

INPLASY PROTOCOL

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Conflicts of interest:
None.

INTRODUCTION

Review question / Objective: Exercise-conditioned human serum affect the hallmarks of cancer of cancer cell lines?

Effect of exercise-conditioned human serum in hallmarks of cancer: systematic review and meta-analysis of in vitro studies

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Review question / Objective: Exercise-conditioned human serum affect the hallmarks of cancer of cancer cell lines?

Condition being studied: Our study can help to understand if and how physical exercise affects cancer cells, some studies were developed that incubated cancer cells lines with serum from animals or humans. These studies used different design and methods for analysis the effect of acute or chronic physical exercise in some of the hallmarks of cancer cells like sustentation of proliferative signaling and evading growth suppressors and resisting to cell death, as study as the mechanisms involved. The results show that effect of conditioned serum don't had the same magnitude on all studies included similar design studies and with same type of cancer cell. The results can promote some doubts about the exclusive effect of physical exercise in different cancer cells and in different hallmarks of cancer cells.

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 18 December 2020 (registration number INPLASY2020120096).

Rationale: To understand if and how physical exercise affects cancer cells, some studies were developed that incubated cancer cells lines with serum from animals or humans. These studies used different design and methods for analysis the effect of acute or chronic

physical exercise in some of the hallmarks of cancer cells like sustention of proliferative signaling and evading growth suppressors and resisting to cell death, as study the mechanisms involved. The results show that effect of conditioned serum don't had the same magnitude on all studies included similar design studies and with same type of cancer cell. The results can promote some doubts about the exclusive effect of physical exercise in human cancer cells and in different hallmarks of cancer cells.

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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 Malignanc* OR cancer* OR carcinoma) AND (cell* OR "cell culture" OR "in vitro")). This combination was inserted into searches of 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 and abstract into each database. Research procedures were carried out on July of 2020.

Participant or population: Serum of Participants from different age and different characteristic (Healthy Women; Breast Cancer Patient; Women After Cancer Treatment; Young and Old Healthy Men; Men Considered To Be Risk; and Male Colorectal Cancer Survivors), and different Human cancer cell lines.

Intervention: The intervention is of different types of physical exercise: Combined, Resistance Training, High Intensity Exercise, Aerobic Exercise, as with different frequency: acute (single session) and or chronic lasting at least three weeks up to several years.

Comparator: The effect of exercise-conditioned human serum in hallmarks of human cancer cells were compared to the effect of the serum collected at rest in hallmarks of human cancer cells.

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. Qualitative data from the different articles was selected, extracted, and organized in a specific table, follo.

Eligibility criteria: The inclusion criteria used to determine which articles would be selected for the present study were: a) had an In Vitro design; b) using human exercise-conditioned serum for stimulated of human cancer cell lines; c) physical exercise as an intervention tool and without any other parallel secondary type of intervention (e.g., diet); d) published in English before July 2020.

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 exercise-conditioned human serum reducing sustentation of proliferative signaling and evading growth suppressors and reducing the resisting cell death. We expected a moderate to large effects. Meta-analysis was conducted for one Hallmark of Cancer when at least three studies investigated it. Effect size was calculated using the software Comprehensive Meta-Analysis. The effect-size metric selected was the standardized difference in means (standard difference in means) as all studies evaluated the same outcome variable, but with different criteria. Data extracted for effect-size calculations from the different studies included Sample Size, Statistical Significance and Effect Direction. All results of different samples were used in the meta-analysis, excepted the data of assays that used the same sample with different time of incubation. 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/ January.

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 datas 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; One table for each hallmark of cancer with synthesis of the articles selected on the effects of acute and chronic with sistematized information of each study: Authors, contry, type of cancer, sample characteristic, study design, exercise characteristic, main outcomes and output; One figure with summary of descriptive and inferential statistics of results for each study and overall effect size of the effect of the acute-exercise-conditioned human serum for each hallmarks of cancer. One figure of funnel plot of standard error by std diff in means for each qualitative analysis.

Subgroup analysis: We included randomized or Non-randomized experimentals in vitro study, with control Group (rest serum) and Exercise Group (serum collected sooner, 4h, 24h after exercise intervention) with In Vitro design that evaluated human exercise-conditioned serum for stimulated of human cancer cell lines. The participants were from different

countries with different age and different characteristic (Healthy Women; Breast Cancer Patient; Women After Cancer Treatment; Young and Old Healthy Men; Men Considered To Be Risk; and Male Colorectal Cancer Survivors). The cell lines were used from different cancers (Prostate; Breast Cancer; Lung Cancer; Colon Cancer; at cell culture and complementary assays that evaluated two hallmarks of cancer cell.

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: cell culture; tumor; anticancer activity; physical activity; sport; cancer risk.

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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