

# INPLASY PROTOCOL

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**Review Stage at time of this  
submission:** Data analysis.

**Conflicts of interest:**  
None.

## INTRODUCTION

**Review question / Objective:** How exercise-conditioned human serum affect the viability of human cancer cell cultures?

## Effect of exercise-conditioned human serum on the viability of cancer cell cultures: A systematic review and meta-analysis

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**Review question / Objective:** How exercise-conditioned human serum affect the viability of human cancer cell cultures?

**Condition being studied:** Our study can help to understand if and how exercise affects the viability of human cancer cell cultures. Some studies, with different designs have analysed the effect of acute or chronic physical exercise on the viability and apoptosis of cancer cells, incubating cancer cell lines with animal or human serum. The results show that the effect of conditioned serum did not have the same magnitude in all studies. These results raise some doubts about the exclusive effect of exercise on the viability and apoptosis of human cancer cell cultures.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 December 2020 and was last updated on 13 March 2021 (registration number INPLASY2020120096).

**Rationale:** To understand whether and how exercise affects cancer cells, some studies have been carried out that have incubated cancer cell lines with animal or human serum. These studies used different design and methods for analysis the effect of acute or chronic exercise on the viability

and apoptosis of cancer cells cultures, as study the mechanisms involved. The results show that the effect of conditioned serum does not have the same magnitude in all studies including similar design studies and with the same cell lines. The results raise some doubts about the exclusive effect of exercise on the viability of human cancer lines, as well as whether there is a difference between serums conditioned by exercises of different intensities.

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## METHODS

**Search strategy:** Search strategies followed the PRISMA guidelines and were based on the following descriptor terms and keywords defined by the authors and indexed to the Medical Subject Headings (MESH, U.S.National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894): ((exercise\* OR "physical activity" OR sport\* OR training OR "resistance training" OR "aerobic training" OR "high intensity interval training" OR "physical exercise") AND (neoplasm\* OR tumor\* OR malignant\* OR cancer\* OR carcinoma) AND (cell\* OR "cell culture" OR "in vitro")). This combination was used to search the following academic journal data bases: US National Library of Medicine National Institutes of Health, Web of Science, SPORTDiscus and Scopus. The advanced options were carried out using the filter by title into each database. Research procedures were carried out in July 2020.

**Participant or population:** Participants' characteristics vary significantly across the

studies and include healthy sedentary women, breast cancer patients, women after cancer treatment, healthy sedentary men, men considered to be at risk of prostate cancer, and male colorectal cancer survivors as well cancer cell lines that include prostate cancer cell, breast cancer cell lines, lung cancer cell lines and colon cancer cell lines.

**Intervention:** The intervention occurs by different types of exercise (a single session) or training (repeated exercise sessions performed periodically) performed were: (1) integrative (two or more activities by exercise (e.g. strength exercise plus cycling exercise) at intensities between 50% to 95% of their VO<sub>2</sub>max or one maximal repetition at workload resistance); (2) high intensity (cycling intervals with active rest periods at 85–95% of their VO<sub>2</sub>max); (3) moderate intensity (ergometer cycling at 50%-65% of their VO<sub>2</sub>max).

**Comparator:** The study compare the effect of exercise-conditioned human serum to the corresponding pre-exercise serum on the viability of cancer cell cultures. Study designs to be included: The PRISMA Statement positioning guidelines were followed to assist the design of this study. These guidelines describe the four stages (identification, screening, eligibility, and final selection) required to search and select manuscripts for a systematic review and feature the option of illustrating procedures in a flowchart. The PRISMA presents the PICOS acronym which helps making research questions and systematic searches more effective. Qualitative data from the different articles were selected, extracted, and organized in a specific table, following the PRISMA method, i.e., including authors, year and country, number of participants included, their age and gender, cancer type, intervention characteristics, central outcomes, and the existence of a control group.

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**Eligibility criteria:** The inclusion criteria used to select the articles for the present study were: a) the effects of exercise-conditioned serum were assessed in vitro using human cancer cell lines; b) the exercise-conditioned serum was of human origin; c) exercise was the only intervention tool, i.e., no combined interventions (e.g., diet and exercise) were involved; d) written in English.

**Information sources:** US National Library of Medicine National Institutes of Health, Web of Science, SPORTDiscus and Scopus.

**Main outcome(s):** The main results are focus on the effect of acute and chronic exercise-conditioned human serum on the viability and apoptosis of cancer cell cultures. Our hypothesis is that human serum conditioned by exercise reduces the viability of cancer cells and that this effect is dependent on exercise intensity, when compared to the corresponding pre-exercise serum. Effect size was calculated using the software Comprehensive Meta-Analysis (CMA) (Biostat, Englewood, NJ, USA, version 3.3.070). The effect-size metric selected was the standardized difference in means (standard difference in means) since all studies evaluated the same outcome variable, but with different criteria. Data extracted for effect-size calculations from the different studies included Sample Size (N), Statistical Significance (p value) and Effect Direction. A random-effects model was used for the present meta-analysis as it combines sampling error and between-study variance to estimate effect size. The following thresholds were used to interpret the effect sizes: trivial ( $d < 0.20$ ), small ( $0.21 < d < 0.50$ ), moderate ( $0.51 < d < 0.79$ ), and large ( $d > 0.80$ ). Search - July 2020; Study Selection/Data Extraction - August 2020; Quality Information and Data analysis -

September/October 2020; Submission/Publication - December/ March.

**Data management:** Comprehensive Meta-Analysis; EndNote X7; Excel; Word.

**Quality assessment / Risk of bias analysis:** The Quality of Information from the articles included in the systematic review were evaluated with application of the TREND positioning guidelines (Transparent Evaluation Report with Nonrandomized Designs). The method requires evaluation of a list of 22 items (general criteria) subdivided into 59 sub-items (specific criteria) able to quantitatively assess the QoI. One point is assigned to each completed item and sub-item. All studies with QoI  $\geq 50\%$  were included because they qualify as a highly relevant article for the topic under study. The publication bias was calculated using the software Comprehensive Meta-Analysis (CMA) creating a funnel plot by the standard error (y-axis) and the standard difference in means (x-axis) to determine whether the plot was balanced. Because the interpretation of the funnel plot is sometimes subjective, different tests such as the Begg, the Mazumdar, and the Egger have been proposed to quantify bias and test the relationship between sample size and effect size. In the present study, the Egger's test was used to check publication bias as suggested by Borenstein et al.

**Strategy of data synthesis:** Data from search were imported to EndNote X7 and the effect size was calculated using the software Comprehensive Meta-Analysis. All data were synthesised in figures and/or tables: One figure with the scheme of information about the different phases of systematic search through the positioning PRISMA guidelines; one table with the TREND Assessment Protocol results; two tables with systematized information of each selected study that analysed the effects of acute and chronic on the viability and apoptosis of cancer cell cultures (authors, country, type of cancer, sample characteristic, study design, exercise characteristic, main outcomes and output); Three figure with summary of descriptive

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and inferential statistics of results for each study and overall for the: effect of acute exercise-conditioned human serum on the viability of cancer cell cultures, effect of high intensity acute exercise-conditioned human serum on the viability of cancer cell cultures and effect of serum conditioned by moderate-intensity acute exercise or by an acute integrative exercise of moderate- and high-intensity on the viability of cancer cell cultures. One figure of funnel plot of standard error by std diff in means for each qualitative analysis.

**Subgroup analysis:** We do not performed any subgroup analysis or other sensibility analysis.

**Sensibility analysis:** We do not performed any subgroup analysis or other sensibility analysis.

**Language:** Language limits will be imposed only on the inclusion criteria - English.

**Country(ies) involved:** Portugal.

**Keywords:** cellular studies; tumour; anticancer activity; physical activity; cancer prevention; cancer management.

**Dissemination plans:** The study will be submit for publish in in international journals with impact factor and will be dissemination to different scientific and social networks as well in to Scientific activity spreading actions

**Contributions of each author:**

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