A Deeper Dive into Exercise Interventions to Prevent or Mitigate Cancer Treatment-Related Aging – From Preclinical to Population Science Frequently Asked Questions (FAQ)

Webinar held September 12, 2022
The recorded webinar is available at:
https://cancercontrol.cancer.gov/brp/events/exercise-interventions-prevent-cancer-treatment-related-aging

Questions from Dr. Keri Schadler's presentation

Q1: Are changes in tumor vasculature tumor specific?

A1: Based on mouse models, I believe there is some variation between tumor types (for example, the vasculature in orthotopic Ewing sarcoma changed to a much lesser degree than vasculature in melanoma or pancreatic cancer in response to exercise). So far, we have examined Ewing sarcoma, melanoma, and pancreatic models and always see some evidence of improved vascular function (e.g., increased lectin perfusion, decreased dextran leakage, increased vessel elongation or pericyte coverage, opening of lumens, or several of these at the same time). Regardless of the changes observed, all models in which we tested exercise + chemotherapy enhanced chemotherapy efficacy. Exercise alone had no effect on pancreas tumor growth, decreased Ewing sarcoma growth, and had varying effects depending on the melanoma model.

Q2: How difficult might it be for someone receiving treatment to exercise at the vigorous level suggested here that is necessary?

A2: This is often a concern. There is work being done at Memorial Sloan Kettering Cancer Center, led by Drs. Lee Jones and Jessica Scott, that indicates that patients with breast cancer can do High Intensity Interval Training. I think that this means that patients with some cancer types can do very intense exercise. However, most patients with pancreatic cancer are very ill and weak, and I would be surprised if many can do truly vigorous exercise. Still, our pilot study data and the initial evaluations of our recently completed randomized controlled trial (RCT) of patients with pancreatic ductal adenocarcinoma (PDAC) undergoing neoadjuvant therapy, suggest that the intensity of exercise that patients are doing is sufficient to induce tumor vascular remodeling.

In my mind, there may be a few ways to reconcile the fact that in mice, the intensity needs to be closer to vigorous intensity exercise, whereas in patients, it looks like moderate intensity exercise may be sufficient. Most likely, exercise that is "vigorous" for a mouse does not directly translate to "vigorous" for a human because the intensity and the physiologic response to different intensities is likely not a 1:1 correlation between mice and humans. Similarly, we did not actually measure VO2 max in the mice or the patients, so our estimates of how intensely they are exercising are exactly that: estimates. Finally, for patients who are very deconditioned, possibly sarcopenic, and quite ill, what appears like "moderate" exercise (e.g., neighborhood walking) may actually equate to something more intense.

Q3: Were the immune cell experiments done in syngeneic mouse models?

A3: Yes, the cell line used for orthotopic PDAC tumors was KPC-4662, derived from a *LSL-Kras$^{G12D/+}$; LSL-Trp53$^{R172H/+}$; Pdx1-Cre* mouse on a C57Bl/6 background, and they were grown in C57Bl/6 mice.

Q4: Would the effects shown in the webinar be seen in those with Central Nervous System (CNS) tumors? Does exercise help treatments cross the blood brain barrier?

A4: I would love to collaborate with a CNS mouse model researcher to investigate this research question. At this time, I am not aware of any data that answers this question. However, Dr. Maria Swartz at The University of Texas MD Anderson Cancer Center is conducting a small clinical study examining the relationship between exercise, physical function, and cognitive function in adolescent/young adults with CNS tumors.

Q5: Is the orthotopic model used in your studies similar in aggression to the histological characteristics seen in patients?

A5: The model we used for these studies, orthotopic KPC-4662, has what I would characterize as more desmoplastic stroma than subcutaneous models but less than what I typically think of in patient tumors. We are in the midst of repeating these studies using an HY15549 model, which has substantially more desmoplastic stroma (very close to patient tumors). Both models metastasize in patterns similar to what is seen in patients, and the vasculature in both models looks similar to what is seen in patients.

Q6: Do you know the baseline exercise levels of the participants in the study that you described? In addition, based on your studies, what would you recommend for exercise interventions for patients (e.g., intensity, time)?

A6: For the first pilot single arm study, the International Physical Activity Questionnaire (IPAQ) was used to gather information about patients' physical activity levels for the 7 days prior to study enrollment. Based on this, the IPAQ score for evaluable patients at baseline was mean 631 +/- 758 st dev MET-minutes/week. The data were published by Ngo-Huang et al, 2017.

Ngo-Huang A, Parker NH, Wang X, et al. Home-based exercise during preoperative therapy for pancreatic cancer. *Langenbecks Arch Surg*. 2017;402(8):1175-1185. doi:10.1007/s00423-017-1599-0

For the recently completed RCT in patients with PDAC undergoing neoadjuvant therapy, we used Godin Leisure Time Activity Questionnaires to assess baseline activity levels in patients, but the data have not yet been analyzed.

In terms of exercise recommendations, this is a bit beyond my expertise, but I recommend sticking to the ACSM guidelines until we have definitive proof that something should be changed. In our pilot study, patients were asked to exercise at least 2x per week for 30-minutes at moderate-to-vigorous aerobic activity and 3x per week for 20 minutes of strengthening. For most patients, they did more than the requested aerobic exercise and less than the requested strengthening.

Q7: Were baseline and follow-up physical activity measured via Fitbit or was another measurement tool used?

A7: In the pilot study, the International Physical Activity Questionnaire was used at baseline, pre-op, and post-op evaluation time points. Daily written logs were used throughout the exercise intervention for all 70 participants, and Fitbits were used during the exercise intervention for 50 patients.

In the RCT, for which data are still being analyzed, baseline, pre-operative, and post-operative physical activity was measured by Godin Leisure Activity Questionnaire, and by Fitbit wear throughout the study.

Q8: Were there any notable differences between aerobic vs. resistance training on patient health outcomes if this was measured?

A8: Unfortunately, the studies are not powered to assess the effects of just aerobic vs. just resistance training.

Q9: How does the tumor know that the host is exercising?

A9: This is the million dollar question! Likely, a combination of several factors. For example, exercise causes secretion of myokines and cytokines, such as IL-15 and IL-6 (as shown in work by Kurz and Pedersen), that circulate systemically and interact with tumor cells and immune cells. Exercise also changes the circulating immune cell milieu (nice work done on this by R Simpson, E LaVoy, and others). Of course, exercise also changes things like hormone levels, glucose availability, etc., which will impact tumor growth.

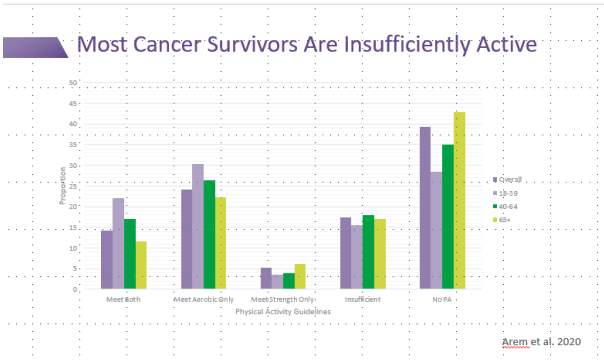
In addition, we have evidence that suggests that endothelial cells within the tumor are likely responding to increased laminar shear stress (mechanical signaling) induced by exercise-increased blood flow. It is likely that exercise changes the tumor by both systemic circulating factors and local signals such as changes in shear stress.

Q10: How did you determine adherence to exercise Rx? Are they deemed adherent only if they do the recommended minutes?

A10: Yes, exercise adherence was determined based on the minutes of exercise performed, as reported by Fitbit and/or daily exercise logs.

<u>Questions from Dr. Siobhan Phillip's presentation</u>

Q11: During the webinar, a slide was shown (see below). What is the reference for this data?



A11: Arem H, Mama SK, Duan X, Rowland JH, Bellizzi KM, Ehlers DK. Prevalence of Healthy Behaviors among Cancer Survivors in the United States: How Far Have We Come?. *Cancer Epidemiol Biomarkers Prev*. 2020;29(6):1179-1187. doi:10.1158/1055-9965.EPI-19-1318

Q12: Did you consider (or have) a qualitative component that would allow you to learn more about how the intervention was received?

A12: Yes, we conducted an acceptability survey at 3- and 6-months and also did post-participation interviews with about 30 participants to get more information on participants' perspectives.

Q13: Might you consider looking at interaction effects in the factorial design? Maybe some of the components are effective but only the presence/absence of other components.

A13: As recommended by Collins and Kugler, we did not test any interaction effects because no significant main effects were observed and no interaction effects were pre-specified in our conceptual model.

Collins, L.M. and K.C. Kugler, *Optimization of behavioral, biobehavioral, and biomedical interventions.* Cham: Springer International Publishing, 2018. 10(1007): p. 978-973

Q14: Were any of the survivors experiencing exercise intolerance for which the stepped care approach you mentioned might be effective?

A14: We didn't have a systematic way to collect data on exercise intolerance in Fit2Thrive. However, there was variation in meeting physical activity goals, which may have been explained, at least in part, by exercise intolerance and warrants more rigorous and systematic exploration in future studies.