

Is Unsupervised Exercise Following Breast Cancer Safe for All Women?

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Introduction

One in eight women living in developed countries will be diagnosed with breast cancer before the age of 85, with the mean age at first diagnosis approximately 60 years. Stage I represents just under 50% of diagnoses, while 45% of cases are diagnosed at later stages (stages II to IV; the remainder being unknown stage) [1-3]. Breast cancer continues to be the most common cause of cancer-related deaths in women [3,4], and although survival for women with stage I disease is high (98% 5-year relative survival), survival is significantly lower for those diagnosed with more advanced disease stage (i.e., stages II to IV, 83%; an unknown stage, 50%) [1,3,5].

Natural History of Wellbeing and Decline after Breast Cancer

Breast cancer treatment has long been associated with an array of significant and enduring physical and psychosocial consequences, including reduced upper-body function, quality of life, poor body image, fatigue, increases in body weight and adverse changes to body composition [6-9]. Declines in fitness, physical and psychosocial function and quality of life typically occur during the active treatment period. Current conservative estimates from a prospective, cohort study suggested that at six months post-diagnosis, 90% of women report at least one significant adverse treatment effect (including fatigue, pain, lymphoedema, weight gain) and 60% report multiple sequelae [10]. While outcomes improve following treatment completion and up to approximately 12 months post-diagnosis [11], function and fitness typically fail to reach pre-diagnosis levels and remain at levels lower than age-matched norms [12].

Further, beyond the 18-24 month post-diagnosis period, the rate of 'typical' age-related declines in fitness and function are faster for women who have had breast cancer, when compared with age-matched normative data [13].

Physical and Psychosocial Benefits of Exercise

Summarised in multiple meta-analyses and systematic reviews, results from exercise trials involving women with breast cancer clearly demonstrate that exercising during and following treatment leads to attenuation of treatment-related morbidity and multiple physical and psychosocial health benefits, all of which optimise quality of life [14,15]. The clinical relevance of these findings are highlighted by data which demonstrate that outcomes of interest improve to levels higher than pre-diagnosis following participation in exercise during the treatment period; and, levels exceed age-matched norms following participation in post-treatment exercise interventions [12]. Exercise has also been associated with reduced risk of comorbidities for which

breast cancer survivors are at increased risk, including osteoporosis, diabetes, and heart disease [16,17]. Further, results of a meta-analysis of findings derived from cohort studies demonstrated that exercising post-diagnosis is associated with 41% reduced all-cause mortality, 34% fewer breast cancer deaths, and 24% reduced risk of disease recurrence; this effect was independent of other prognostic factors including stage of disease and being overweight or obese [18]. Thus, incorporating exercise into standard breast cancer care has real potential for positively influencing the lives of women with breast cancer.

Patterns of Physical Activity Following Breast Cancer Diagnosis

Evidence from population-based breast cancer cohort studies demonstrate that the minority of women (~30%) participate in sufficient levels of physical activity (>150 minutes/week) post-diagnosis and the majority (>60%) experience declines in exercise levels post-diagnosis, with levels failing to return to pre-diagnosis levels even 2-years post-diagnosis [19-21]. Importantly, insufficient levels of exercise and declines in exercise following breast cancer are associated with higher rates of: fatigue, sleep disturbance, cognition problems, reduced upper-body function and overall function, depression and anxiety, and lower quality of life [10,22-25].

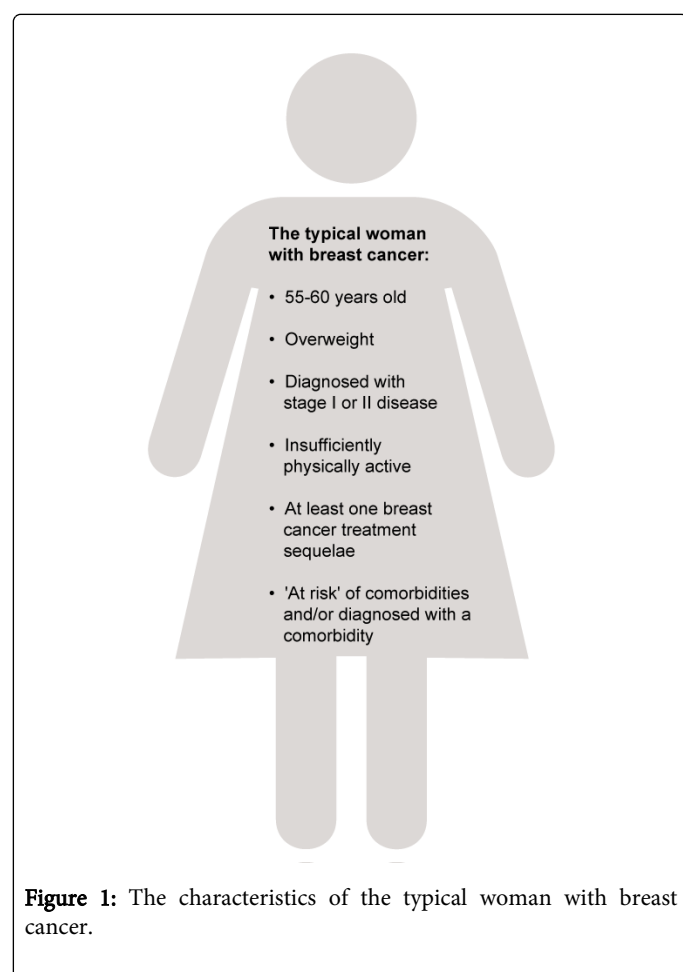
Exercise Prescription Guidelines

Numerous studies have been conducted among women with breast cancer and substantial evidence is now available from exercise trials for breast cancer survivors during and after treatment. Specifically, aerobic and resistance training is widely accepted and promoted as safe and beneficial for women during and following breast cancer treatment [26-28].

In practice, this advice is given in writing and exercise is prescribed to be performed by the survivor in an unsupervised setting (e.g., home or community). At best, survivors are offered a brief program supervised by someone with minimal training in the potential risks of exercise after breast cancer. However, it has been suggested that a response bias exists in exercise intervention trials, with participants likely to be younger, healthier, and have a history of exercise participation, compared with the wider breast cancer cohort. Therefore, questions remain about the appropriateness of these exercise guidelines for all women diagnosed with breast cancer.

Characteristics of Participants in Exercise Intervention Trials Conducted During or Following Treatment: Findings from a Systematic Literature Review

We performed a literature review to compare 1) the eligibility criteria of exercise and breast cancer studies conducted during and following treatment for breast cancer and 2) the characteristics of recruited samples to the 'typical' breast cancer survivor. We hypothesized that safety, feasibility and potential effect of exercise during or following treatment for breast cancer in a 'typical' women with breast cancer (aged 55-60 years, engages in insufficient levels of weekly physical activity, is overweight, has one or more breast cancer treatment sequelae and may also have another comorbidity [e.g., osteopenia, hypertension], Figure 1) is yet to be properly established.



The data used to determine these characteristics come from population norm data as well as findings from cohort studies describing women post breast cancer.

The meta-analysis by Speck et al. [15] was used as the basis for the database search. Included studies were those published in English, included adult women diagnosed with breast cancer (studies including other cancers in addition to breast cancer were included if the breast cancer data was reported separately), evaluated an intervention designed to increase physical activity and included a concurrent comparison group.

PubMed search terms were “(exercise or physical activity)” and “cancer”, with 31 March, 2014 defined as the end of the search period. Abstracts were reviewed to identify potentially eligible studies for inclusion in the review, with eligibility subsequently confirmed via review of full text. Inclusion and exclusion criteria, and relevant baseline characteristics of study sample, were extracted for each study. Where possible, baseline characteristics were compared with United States of America, Canadian and Australian normative ranges for breast cancer survivors (data sourced from government publications and longitudinal cohort studies, [2,3,29,30]).

73 studies met the criteria for inclusion in this literature review; 25 studies evaluating exercise during treatment, and 48 studies evaluating exercise after breast cancer treatment (Table 1). A typical exercise program in these studies consisted of 30 minutes of supervised, moderate-intensity aerobic or mixed (aerobic and resistance) exercise, three times a week for 2-3 months. However, the prescriptive characteristics varied greatly across studies with mode being aerobic-only, resistance only or mixed type. Aerobic-based exercise was prescribed for durations of 10-60 minutes per session and 20-300 minutes/week with exercise frequency of 1-7 days of exercise/week. Exercise intensity ranged from light to vigorous.

Resistance-based exercise prescription ranged from 1-4 sets of 6-20 repetitions at intensities of 50-80% of one-repetition maximum, 2-3 times per week, targeting small and large muscle groups. An example of a more novel exercise prescription was one that included additional exercises such as lower body impact loading involving jumping whilst wearing a weighted vest [31]. The progression of the exercise program or the degree to which programs were individualized was usually not well defined, but when described was reflective of applying standard exercise prescription principles.

Studies with the following exclusion criteria	Studies of exercise trials	
	During treatment (n= 25) ^a n (%)	After treatment (n=48) ^b n (%)
Comorbidities and medical conditions		
Obesity (Body Mass Index>35, >40 or >50 kg/m ²)	2 (8) [47,52]	7 (15) [54,59,75,82,83,95,96]
Hypertension	9 (36)	11 (23)

	[37-39,42,43,46,49,51,53]	[12,54,60,62,72,73,75,80,82,100,101]
Known cardiac disease /uncontrolled/ severe/ cardiovascular disease	14 (56) [34,35,37-39,41,43-49,51]	17 (35) [12,55,60,62,67-69,72,73,76-80,84,85,102]
Acute or chronic respiratory disease	10 (40) [34,37,41,43-49]	3 (6) [67,84,102]
Psychological or psychiatric disorders/ diseases (current and/or history)	11 (44) [33,38-40,43-45,50, 52,53,97]	10 (21) [12,57,60,61,70,78,86,92,99,102]
Neurological/ cognitive dysfunction	4 (16) [37,47-49]	1 (2) [99]
Thyroid disease/uncontrolled	0 (0)	2 (4) [12,60]
Diabetes/type II diabetes	1 (4) [53]	9 (19) [12,60,64,65,68,73,76-78]
Renal or hepatic disease	1 (4) [97]	0 (0)
Major orthopaedic limitations/verified osteoporosis/ severe arthritis/high risk of fracture	3 (12) [35,50,52,97]	12 (25) [31,55,69,72,76,78-80,85,92,100,101]
Symptomatic bone metastases/ known metastatic disease	4 (16) [44,45,97,98]	12 (25) [12,57,58,61,67,72,73,79-81,86,102]
Infection, immune or endocrine abnormality	2 (8) [50,98]	7 (15) [12,60,67,80,96,101,102]
Disease- and treatment-related sequelae		
Insomnia	0 (0)	1 (2) [61]
Severe nausea	1 (4) [52]	1 (2) [92]
Anorexia	0 (0)	1 (2) [92]
Lymphoedema	0 (0)	2 (4) [62,101]
Uncontrolled pain/ bone pain/ > 2 on 0-10 pain scale	2 (8) [52,98]	1 (2) [62]
Abnormal levels in blood tests	1 (4) [46]	0 (0)
Incomplete axillary surgery / trans-abdominal rectus abdominus muscle reconstructive surgery	2 (8) [38,39]	0 (0)
General exclusion relating to physical function, overall health and/or ability to exercise, e.g., "any medical (physical and/or psychological) conditions that may limit participation"	16 (64) [33-36,40-48,52,53,97]	28 (58) [54,56,58,59,61,62,67,68,70,72-80,82-86,90,91,96,99,102]
a[32-53,87,97,98] b[12,31, 54-86,88-96,99-102]		

Table 1: Number of exercise studies for women with breast cancer conducted during and after treatment with specific exclusion criteria.

The majority of studies (77%)[12,32-86] restricted eligibility on the basis of medical conditions, physical function, or treatment-related sequelae (Table 1), with studies listing between one and eight of the following conditions as reasons for exclusions:

Comorbidities such as hypertension, cardiac conditions or cardiovascular disease, mental health issues (e.g., anxiety or depression psychiatric conditions), cognitive dysfunction, orthopedic conditions, obesity (various body mass index cut-offs), diabetes, thyroid disease, renal disease; Treatment-related sequelae such as severe nausea, low functional performance (e.g. Zubrod scale: "Symptomatic, >50% in bed, but not bedbound"), uncontrolled pain, lymphoedema, insomnia, infection risk, immune or endocrine abnormality or bony metastases; and/or a global exclusion statement relating to limited function or potential exercise contraindications. For example, "any medical (physical and/or psychological) conditions that may limit participation" (60% [44/73] included a statement similar to this in the exclusion criteria).

Four studies did not report any exclusion criteria [31,87-89] and 13 studies targeted recruitment of women who had a specific condition or disease burden (including obesity [based on BMI] [n=3] [90-92], lymphoedema [n=3] [93-95], low bone mineral density [n=2] [96,97], advanced/stage IV disease (n=1) [98], or high pain or fatigue, reduced function or a combination of these conditions [n=4] [86,99-101]). Thirty one of 73 studies excluded women who reported regular weekly physical activity [31,36,37,41,45,47-50,53-56,58,62,64,65,68-70,74-79, 82,84,86, 92,102] (eligibility definitions ranged from excluding women who engaged in physical activity one or more times or for more than 40 minutes each week, to excluding only very active women [those who engaged in ≥ 250 minutes of moderate physical activity or equivalent each week]).

The average age of participants for the majority of studies (42/73) [31,32,37-43,45-54,57-59,61,63,66-70,72,74,76,78,79,84,87,88,97,98,100,101] was younger than the estimated international average age of women diagnosed with breast cancer (<56 years versus 56-61.5 years, respectively). In fact, one half of women diagnosed with breast cancer in the United States are aged over 65 years [103]. Almost one-third of studies (n=20) did not report on stage of disease of participants [32,34,35,37,43,49,51,58,59,66,71,73,80,81,84,91-93,96,99]. For those studies that did (n=53), most (81% [12,31,33,36,38-42,44-47,50,53-55,60,61,63-65,67-70,72,74,75,79,82,83, 85-90,95,97,100,101]) recruited participants with stages I-III breast cancer, with the proportions of women with stage I versus II+ considered similar to population norms. Three studies reported inclusion of stage IV disease [56,77,98].

Of the 42 studies that did not exclude women based on baseline physical activity levels [12,32-35,38-40,42-44,46,49,51,52,57,59-61,63,66,67,71-73,80,81,83,85, 87-91,94-101], physical activity levels of the sample were only described in 43% and 46% of studies conducted during [32,37,38,42,45,49,53] and following [12,60,64,65,69,72,80,83,85,90,91,100] treatment respectively. Of those that reported baseline physical activity data, between 30-60% of the samples were regularly active before commencement of the intervention. Past physical activity level (e.g., physical activity levels pre-breast cancer) was reported in 3 studies; 49-75% of participants in these studies were regularly physically active prior to breast cancer diagnosis [40,51,80]. The presence of comorbidities or treatment-related sequelae was not reported by any included study.

No serious adverse events were reported in any of the studies included in this systematic review. Adverse events that were reported were similar to those that would be expected in a non-cancer population and were considered minor and acute. Examples include an individual mentioning "knee discomfort" [87], a mild hematoma at

the site of a blood draw and two participants who were referred to their usual health care provider due to elevated blood pressure during a treadmill fitness test (they remained in the exercise intervention with no further events [102]).

Implications of Findings

Findings from the systematic literature support the notion that women participating in exercise trials conducted during or following treatment for breast cancer tended to be younger, more likely to have less advanced disease, and were likely to be more well than the 'typical' woman with breast cancer. Two key findings support this suggestion. First, eligibility criteria of the majority of studies restricted the ability to recruit samples representative of the wider breast cancer population. For example, population data suggests 20% of women aged 50-69 years have one or more comorbidities at the time of breast cancer diagnosis and this rate increases to 55% for older women [104]. The most common comorbidities across all age groups of women with breast cancer are cardiovascular disease, diabetes, chronic obstructive pulmonary disease and stroke [17,104]. Yet, these are the same concerns listed as exclusion criteria for some studies included in the review. Second, based on reported sample characteristics, women in exercise trials were of younger age and few studies included women with advanced disease.

Quantifying the extent (or lack thereof) to which exercise samples were representative of the wider breast cancer population was hindered by the lack of information reported on important patient-characteristics including pre-diagnosis and baseline physical activity levels, weight and proportions in the healthy versus overweight categories, as well as presence of treatment-related side effects and/or comorbidities. However, the absence of this information provides strength to the suggestion that findings from exercise intervention trials lack generalizability to the wider breast cancer population. Evidence from cohort studies clearly highlights the relationship between lower levels of physical activity post-breast cancer and older age, more advanced disease, presence of treatment-related side effects and/or other comorbidities [105-107]. Therefore, it can be assumed that women with these characteristics would be less likely to volunteer for participating in an exercise trial, and they may be less likely encouraged to do so by clinic staff. That is, time constraints within the clinic and competing priorities may influence the type of woman who ultimately gets invited to participate in an exercise trial. For example, discussions about an exercise trial would be more difficult to have with a woman who has upcoming adjuvant therapy and is dealing with lymphoedema, compared with a woman who had a lumpectomy and sentinel node biopsy, and has no treatment-related sequelae. Unfortunately, the lack of inclusion of these women in exercise intervention trials could have implications to study findings relating to safety, feasibility and effect.

While representativeness of findings derived from the broader exercise and breast cancer trial evidence-base is questionable, findings from individual exercise studies within and beyond the breast cancer setting can provide some understanding about safety, feasibility and efficacy of exercise. For example, supervised, progressive exercise programs have been demonstrated to be safe and feasible for bone marrow transplant patients [108,109], colorectal cancer patients [110], and women undertaking chemotherapy for ovarian cancer [111]. These patient groups could be considered more unwell than the average woman with breast cancer. Further, non-randomised trial evidence has demonstrated women with advanced breast cancer can

safely and feasibly participate in exercise trials [112,113]. However, again, the exercise intervention tested was supervised and prescription individualised. With respect to efficacy of exercise, it is plausible that the potential benefit accrued through exercise is in the conservative direction. More advanced disease, presence of comorbidities, poorer lifestyle characteristics and more problematic recoveries are associated with lower levels of function, fitness, quality of life and survival. Therefore, assuming exercise is safe and feasible, capacity for positive change via exercise is likely much higher for the 'unwell' woman with breast cancer compared with the younger, healthier woman.

Undoubtedly, the field of exercise and breast cancer has developed considerably since the pioneering studies published in the early 1980s. Over time, sample sizes have generally increased, quality of design and reporting has improved significantly, cancer cohorts other than breast have been evaluated and findings from large efficacy, as well as effectiveness trials, are available. The findings from these studies have provided the platform from which exercise recommendations for cancer survivors have been developed, with these guidelines endorsed and promoted by various national exercise and cancer organizations [26-28]. However, it is important to remember that over 80% of participants in exercise and cancer trials are women with breast cancer [15] and the findings from the review presented in this commentary highlight the potential for participant bias, with that bias having potential implications about what we know regarding exercise safety, feasibility and effect.

Recommendations for Future Research

To continue to advance knowledge, pragmatic studies with representative samples evaluating 'real-world' exercise trials, as well as more studies with eligibility criteria that target subgroups of the breast cancer population that are currently under-represented in exercise trial, are needed. Involving oncology clinical professionals as stakeholders in future research may assist with understanding why referrals occur or do not occur within the population of breast cancer survivors. Further, developing an understanding as to why women participate in exercise trials and/or participate in regular exercise without programmatic support would provide useful insight into how to get and keep women active during and beyond their breast cancer experience. Findings from such research will help address research gaps and aid the international endeavor of incorporating exercise into standard cancer care.

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