Title: Physical activity and exercise guidelines for people with cancer: why are they needed, who should use them, and when?

Target audience: nurses, clinicians and allied health professionals involved in the provision of cancer care.

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Abstract:

Objectives: This report describes why there is a need for cancer-specific physical activity and exercise prescription guidelines, how the recommendations in the guidelines were derived, and how these guidelines can be used and by whom, to reduce cancer-related burden.

Data Source: Professional organizations and peer-reviewed manuscripts.

Results: Higher physical activity levels post-cancer diagnosis has been consistently associated with improved morbidity and/or survival outcomes for all-cancers studied to date. As such, although physical activity recommendations for those post-cancer are largely generic and tend to replicate physical activity guidelines endorsed for healthy adults, the cancer-specific epidemiological evidence-base suggest this to be appropriate. These guidelines should be endorsed and promoted by all members of the cancer care team, across all phases of cancer survivorship. Cancer-specific exercise prescription guidelines are supported by a clinical trial evidence-base and enable targeted exercise prescription for the benefit of the individual patient. Any member of the cancer care team can refer patients at any time to exercise professionals, who will use these exercise guidelines to direct their provision of exercise as medicine.

Conclusion: The prevention of physical activity declines and small increases in physical activity levels during and following cancer treatment is appropriate for the majority. Further, physical activity promotion, alongside incorporation of planned, purposeful, targeted and individualised exercise, has significant potential for reducing morbidity and mortality of cancer worldwide.

Implications for Nursing Practice: Nurses are well-placed to regularly encourage patients to participate in physical activity, and to refer patients to exercise professionals, during and following their cancer treatment.

Key words: exercise, physical activity, cancer, guidelines, prescription, survivorship

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Practical Implications:

- Cancer-specific evidence supports that promotion of broad public health messages related to physical activity, including *move more, sit less and be active for life*, as well as, *it is never too late to start, start slow and build gradually, doing something is better than nothing, and more is generally better than less*, will likely be appropriate for the majority of people diagnosed with cancer and should be promoted by all members of the cancer care team across all cancer survivorship phases.
- Exercise oncology prescription guidelines enable identification of appropriate dosage at any given time for any given individual and should be used to guide clinical practice for those with skills and experience in using exercise as medicine (exercise professionals).
- Participation in physical activity and targeted exercise prescription as part of cancer care, throughout all phases of cancer survivorship, has significant potential to reduce global burden of cancer.
- Nurses are well placed to regularly endorse and recommend patients to participate in physical activity, to refer patients to exercise professionals for individualized exercise prescription, and to lead all members of the cancer care team to do so.

Introduction: Global Cancer Burden

With more than 18 million new cancer diagnoses each year, and more than 9 million annual cancer-related deaths, cancer now accounts for the second largest disease burden globally.¹ While, societal, economic and lifestyle characteristics influence regional differences in common cancer types across the world, cancers highly associated with lifestyle factors, including physical activity levels, are increasing.¹ Reducing the growing cancer-related burden is a global priority, and improving physical activity rates and exercise participation post-cancer will help achieve this goal.

An exponentially expanding epidemiological and trial evidence base demonstrates that higher physical activity levels and exercise intervention post-diagnosis is associated with prevention and better management of treatment-related side effects, and improved function, quality of life and survival.^{2, 3} This consistent and compelling cancer-specific evidence has enabled the development of physical activity and exercise prescription guidelines for those diagnosed with cancer.⁴⁻⁶ This report describes why there is a need for cancer-specific physical activity and exercise prescription guidelines, how the recommendations in the guidelines were derived, and describes who should use which guidelines in their clinical practice in an endeavour to reduce cancer-related burden.

The need for cancer specific physical activity and exercise prescription guidelines:

While all cancers are characterised by the presence of abnormal cells with abnormal growth, the term ‘cancer’ encompasses several hundred diseases, diverse in nature, with diverse treatment options within and between any given cancer type.⁷ Treatment advances observed over the past decades have contributed to global improvements in survival rates following the majority of cancer types. Nonetheless, treatment brings risk of adverse events and toxicities,

and typical age-related functional declines are accelerated by the physiological impact of treatment, contributing to the presence of adverse effects and prematurely threatening overall function, health, quality of life and survival (Figure 1).³ As treatments for cancer have evolved, so too has the type and severity of treatment-related side effects that present. Nonetheless, some observations have remained consistent: (1) the majority of side effects tend to peak during active treatment, some of which are acute, resolving with or without intervention, while others remain persistent; (2) the presence of a pre-treatment symptom is associated with the presence or worsening of symptom(s) during or after treatment; (3) the presence of one side effect increases risk of developing additional side effects; and (4) the presence of cancer and its associated treatment increases risk of developing new cancers, recurrence and/or other chronic disease, such as cardiovascular disease, osteoporosis and type II diabetes.³ Determining what constitutes safe and effective physical activity and exercise prescription guidelines in the cancer population is dependent on the consideration of the complexities surrounding the disease and its treatment.

Cancer specific physical activity and exercise prescription guidelines:

Physical activity guidelines: The World Cancer Research Fund/American Institute for Cancer Research's (WCRF/AICR) Continuous Update Project represents the world's largest source of physical activity and cancer survivorship research, and produces guidelines based on findings from original research, and review of guidelines produced by other cancer organisations (e.g., National Comprehensive Cancer Network, American Cancer Society), as well as clinical and exercise associations (e.g., American College of Sports Medicine, American Society of Clinical Oncology). Overall, being physically active as part of everyday life and to walk more and sit less is endorsed.⁸ While not explicit, encouraging cancer

survivors to stay as active as possible represents efforts to improve physical activity levels in cancer survivors overall (who are less likely to participate in sufficient levels of physical activity for health compared with those who do not have cancer), and to prevent the physical activity declines typically observed during the treatment period.

More specific recommendations endorsed by cancer-associations worldwide, such as engage in 150 minutes or more of at least moderate-intensity physical activity each week and include muscle strengthening exercises at least twice a week, are also recognised by the WCRF/AICR.⁸ Recent meta-analyses using data derived from observational studies and exercise trials comparing highest versus lowest levels of post-diagnosis physical activity showed that for all-cancer and up to 11 specific cancers, hazards of all-cause and cancer-specific mortality was reduced (HRs: 0.58-0.79 and 0.57-0.79, respectively).² Inverse dose-response relationships between physical activity and breast cancer-specific and all-cause mortality were also identified, with steep reductions in risk up to 10-15 MET-hours/week, which equates to approximately 150 minutes of moderate-intensity physical activity per week.² Dose-response relationships between physical activity levels and other outcomes including fitness, function and quality of life have also been observed, with higher levels of physical activity associated with better outcomes, at least up until a point.^{9,10} While the total physical activity dose at which the relationship seems to plateau may differ depending on the outcome of interest, 150 minutes of moderate intensity activity seems generally appropriate for the majority of outcomes. As such, while cancer-specific physical activity guidelines are somewhat generic and largely replicate those promoted to healthy adults, the cancer-specific evidence suggests it is appropriate to do so.

Limitations of the original research contributing to the development of guidelines also need to be considered when deriving subsequent recommendations. Some limitations of note include the inability to infer causation, heterogeneity across studies in physical activity

assessment method and timing of measurement, and limited studies involving cancer types beyond breast, colorectal and prostate.^{2,9} As such, the ability to use findings to guide specific recommendations around mode of activity, and timing, frequency and duration of sessions is currently somewhat limited. Nonetheless, the strength and consistency of findings reported to date support that regular and broad endorsement of current physical activity recommendations for all cancer patients is warranted.

The target audience for these guidelines are *all* members of the cancer care team and *all* cancer patients. The timing of promotion of these guidelines to patients is at *any*, and ideally *multiple, times* across the cancer survivorship trajectory (Figure 2). With regular discussion of physical activity levels between one or multiple members of the cancer care team and a patient, at multiple time points, positive population-level improvements in physical activity (by way of minimising declines in physical activity that typically occur during the treatment, or increasing, even if minimally, physical activity during and beyond treatment) would contribute to reducing burden of cancer (Figure 3). Nurses are well-placed to lead discussion about physical activity and exercise since they: 1) naturally develop trust and rapport with patients who are often overwhelmed with information; 2) commonly provide education to patients on several aspects of cancer care (e.g. managing side effects, taking medication) and 3) have high frequency and regular contact with patients.^{11, 12}

Exercise prescription guidelines: While the weight of the epidemiological evidence gives permission for endorsement of physical activity as a means of improving quality and quantity of life following a cancer diagnosis, the use of exercise as a form of treatment to improve individual outcomes requires more detailed consideration of the cancer-specific trial evidence-base. Recently, the Exercise and Sports Science Australia (ESSA) and the American College of Sports Medicine (ACSM) critically appraised this evidence base to update their

exercise prescription guidelines for cancer survivors that were first published in 2009 and 2010., respectively^{13, 14} The ACSM guidelines provide exercise prescription recommendations specific to cancer outcomes with a sufficient evidence-base available to do so.⁶ These included fatigue, physical functioning, anxiety, depressive symptoms and health-related quality of life. The ESSA guidelines use the wider evidence base (including outcomes with weaker evidence) to present an exercise prescription framework that enables the application of cancer-specific considerations for individualisation, specificity, safety, feasibility and progression of exercise for all patients.⁴ The ESSA guidelines also provide specific exercise prescription considerations for the presence of haematological, musculoskeletal, systemic, cardiovascular, lymphatic, gastrointestinal, genitourinary and neurological disease- and treatment-related concerns.

Balancing the strengths with the limitations of the above evidence-base is clearly important when devising individualized, targeted exercise prescription. For example, serious adverse events with exercise during and following cancer treatment have been reported at <5%, with no life-threatening adverse event or death associated with exercise reported in any exercise and oncology clinical trial.^{15, 16} Also, exercise is considered highly feasible for cancer survivors as is supported by low withdrawal and high adherence rates, even when reviews have focused on cancer cohorts considered at higher-risk of harm (e.g., those with stage II+ disease and at least one additional comorbidity) and less likely to adhere to exercise targets, and are similar irrespective of intervention duration, exercise type and frequency evaluated and level of supervision provided¹⁶. As such, these findings support that exercise is safe and feasible for people with cancer. However, exercise trials are renowned for recruiting younger, healthier (fitter) cancer survivors who have a history of exercise pre-diagnosis.¹⁷ This ‘sample bias’ may make it less likely to observe harm (injury or worsening treatment-related side

effects, disease progression or death and/or loss of confidence, dignity and sense of control) associated with exercise, and more likely for the sample to adhere to exercise targets.

Efficacy, safety and feasibility findings have been informed from a range of study designs (efficacy through to effectiveness trials) evaluating exercise interventions with varying levels of frequency, intensity, duration and exercise type and overall exercise prescription targets.^{18, 19} Trends in the data suggest that exercise adherence is lower when not supervised, and that higher intensities are more commonly prescribed in efficacy trials (highly supervised), while lower intensity, aerobic only exercise is more common in dissemination trials (low or no supervision).¹⁸ Also, examination of feasibility data presented in any one trial highlights that while overall exercise seems feasible during and following treatment, this is not the case for all participants in these studies (e.g., exercise adherence in any given study may range from 0-100%^{16, 20, 21}). To benefit from exercise, the majority of cancer patients lack understanding and confidence regarding what to do, when and how and therefore require the provision of cancer-specific exercise advice, education and support⁴. Consequently, while endorsing participation in regular physical activity for the majority may be appropriate, ensuring exercise is safe, feasible and effective, requires an individualized, targeted approach that considers cancer-specific factors when determining optimal exercise starting points (including exercise mode, intensity, frequency and duration), appropriate weekly targets and pace of progression (Figure 1). The purpose of the ESSA and ACSM exercise prescription guidelines is to provide evidence-based, cancer-specific advice for appropriately qualified allied health professionals (who have the necessary qualifications, skills and experiences in prescribing exercise to special populations) in their clinical practice.

Phases of cancer survivorship and opportunities for promoting physical activity and integrating exercise into cancer care.

The term ‘cancer survivorship’ can be used to encompass the period of time from first cancer diagnosis through to end of life, including pre-treatment, active treatment (with curative, prevention of progression or palliative intent) and post-treatment phases (Figure 2). The duration of each phase may range from less than one week through to several years, with a range of factors (e.g., age, type and stage of cancer, place of residence) influencing duration. Promotion of physical activity guidelines is relevant across all phases of cancer survivorship for the majority and has the intent on improving physical activity levels when relevant or keeping cancer survivors as active as possible for as long as possible. In contrast, survival expectations, presence, severity and risk of developing new treatment-related side effects, life goals and priorities, as well as anticipated duration of treatment (or treatment cessation) will influence the perceived urgency to achieve patient-driven objectives/goals through exercise prescription during each survivorship phase. Further, the potential for benefit through exercise and subsequent exercise prescription goals will require monitoring and redefining over time as a patient transitions between phases of cancer survivorship. The multiple phases of cancer survivorship highlight the numerous opportunities that present for endorsement and promotion of participation in physical activity and using exercise as medicine following a cancer diagnosis. Due to the frequency of contact and as a consequence of this contact typically spanning all phases of cancer survivorship, oncology nurses can play a central role in these endeavours.

The practical application of physical activity and exercise prescription guidelines

Knowledge about the existence and context of physical activity and exercise prescription guidelines differ between countries, and within any given country the perceived importance of these guidelines varies. Time constraints, limited access to allied health professionals skilled in oncology exercise prescription, and reimbursement (or lack thereof) continue to represent

major challenges that need to be overcome for cancer burden to be systematically reduced through physical activity and exercise. Additionally, the role of “physical activity educator” is not assigned to, nor adopted by a particular oncology team member and as such is a conversation commonly neglected. A potential way to fill this void is for nursing staff to add key messages about physical activity and exercise within already existing education sessions, whereby topics such as managing treatment-related side effects are routinely addressed. In doing so, this would allow for the formal introduction and discussion about physical activity and exercise being an important part of cancer care. Subsequent to these formal discussions, more informal ‘check-ins’ could then occur at multiple cancer survivorship phases, which may provide opportunities for referral to exercise professionals or to existing cancer rehabilitation programs.

While there are a growing number of community-based, supervised, group exercise programs available at no or relatively low-cost for cancer survivors across the world, and access to allied health professionals with skills in exercise oncology have improved, inequities in access and reimbursement remain. Those of lower socioeconomic status, residing outside urban cities, as well as those with higher needs (such as those with higher stage disease, persistent treatment-related toxicities, additional comorbidities or chronic disease and those who are sedentary or insufficiently active) are more likely to lack access and reimbursement.²²⁻²⁴ Nonetheless, cancer care can be improved immediately if all members of the health care team encourage and promote international physical activity recommendations to their patients, as soon as possible and as often as possible. Further, all members of the clinical team can take responsibility for encouraging patients to access exercise professionals for the purposes of integrating targeted, exercise prescription into cancer care. Oncology nurses could lead the way in these endeavours, while also encouraging other members of the cancer care team to do so. Of note, lack of awareness regarding availability of exercise

professionals or cancer rehabilitation programs should not prevent members of the cancer team to promote physical activity and exercise. Instead, with encouragement patients themselves can be empowered to play an active role in identifying affordable and accessible exercise services.

Ongoing and future cohort and trial studies will continue to push the boundaries of evidence, which in turn will help refine physical activity and exercise prescription guidelines for cancer patients over time. Large, epidemiological studies that integrate objective measurement of physical activity, such as the AMBER study,²⁵ will better determine minimum and maximum threshold for benefit from physical activity and to what extent timing of physical activity (pre-diagnosis, during treatment, post-treatment), cancer type (or subtype) or other factors may influence these limits. Findings from exercise clinical trials designed to evaluate understudied outcomes, such as survival, adherence to adjuvant treatment, cost-effectiveness, and/or trials that focus on understudied groups, will be used to refine targeted exercise prescription guidelines. Further, international research efforts, which can quantify health care savings through exercise in cancer management may help improve funding of service provision in the future. There currently exists ongoing clinical trials, which are specifically designed to evaluate the effect of exercise during and following treatment for colorectal, metastatic prostate, ovarian cancer and for allogeneic haemopoietic stem cell transplant patients, on survival outcomes²⁶⁻²⁹. Positive findings from these studies would demonstrate cause-and-effect whereby targeted exercise directly improves survival outcomes, and would consequently provide strong argument for incorporating exercise into best practice cancer management. Unfortunately, until exercise is proven to benefit cancer survival outcomes cost-effectively, improvements in the current reimbursement setting may be limited and will likely be reliant on consumer advocacy.

While ongoing and future research efforts continue to address evidence gaps, it is nonetheless already clear that the tide has turned – the strength and consistency of the current epidemiological and trial evidence clearly supports promotion of physical activity, alongside targeted, exercise prescription, to those with cancer. Further, through application of these guidelines in cancer care, the potential for population and individual benefit and subsequent reductions in global cancer burden is significant.

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Figure Legend

Figure 1: The accelerated aging process associated with cancer and its treatment.

Figure 2: Phase of cancer survivorship and potential benefit through application of physical activity and exercise prescription guidelines.

Figure 3: Population versus individual recommendations and potential effects.

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