osteoporosis and osteolytic bone lesions putting patients at high risk of bone fractures (Edwards et al. 2008), and head and neck cancer, a disease associated with tobacco and alcohol abuse with increased presentation of cardiovascular disease (Mukerji et al. 2007; Nouraei et al. 2007). These clients are considered high risk and a PARmed-X referral to a physician or other allied heath professional is required for ECG, exercise testing, and even a bone scan (for persons with multiple myeloma). If testing is unremarkable, clients are cleared for physical activity. If testing is remarkable, and of course, depending on the result, clients may be cleared for supervised exercise training in a certified rehabilitation program or recommended for no structured exercise or physical activity.

Conclusion no. 4: Conventional and novel cancer therapy, particularly anthracycline- or trastuzumab-containing regimens, can have a broad range of adverse effects on the cardiovascular system that may increase the risk of an AE and have direct implications for the exercise prescription.

Recommendation no. 4: Clients undergoing therapies known to cause cardiotoxicity (e.g., anthracyclines, trastuzumab) require PARmed-X referral to a physician or other allied heath professional for blood and ECG tests and possibly exercise testing and cardiac imaging (Level 3, Grade B).

Patients with advanced (inoperable) disease will likely be receiving palliative therapy and hence will be captured by this question. Given that a large majority of these clients are likely to be older, heavily pretreated, and present with a range of comorbid conditions, exercise testing is recommended in the absence of extensive skeletal or visceral metastases. If testing is remarkable, and depending on the result, clients may be cleared for supervised exercise training in a certified rehabilitation program. Few medical centers currently provide cancer-specific rehabilitation programs but other standard certified programs (i.e., cardiac or pulmonary rehabilitation) are likely appropriate. Further research is required to determine whether a PARmed-X referral – screening is required for clients currently receiving other forms (nonanthracycline or trastuzumab) of cancer therapy.

Conclusion no. 5: Prior treatment with anthracycline- and (or) trastuzumab-containing regimens is associated with a diverse range of subclinical cardiovascular complications years or even decades following initial diagnosis that may increase the risk of an AE and have direct implications for the exercise prescription.

Recommendation no. 5: Clients who have received prior anthracycline- or tratuzumab-containing regimens are considered moderate risk, and require a PARmed-X referral to a physician or other allied heath professional for ECG and exercise testing. Clients who have not received prior anthracycline- or trastuzumab-containing chemotherapy are considered low risk, do not require a PARmed-X referral, and should be encouraged to exercise at low and (or) moderate intensity exercise (Level 3, Grade B).

Areas of research requiring further investigation

This review provided persuasive information for investigation of the following important questions in exercise oncology research:

1. Appropriate exercise testing and training methodology and data reporting of data outcomes and AEs is required among intervention and subjects assigned to the control group. Based on the current evidence, the reporting of exercise testing methodology, and data among adults with cancer suggests that the performance of these tests does not comply with national or international quality guidelines. To this end, we provide a comprehensive overview of the major recommendations for the specific performance of exercise testing in clinical oncology research. The adoption of consistent, standardized formal exercise-testing methodologies and data reporting standards are required to ensure high-quality exercise testing research in clinical oncology.
2. Elucidation of the most appropriate exercise prescription for cancer patients. Currently, the most appropriate and efficacious exercise prescription for cancer patients is not known. Adequately powered clinical trials are required to compare the effects of different exercise prescriptions on physiologic and psychosocial outcomes across different cancer populations. Also, physical activity dose-response studies are warranted.
3. Large-scale randomized trials on survival outcomes as well as biologic mechanisms or clinically-meaningful intermediate surrogate end-points of cancer recurrence and overall survival. Recent observational studies provide promising preliminary evidence that physical activity may favorably impact recurrence and survival outcomes in breast and colorectal cancer patients. Clearly, large-scale randomized trials are not required to confirm these findings. Of equal importance, parallel correlative science studies are required to elucidate the biologic mechanisms

underlying the hypothesized beneficial effect of physical activity on recurrence and survival outcomes in cancer populations.

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