INPLASY PROTOCOL

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None.

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 cancer cell lines viability?**
Condition being studied: **Our study can help to understand if and how exercise affects the viability of cancer cells. Some studies, with different designs have analyzed 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 physical exercise on the viability and apoptosis 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 07 January 2021 (registration number INPLASY2020120096).

INTRODUCTION

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

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 proliferation, growth and apoptosis, 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 cell lines viability.

Condition being studied: Our study can help to understand if and how exercise affects the viability of cancer cells. Some studies, with different designs have analyzed 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 physical exercise on the viability and apoptosis of cancer cells.

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 viability and apoptosis of cancer cell lines were compared to the effect of the serum collected at rest in viability and apoptosis cancer cell lines.

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 in viability and apoptosis cancer cell lines. We expected a moderate

to large effects. Meta-analysis was conducted for the effects of acute exercise-conditioned human serum on the viability of cancer cell lines, and taking into account the intensity of the exercise performed before blood collection. 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/ 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 ≥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; two tables with systematized information of each selected study that analyzed the effects of acute and chronic in proliferation, growth and apoptosis of cancer cell lines (authors, country, type of cancer, sample characteristic, study design, exercise characteristic, main outcomes and output); Three 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 in cancer cell lines viability, as the effect of high intensity acute exercise-conditioned human serum and moderate intensity acute exercise-conditioned human serum in cancer cell lines viability. 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: 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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