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Muscular endurance and progression rates of early-stage invasive ductal carcinoma: A pilot study

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With hundreds of studies to date, it is widely believed that regular physical exercise reduces risk of cancer incidence. In breast cancer, cohort studies and case-control studies estimated a 20–30% risk reduction, respectively. Similar results arise from studies on other types of cancer. A recent meta-analysis found a significant risk reduction in 13 types of cancer, including breast, with self-reported leisure time moderate physical activity, equivalent to 150 weekly minutes of intensive walk¹.

One factor contributing to reduced-incidence is slower progression rate from precancerous lesions to invasive cancers. Since the 1940s, support for the hypothesis that aerobic exercise slows solid tumor progression has come from animal studies, with evidence across different types of solid tumor and various rodent models. More than two-thirds of these studies demonstrated growth inhibition resulting from aerobic training².

Progression of early-stage solid tumor crucially depends on glucose uptake, and on lactate production and clearance capacities. Here the skeletal muscles act as a unique organ, with systemic effects on the metabolic state of other tissues and on the host's immune competence.

The aim of this study was to develop a measurement protocol that assigns an individual muscular endurance score, so that it could be used to test whether a correlation exists between breast tumor progression rates in the early stages of the disease and muscular endurance profiles in humans. The protocol consists of measuring 10 blood lactate

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concentration levels with a handheld lactate analyzer (Lactate Plus, Nova Biomedical, MA) during 15 minutes incremental pedaling session followed by 15 minutes of rest, and plotting them on a curve. The area under the curve, normalized by the power output during the pedaling session and the subject's age, is converted into an individual score between 0.5 and 3 (figure 1). The score was consistent with self-perception of subjects of their physical fitness. The lowest (most aerobic) scores were obtained for a competitive swimmer (0.656) and a yoga practitioner (0.925) who exercise daily for 60 minutes. The highest (most glycolytic) scores (2.28) were obtained for extremely sedentary subjects. Roughly speaking, "couch potatoes" are expected to score above 2 on our scale, while trained athletes would score below 1.

The protocol was tested on 14 healthy females, replicated after 13 months and was found to be robust (figure 2). It was applied to 14 recently diagnosed T1–T2 invasive ductal carcinoma patients before any treatment, so that their documented tumor growth rate could be compared with their score. The growth rate was calculated from tumor volumes measured in two time points, the diagnostic mammogram and an earlier mammogram where the tumor could be identified in retrospect. Time interval between the two mammograms ranged between 231 and 1223 days (mean 555 ± 301 , median 390). The diagnostic modality was kept fixed between the 2-point-measurements. The reason we resorted, like others before us, to such retrospective method in tumor volume measurements is that diagnosed patients usually are anxious to get treatment, and the short time span between diagnosis and treatment impedes collection of forward looking data.

Healthy group characteristics: 14 nonsmoking females, all Caucasian, age range 36–67 (mean 51 years ± 9), 7 of whom were premenopausal. BMI range 21.1–43.1 (mean 27.9 ± 7.14). IDC group characteristics: 14 nonsmoking females, 10 Caucasian, 3 African American, and 1 Latino. Age range 48–78 (mean 57 years ± 7), 1 of whom was premenopausal. BMI range 20.8–40.8 (mean 30.06 ± 5.61). Significant difference in age but not in BMI between the groups was detected ($p=0.0498$ and $p=0.4014$, respectively).

The findings are summarized in Figures 3 and 4. Mean doubling was 185 days ± 122 . Mean muscular endurance score was 1.92 ± 0.25 . Both variables were log-normally distributed. A significant Spearman's correlation ($n=14$; $r=-0.859$; $p<0.001$) was found between the log transformed muscular endurance score and the log transformed tumor doubling time: the more aerobic and less glycolytic the subjects' profile is (i.e., the lower the muscular endurance score), the longer is the doubling time of the tumor. No correlations were detected between the log transformed tumor growth rates and age, BMI, or molecular subtype, or between the log transformed muscular endurance score and age or BMI in the combined cohort.

Additional data is required to estimate the relation between our method and other methods for quantifying aerobic fitness. There are several approaches to doing so, that range from mere qualitative and non-invasive tests such as the one-mile-walk, to more rigorous and demanding methods such as the $\dot{V}O_{2\max}$ test, or the highly quantitative and invasive lactate threshold test involving isotope tracers. Here a tradeoff was sought between these two extremes. Considering the constraints on the study population, blood lactate concentration

was chosen as a surrogate for the more demanding and invasive tests. Additional support for this choice comes from the documented linear relation between Lactate Thresholds and $\dot{V}O_{2\max}$ test results.

Finally, it is hypothesized that traditional risk factors are less relevant for the question of the *progression rate* of the disease in its pre-clinical and early clinical stages. BMI may contribute to risk assessment of the *onset* of the disease given its implication in other morbidities, and molecular subtypes may inform therapeutic decisions, but neither appear to answer the question how fast does a tumor grow in its early stage. The answer to this question, this study propagates, lies in metabolism and immune competence, both of which are enhanced by endurance exercise.

With additional corroboration, the method presented here could establish muscular endurance as an additional factor in assessing risk for screening purposes.

References

1. Moore SC, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med. 2016; 176(6):816–25. [PubMed: 27183032]
2. Ashcraft KA, et al. Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis. Cancer Res. 2016; 76(14):4032–50. [PubMed: 27381680]

Figure 1. Lactate concentration curves

Muscular endurance score, DT and mean power for Subject 2 were 1.6892, 393, and 75.6W. Score, DT and mean power for Subject 10 were 2.2716, 56, and 38.4W. While the absolute area under the curve for subject 10 is smaller than for subject 2, once we normalize it with mean power output it yields a higher score (hence less aerobic and more glycolytic profile).

Figure 2. Robustness of the scoring algorithm

7 subjects out of 14 healthy subjects were randomly chosen for replication after 13 months. Variation in score in the two time periods for the same individual in the replicated subset ranged between 0.3%–2% relative to the scoring scale of 3 (mean $1.11\% \pm 0.74$).

Figure 3. Muscular endurance score as a predictor of doubling time of T1–T2 invasive ductal carcinoma - data points

Errors bars in doubling time estimations were calculated with propagation of errors formula from the two volume measurements and the time interval between them.

Figure 4. Muscular endurance score as a predictor of doubling time of T1–T2 invasive ductal carcinoma - correlation

83.88% power was detected of correlation between the two variables at significant level 0.05 with two-sided test.