



LAY ABSTRACT Cod CUP: H55F21000310005

Proposal title. Oncoprotective effect of exercise in breast cancer survivors: breast cancer cell proliferation and systemic adaptations in response to single exercise sessions performed at different intensities

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Rationale. Physical inactivity is associated with an increased risk of breast cancer (BC). The cellular and molecular mechanisms mediating this effect are only partially known. Exercise is associated with improved survival among women with BC and recent studies show benefits in their quality of life.

Objective. We aim to examine if systemic responses to acute exercise in BC survivors could modulate BC cell proliferation and/or intracellular IGF-1/PI3K/AKT/mTOR signalling pathway activation using three-dimensional (3D) BC cell culture models. Particular attention will be focused on the anti-proliferative effect of serum, circulating exosomes and specific antitumor miRNA released pre- and post- exercise on BC cell lines. We also aim to assess if exercise changes the pathological associated systemic factors in BC survivors.

Study Design. Cross-over, open-label, and randomized trial. Subjects will perform two steady-state exercise sessions in randomized order, with randomized permutation blocks, in order to ensure the balance.

Study population and Intervention. Twenty BC survivors will be included. *Inclusion criteria:* 40-65 years; non-physically active; non-metastatic; treated for early-stage BC (stage 0-III); between 6-18 months post-surgery; post chemo- or radio-therapy; with medical clearance to perform maximal exercises. *Exclusion criteria:* uncontrolled hypertension, cardiac or psychiatric illness, other relevant clinical contraindications provided by the oncologists. BC patients will perform 3 sessions of exercise, one preliminary session, and two experimental steady state exercise sessions at a different intensity. Blood samples will be collected before and after each aerobic exercise session. The BC cell lines will be exposed to both pre- and post-exercise serum and isolated exosomes. Changes in patients' functional parameters such as cardiorespiratory fitness, body composition, and pathological associated systemic factors (metabolic, hormonal, and inflammatory) will be evaluated as well.

Preliminary results. We obtained preliminary data from a pilot study in which we evaluated the anti-cancer potential of single aerobic exercise bouts with an *in vitro* 3D cell growth assay, using a triple-negative BC cell line cultured with exercise-conditioned serum. We also provide evidence that the transient serological responses to acute exercise reduces cancer cell growth. Furthermore, we are carrying out a clinical trial with the Unit of Oncology of Urbino Hospital named "Movement and Health Beyond Care" (Movis), under a partnership agreement signed on 4 December 2019. The analyses performed within the Movis include preliminary data available for 32 non-physically active BC survivors. This partnership will allow the BC patients enrolment for the present study.

Detailed description of the translational value of the research and the expected impact on the NHS.

This study will influence research in the field of exercise-oncology, and it will also provide insight into the effects of the exercise-induced systemic changes in relevant molecular pathways related to tumor dormancy and control of BC cell proliferation. Since recent studies have shown that exercise during cancer care reduces the overall healthcare costs per patient, progress in this area would potentially not only yield health benefits but also prove to be a cost-effective health promotion strategy that policymakers could embrace.

