Perspective
Perspective on Irwin et al., p. 522

Exercise for Secondary Prevention of Breast Cancer: Moving from Evidence to Changing Clinical Practice

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Abstract

Relating to the report of Irwin and colleagues in this issue of the journal (beginning on page 522), this perspective discusses exercise training interventions as secondary prevention in breast cancer survivors. Burgeoning observational evidence indicates that prescribing aerobic exercise of 3 hours or more per week could have meaningful mortality and morbidity benefits for breast cancer survivors. Adherence to this exercise prescription, however, will require an infrastructure to guide survivors and to address the common clinical treatment sequelae that might interfere with survivors' ability to regularly perform this level of activity (e.g., symptoms related to estrogen deprivation, arthralgias due to aromatase inhibitors, fatigue, lymphedema, chemotherapy-induced peripheral neuropathy, osteoporosis, upper-extremity functional impairments, and overall functional decline). On the basis of cardiac rehabilitation, a model is proposed to integrate exercise prescription into breast cancer survivor clinical care, with referral to community-based programs for most women. *Cancer Prev Res; 4(4); 476–80. ©2011 AACR.*

The article by Irwin and colleagues appearing elsewhere in this issue of the journal (1) adds to prior strong prospective observational studies demonstrating decreased overall and disease-specific mortality among more versus less physically active breast cancer survivors. A 2010 meta-analysis included 6 prior studies on this topic (2). As with the study of Irwin and colleagues, the meta-analysis analyzed distinct effects of physical activity measured pre- versus postdiagnosis. The meta-analysis summary estimates of the reduction of breast cancer-specific and all-cause mortality for the women who self-reported the most compared to the least pre-diagnosis physical activity were 7% and 18%, respectively. These estimates were based on pooled data from 2 studies each for breast cancer–specific (3, 4) and all-cause mortality (3, 5). Irwin and colleagues reported reductions of 29% for breast cancer–specific and 39% for overall mortality among the most- versus least-active women prediagnosis.

Unfortunately, physical activity levels decline after diagnosis (6) and functional status remains lower among a substantial minority of breast cancer survivors for over 5 years after diagnosis (7, 8). These issues make it difficult to conclude that data on prediagnosis physical activity are relevant for examining the mortality benefit of exercise in

survivors. In short, the women who are active before diagnosis may not be able to be active after diagnosis. Therefore, it is of interest to understand whether physical activity *after* diagnosis confers benefits. In the 2010 meta-analysis, summary estimates based on pooled effects from 4 studies (3, 9–11) showed that breast cancer–specific mortality was reduced 34% and all-cause mortality was reduced 41% for the women who reported being most versus least active postdiagnosis. Irwin and colleagues observed mortality reductions of 39% (breast cancer–specific) and 46% (overall) among women with the most versus least postdiagnosis physical activity in the Women's Health Initiative (WHI) cohort.

Knowing that postdiagnosis physical activity levels are associated with mortality outcomes of breast cancer survivors moves us past the limiting viewpoint that lower mortality results from pre- rather than postdiagnosis activity and further builds the case for postdiagnosis exercise interventions as secondary prevention (i.e., prevention of second cancers and mortality in survivors). However, there are still limitations to the conclusion that benefits result from postdiagnosis physical activity, including the possibility that women who are not able to be active after a cancer diagnosis may differ in other ways that explain their poorer outcomes. For example, women who are inactive postdiagnosis may have had higher stage disease and thus may be more likely to experience recurrence or mortality. Irwin and colleagues address this limitation in an analysis of WHI data showing that mortality benefits are roughly equivalent across disease stage. Another limitation in interpreting postdiagnosis data is the possibility that differences (other than disease stage) between postdiagnosis active and inactive women somehow preclude the usefulness

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of intervening to increase activity level. Irwin and colleagues used the unique pre- and postdiagnosis physical activity data in the WHI dataset to address this limitation. They demonstrated that women who increase physical activity after diagnosis or remain active after diagnosis have a meaningful overall (33%) mortality benefit, although disease-specific mortality did not decline with increased activity after diagnosis. Irwin and colleagues use their WHI cohort findings in the context of earlier findings (2) to call for a large randomized controlled trial (RCT) of exercise in preventing breast cancer recurrence and improving mortality outcomes.

There are multiple challenges inherent in doing an exercise intervention trial with a primary outcome of breast cancer recurrence or mortality, including the requirement of large sample sizes and/or many years of follow-up due to the small number of events per year. Efforts are underway in the United States and Australia to make a large exercise intervention RCT happen. However, it is important to note that a definitive secondary prevention trial was never accomplished for exercise and heart disease (12). The individual trials were ultimately underpowered to detect a significant treatment effect. One common observation from these trials was that there were fewer outcomes in the control group than expected (13). It was suspected that the level of care provided to the "usual care" control groups may have exceeded the usual care provided to similar patients not participating in the trial. This excess of "usual care" is likely to be an issue for trials of exercise for secondary prevention of breast cancer as well. Several meta-analyses, the first of which was published in 1988 (12), pooled effects across trials and finally established the benefits of exercise for mortality outcomes after myocardial infarction. Of interest, Medicare started reimbursing for cardiac rehabilitation programs in 1982 (14), 6 years prior to published evidence of mortality benefit. Therefore, the process of developing and disseminating exercise programs for cardiac patients was based not solely on mortality but on other merits as well including functional and health care–cost benefits. Is it possible that the same would hold true for breast cancer survivors?

As with cardiac patients, facing the risk of recurrence and mortality is only one of multiple challenges common to the cancer survivorship experience. Breast cancer survivors also face the risk of significant clinical sequelae of cancer and its treatments, and these issues will need to be addressed if we are to intervene with exercise for mortality benefit. In heart disease, people at a high risk of cardiac arrhythmias are not ready to buy a home treadmill and/or head to the local fitness center for unsupervised exercise. Analogously, breast cancer survivors with or at risk for functional disability, arthralgia, fatigue, neuropathy, or lymphedema may also require a structured rehabilitation option before eventually progressing to safe unsupervised exercise. But how often do these clinical morbidities occur? What is the evidence that exercise can have a beneficial impact on these morbidities? And how do we keep women who need a structured

rehabilitation option safe from harm while avoiding the creation of unnecessary barriers to start an exercise program for the women for whom these morbidities are highly unlikely?

Common clinical sequelae of breast cancer treatment include symptoms related to estrogen deprivation, arthralgias due to aromatase inhibitors, fatigue, lymphedema, chemotherapy-induced peripheral neuropathy, osteoporosis or reduced bone health, upper-extremity functional impairments, and overall functional decline (7, 8, 15–19). The prevalence of each of these individual sequelae varies according to treatment. For example, the 50% incidence of chemotherapy-induced peripheral neuropathy is specifically associated with the agent paclitaxel (18). Published estimates of lymphedema incidence range from 3% for women who undergo sentinel lymph node biopsy and no radiation (20) to 70% in women who undergo axillary dissection (21). To our knowledge, however, there are no studies that account for overlapping treatment sequelae to provide an overall estimate of the proportion of breast cancer survivors who experience at least one of the aforementioned sequelae during the first or second year after diagnosis. What if a woman received paclitaxel and had an axillary dissection? How many women have chemotherapy-induced peripheral neuropathy combined with lymphedema or have only one or the other? It seems unlikely that the women who experience neuropathies never experience lymphedema, so adding up the cumulative incidence proportions would not be appropriate. On the opposite extreme, it also seems exceedingly unlikely that the women who experience lymphedema are the only ones experiencing neuropathy, so assuming that the morbidity with the highest cumulative incidence is equivalent to the proportion that will experience any clinical morbidity is also inappropriate. Evidence regarding exact prevalences of these sequelae in survivors remains to be clarified, but it seems reasonable to conclude that a significant proportion of survivors experience at least one and that all are at risk for at least one at some point during their survivorship experience.

The descriptive epidemiology of clinical morbidities after breast cancer is further challenged because these morbidities do not all occur at the same time point during or posttreatment in different women. Differences in the cumulative incidence of common clinical treatment sequelae across studies can be explained by the length of prospective surveillance, the methods used to discern whether the problem is present (patient-reported outcomes vs. objective assessment vs. physician assessment) and the threshold for diagnosis (e.g., "any pain" vs. "pain that interferes with function on a daily basis"). The lymphedema literature illustrates the issue of length of prospective surveillance. Norman and colleagues (22) followed 631 women prospectively for 5 years after breast cancer diagnosis. A clinically validated patient-reported survey to detect lymphedema was administered at 7- to 9-month intervals. At 1 year of follow-up,
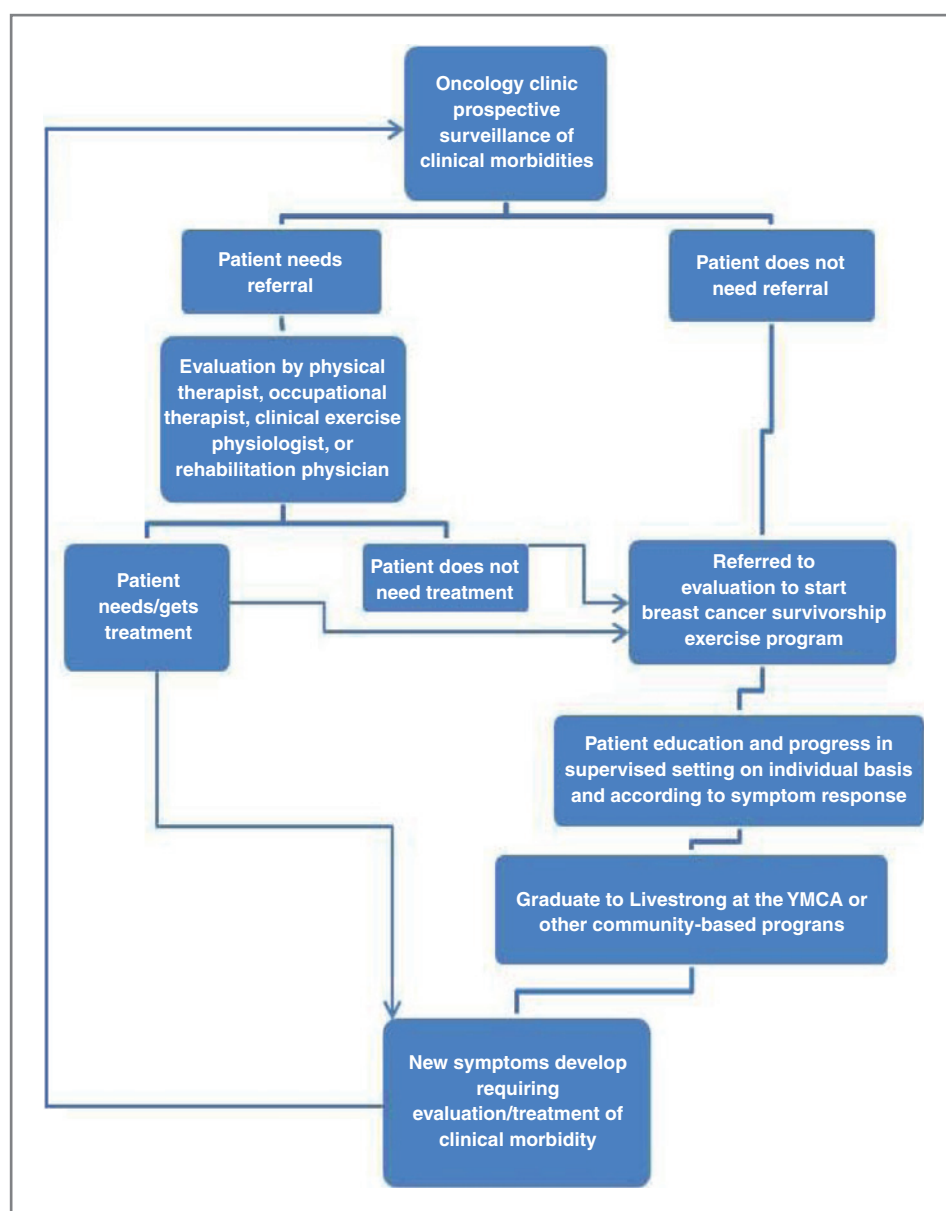
Figure 1. A proposed model for prescribing exercise in breast cancer survivors, beginning with triaging survivors in the oncology clinic for those who do versus do not need referral for treatment sequelae prior to an exercise prescription.

the cumulative incidence was 26%. After 4 more years of follow-up, however, the 5-year cumulative incidence was 42%.

The evidence that exercise is useful for a variety of clinical treatment sequelae in breast cancer survivors is compelling. There have been over 68 RCTs of exercise to improve clinical treatment sequelae in thousands of breast cancer survivors (23). More specifically, there are clinical trial data supporting the use of exercise for prevention and/or treatment of fatigue, reduced functional status, upper-body limitations, and lymphedema (23–28). Dr. Irwin leads an ongoing trial of exercise to control arthralgias (ML Irwin, personal communication, February 17, 2011). The potential of exercise for improving chemotherapy-induced peripheral neuropathy remains to be explored.

A significant proportion of survivors may need to deal with these clinical sequelae to safely participate in exercise at the level required for the mortality benefits observed by Irwin and colleagues (1) and other similar studies. Furthermore, the motivation for survivors to exercise may come more from these short-term clinical issues than from ultimate mortality benefit. Behavior theory supports the notion that setting short-term goals enhances behavior change (29). Along these lines, survivors may be more motivated to exercise to improve symptoms of arthralgia or lymphedema than to prevent mortality. Therefore, forward progress in getting women to exercise for the long-term goal of mortality benefit may be aided by developing a new infrastructure for prospective surveillance and treatment of common breast cancer sequelae. This infrastructure, which

starts with oncology clinicians triaging survivors who do versus do not need referral for treatment sequelae, might go a long way toward bridging the gap between the ongoing fear of oncology clinicians regarding the safety of exercise (particularly during treatment) and the bold "just do it" attitude espoused by exercise enthusiasts who fear the creation of unnecessary barriers to starting exercise for breast cancer survivors.

The model of cardiac rehabilitation may be informative on this issue (14). Phase 1 rehabilitation for cardiac patients typically takes place in-hospital. The analogy for breast cancer patients would be that the in-hospital short-term rehabilitation needs immediately postsurgery. This regimen should already be standard of care but may not actually happen in all hospitals. Phase 2 cardiac rehabilitation is a highly supervised outpatient program that may take place up to 3 times weekly and last several months. The components of phase 2 cardiac rehabilitation include smoking cessation, efforts to improve dyslipidemia, and hypertension, weight loss (when needed), exercise, symptom management, efforts to assist in returning to work, and interventions for stress and psychological well being. Although likely requiring far fewer sessions, an analogous program for breast cancer survivors probably could use some of these phase 2 cardiac elements. Phase 3 cardiac rehabilitation is community-based unsupervised exercise programming in settings like a YMCA. A current program at many YMCAs across the United States called "LiveSTRONG at the YMCA" would serve nicely as phase 3 rehabilitation for breast cancer survivors.

Figure 1 proposes an approach to appropriately and safely refer breast cancer survivors to community-based rehabilitation programs. For the majority of early-stage breast cancer survivors, it should be noted that the triage system skips phase 1 and that phase 2 would likely include only 1 or 2 sessions to review the survivor's specific clinical profile, provide personalized education regarding her risk of clinical treatment sequelae, develop an exercise program appropriate for her current health and fitness abilities and goals, and educate her regarding medical follow-up if symptoms of the common clinical treatment sequelae develop. She could then be referred to phase 3 community programming such as LiveSTRONG at the YMCA. Market research commissioned by the YMCA and the Lance Armstrong Foundation indicates that the first sources cancer

patients turn to for exercise advice are clinical oncologists and the cancer center (30). Furthermore, Jones and colleagues (31) have demonstrated that advice from an oncologist to do more exercise is effective in increasing physical activity in breast cancer survivors. These findings support the value of the development of an infrastructure at the oncology clinic that would refer women to LiveSTRONG at the YMCA or other community-based exercise programs for cancer survivors. This model (Fig. 1) addresses the need to have a safety net for these community programs in the event that clinical treatment sequelae develop after starting exercise. This safety net would support the sustainability of the community programs.

The push for a large secondary prevention RCT of exercise will undoubtedly continue, as will trials with surrogate biomarkers as primary outcomes and hopes for long-term follow-up and data pooling when enough follow-up time accrues to make it useful to do so. Regardless of how the field presses forward in obtaining causal evidence of a link between physical activity and mortality outcomes in breast cancer survivors, the translation and broad, sustained dissemination of the results will require an infrastructure that will guide survivors toward being able to perform more than 3 hours of weekly exercise. The sizable proportion of survivors who experience clinical treatment sequelae strengthens the rationale for developing this infrastructure and guidance. Cardiac rehabilitation centers are generally undersubscribed, and minimal retraining of the highly qualified staff at these centers may be a low-cost option for developing the proposed model to support exercise programming in breast cancer survivors. Establishing the efficacy and cost effectiveness of such breast cancer rehabilitation programming is vital to the long-term goal of establishing a standard of breast cancer clinical care that includes prescribing exercise for secondary prevention of breast cancer, as proposed by Irwin and colleagues (1).

Disclosure of Potential Conflicts of Interest

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