Clinical Cancer Research

Exercise as a Candidate Antitumor Strategy: A Window into the Future

Graeme J. Koelwyn[1] and Lee W. Jones[1,2]

Observational findings suggest exercise is associated with improved outcomes in early-stage breast cancer. However, whether exercise has biological activity in patients with breast cancer has not been investigated. Preoperative window of opportunity studies provide a setting in which to test the short-term effects of novel treatment strategies on validated surrogates.

See related article by Ligibel et al., p. 5398

In this issue of *Clinical Cancer Research*, Ligibel and colleagues (1) report on a window of opportunity trial testing exercise on changes in the proliferation marker Ki-67, as well as other biological outcomes in 49 women with operable breast cancer. Observational data indicate that higher levels of self-reported physical activity and exercise (i.e., leisure-time physical activity) are inversely associated with the primary risk of breast cancer (2), as well as cancer outcomes after breast cancer (3). These observational data provide the initial foundation for definitive trials; however, several major knowledge gaps currently prevent the rational development of such trials. These include the following: (i) demonstration of antitumor activity in smaller signal-seeking trials, (ii) optimal dose (and schedule), and (iii) predictors of response. In this translational commentary, we evaluate how the findings of Ligibel and colleagues begin to address these gaps (Fig. 1).

Investigation of the safety, toxicity, and initial antitumor activity of nonpharmacologic strategies such as exercise is not possible in end-stage patients where novel therapies are traditionally pioneered. Arguably, the only oncology setting in which to test such strategies as single agents (without concurrent anticancer therapy) is the preoperative "window" setting. However, window studies are challenging to conduct and testing behavioral strategies in this setting is even more difficult given high patient burden. Thus, we commend Ligibel and colleagues for conceiving and for successful execution of this study. In terms of activity, no difference in the primary end point of cell proliferation (Ki-67) was observed either within or between the exercise and control groups. As such, this is a negative study for the primary end point. There were also no changes in the other prespecified antitumor markers such as apoptosis and insulin receptor expression. Of note, reduction in presurgical Ki-67 is only established as a bona fide surrogate marker in postmenopausal hormone receptor–positive breast cancer. The patient cohort in the Ligibel and colleagues study included all clinical breast cancer subtypes—the prognostic or predictive value of Ki-67 in all subtypes is not established. The authors further interrogated alterations in the breast tumor microenvironment (TME) using an unbiased approach with RNA sequencing of bulk breast tumor tissue. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis identified several enriched pathways in the exercise group only; many of these were immune related including NF-κB signaling, natural killer cell–mediated cytotoxicity, and T-cell receptor signaling. These novel findings raise several additional important questions including how does the breast TME immune cell composition and phenotype evolve during exercise treatment? Do changes in the immune cell landscape correlate with alterations in intratumoral inflammatory or metabolic pathways? Does exercise differentially regulate cancer cells versus other "normal" cells in the TME? If so, can exercise enhance the efficacy of checkpoint blockade therapy? And ultimately, do these changes associate with other readouts of biological or clinical activity?

A critical consideration when evaluating the antitumor activity of any medical intervention is identification of the biologically effective (and feasible) dose. In the context of exercise, the following two factors need to be considered: (i) what is the planned dose and prescription regimen used to deliver the planned dose, and (ii) was the treatment successfully delivered as planned (i.e., compliance)? In the Ligibel and colleagues trial, the planned dose was for each patient to achieve an absolute exercise volume of 220 minutes per week; this was achieved using resistance (∼40 minutes/week) and aerobic modalities (∼180 minutes/week), via two supervised sessions per week of approximately 60 to 90 minutes/session, with the remaining aerobic "dose" achieved via home-based sessions (and monitored using pedometers). All sessions were reported to be moderate-intensity. The exercise "dose" associated with reductions in either the primary incidence of or relapse of breast cancer in observational studies varies considerably but does appear to include approximately 180 minutes of aerobic exercise per week. Use of exercise doses identified in observational studies to support testing in clinical trials, however, is problematic due to the well-established limitations of self-reported exercise data plus all observational studies examining the exercise–cancer link have only assessed exercise at one time point. Thus, the change in exercise exposure needed to impact cancer outcomes is not known. The link of resistance training to cancer susceptibility or progression is also not clear.

[1]Memorial Sloan Kettering Cancer Center, New York, New York. [2]Weill Cornell Medical College, New York, New York.

Corresponding Author: Lee W. Jones, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065. Phone: 646-888-8103; Fax: 646-888-4588; E-mail: jonesl3@mskcc.org

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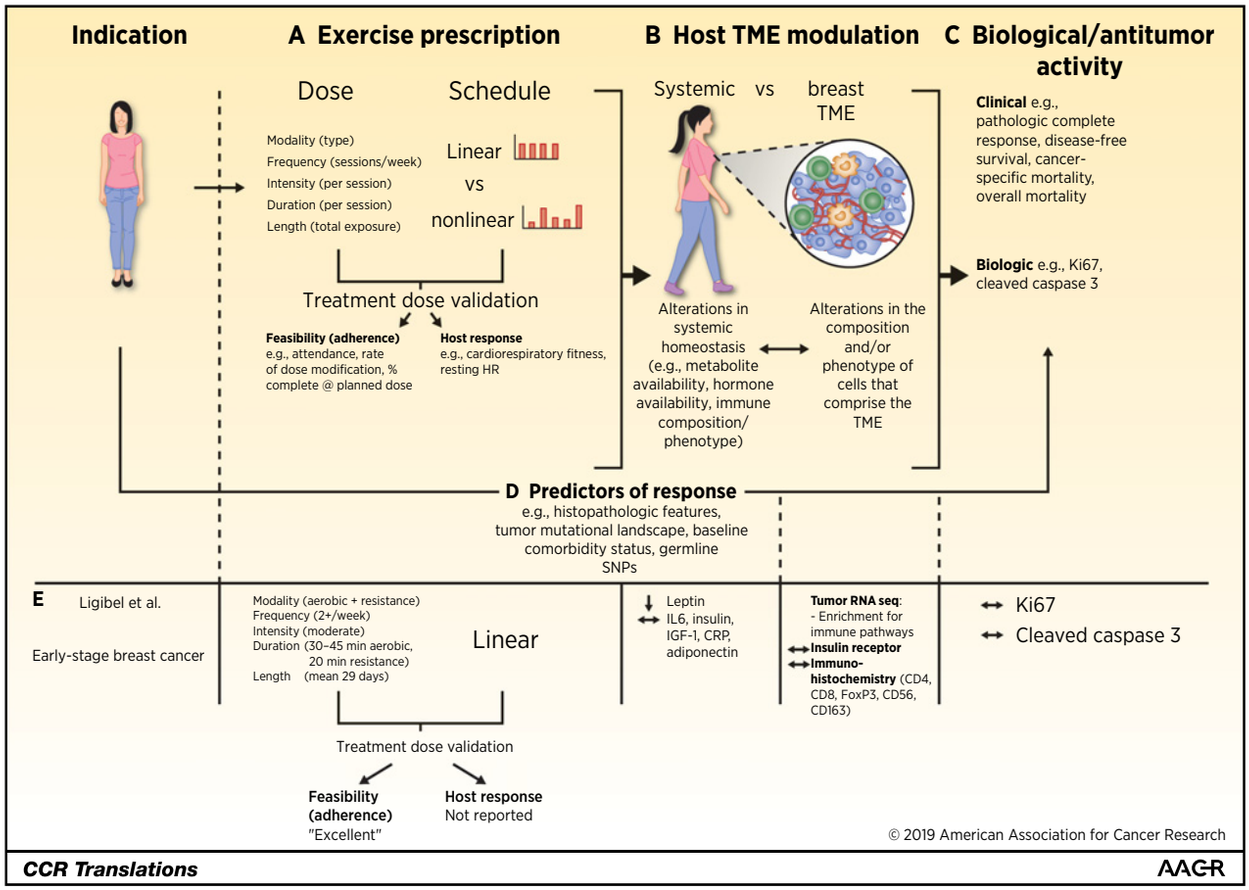

Figure 1.

Development of exercise as a candidate antitumor strategy in breast cancer. In the development of exercise as a nonpharmacologic antitumor strategy, several major knowledge gaps require elucidation; these include the following: **A,** the determination of the biologically effective dose (e.g., modality, frequency, intensity, duration of each session, as well as the length of exercise exposure) and schedule of exercise treatment. Treatment dose validation can be assessed by both adherence to the planned prescription as well as host response. **B,** The effect of exercise treatment on the host and TME can be evaluated by markers of biological or clinical activity such as but not limited to Ki67, cleaved caspase-3, and/or clinical endpoints such as pathologic complete response, and disease-free survival (**C**). Observed effects can be further examined to explore predictors of response (**D**). The findings of Ligibel and colleagues are presented using this framework (**E**).

In terms of compliance, Ligibel and colleagues reported that the exercise group, on average, significantly increased total exercise by 203 minutes per week, which was considered "excellent" adherence. Reporting of other compliance metrics such as mean (range) attendance to supervised sessions, rates of dose modification, or discontinuation in attended supervised sessions, as well as the percent of sessions that were completed at the target dose intensity, and the proportion of patients achieving the goal of 220 minutes per week as planned for all weeks "on treatment" would have been of interest. Other potential markers of interest include changes in measures of host physiology such as cardiorespiratory fitness or resting heart rate; although not primary end points, these measures can act as a manipulation check, essentially the pharmacokinetic equivalent for an exercise trial. Finally, the current working hypothesis posits that exercise regulates the breast TME via alterations in the systemic (host) milieu as reflected in a reduction in the circulating bioavailability of numerous growth factors, hormones, and immune cell subsets (4). Changes in several circulating factors were assessed by Ligibel and colleagues but results were rather unremarkable (Fig. 1). Taken together, it is plausible that a higher dose and/or length of exposure may be required to significantly modulate the selected biological end points.

The final consideration is identification of patients for which the treatment intervention is the most efficacious (i.e., predictors of response). The prevailing dogma is that all patients respond to exercise; however, emerging data suggesting breast cancer response to exercise may differ as function of clinical or molecular subtype (5). Unfortunately, secondary analyses by Ligibel and colleagues did not reveal that effects of exercise differed as a function of clinical subtype. Interestingly, biological activity of metformin may differ as a function of pretreatment (baseline) fasting insulin levels; although, purely exploratory similar analyses would have been of interest in the Ligibel and colleagues trial.

So how does the study and findings of Ligibel and colleagues add to the current evidence base and inform future trials? First, this study provides novel evidence that short-term treatment with exercise can modify the breast TME in patients with breast cancer,

altering the biology of a tissue outside the cardiovascular system. Second, given our discussion above we do not feel the findings of the Ligibel and colleagues are sufficient to support the design and conduction of larger phase II randomized trials of exercise in the adjuvant breast cancer setting. Specifically, significant knowledge gaps regarding biological activity, the recommended phase II dose, and predictors of response remain, which are critical prerequisites for the rational design of larger trials. They do, however, firmly demonstrate the utility of the presurgical setting as an excellent model to comprehensively develop and test exercise as a candidate antitumor strategy.

Disclosure of Potential Conflicts of Interest

L.W. Jones holds ownership interest in Pacylex. No potential conflicts of interest were disclosed by the other author.

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