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TITLE
The impact of continuous and incremental exercise training on breast cancer physiology

HYPOTHESIS:
Aerobic exercise leads to changes in tumor physiology and the host environment that could enhance anti-cancer treatment.

BACKGROUND/AIMS:
An essential hallmark to solid tumor growth is the process of angiogenesis, which calls upon the formation of new vasculature to fulfill the nutritional needs of the growing neoplasm. However, due to the uncontrolled growth of cells, the tumor vasculature network is morphologically and functionally abnormal, characterized by tortuous, unstructured, leaky and immature vessels. This aberrant blood vessel network leads to impaired tissue perfusion and areas of low oxygenation (pO₂ < 10 mmHg). Hypoxia is associated with aggressive progression, dissemination, and therapeutic resistance. It is found in ~40% of breast cancers, and can constitute a major obstacle to anticancer therapy. Many approaches have been focused on improving oxygenation in the tumor but have failed to provide a significant improvement in the clinic.

During exercise mean arterial pressure is increased and blood is shunted to the active muscles. Over time muscle vascularity is improved, as well as, cardiovascular and respiratory function. Regular exercise in cancer patients undergoing therapy has been shown to decrease treatment related side effects and general fatigue.

Due to the aberrant nature of the tumor vasculature, we hypothesize that aerobic exercise may lead to changes in tumor physiology and the host environment that could enhance anti-cancer treatment by improving drug delivery and oxygenation in breast cancer patients.

Our goal was to determine whether different regimens of daily aerobic exercise improved tumor perfusion and oxygenation in a murine breast cancer model.

METHODS:
The effects of daily bouts of moderate intensity treadmill running were studied in mice bearing the syngeneic murine mammary carcinoma (4T1). Our studies examined the effect of daily bouts of exercise for 10 days once tumors reached ~250 mm³. Each group of animals performed one of the following exercise regimens: 30 minutes of exercise at the constant speed and incline of 18 m/min at 10º incline throughout the 10 days of exercise. A constant speed of 18 m/min and progressive daily increase in incline up to 25º. Or a progressive daily increase in speed and incline from 9 m/min at 10º incline up to 18 m/min at 25º incline. Subsequently experiments mice were exercised at 18 m/min at 10º incline, 5 days a week prior to orthotopic injection of tumor cells and continued exercise for 2 weeks during tumor growth. Controls for each treatment consisted of sedentary mice exposed to a stationary treadmill for the equivalent amount of time. At the end of each of the exercise regimen, tumors were harvested, sectioned, stained, and tile mapped to assess physiological changes by immunofluorescence. The detection of open blood vessels (Hoechst-33342) was used as an indirect indicator of perfusion. Tumor hypoxia was determined using the 2-nitroimidazole (EF5). All markers were quantified using Photoshop and ImageJ NIH software.

RESULTS & CONCLUSIONS
Our results indicate that in the 4T1 breast cancer model daily moderate intensity exercise does not significantly alter tumor growth in any of the regimens used. Daily bouts of exercise did significantly increase the number of open tumor vessels indicating improved tumor perfusion, and consequently a decrease in acute hypoxia. However, results also indicate the daily exercise also increased hypoxia measured by EF5, indicating changes in chronic hypoxia.

These results suggest that a daily exercise regimen may have the potential to improve drug delivery to mammary tumors.