Title

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Journal

Cancer Cell, 42(2)

ISSN

1535-6108

Authors

Lavery, Jessica A
Boutros, Paul C
Knight, Daniel
et al.

Publication Date

2024-02-01

DOI

10.1016/j.ccell.2023.12.007

Peer reviewed

HHS Public Access

Author manuscript

Cancer Cell. Author manuscript; available in PMC 2025 February 12.

Published in final edited form as:

Cancer Cell. 2024 February 12; 42(2): 169–171. doi:10.1016/j.ccell.2023.12.007.

Association of exercise with pan-cancer incidence and overall survival

Jessica A. Lavery[1], **Paul C. Boutros**[3,4,5,6], **Daniel Knight**[6], **Tuomas Tammela**[7], **Chaya S. Moskowitz**[1], **Lee W. Jones**[1,2,*]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA

[2]Weill Cornell Medicine, New York, NY, USA

[3]Department of Human Genetics, University of California, Los Angeles, Los Angeles, CA, USA

[4]Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

[5]Institute for Precision Health, University of California, Los Angeles, Los Angeles, CA, USA

[6]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA, USA

[7]Cancer Biology and Genetics Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Epidemiological evidence links exercise with reduced risk of multiple cancers, leading to consensus statements from organizations including the 2018 Physical Activity Guidelines Advisory Committee (PAGAC).[1] However, the evidence supporting these statements is limited by studies with short follow-up periods and a small number of incident cancer events, differences in measurement and definition of exercise in meta-analysis, and potential heterogeneity in cancer screening practices between exercisers and non-exercisers. Additionally, prospective studies have mostly focused on how exercise associates with risk of one specific type of cancer in isolation and focused on incident cancer events without consideration of impact on all-cause mortality (ACM).

We leveraged data from the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial[2–4] to examine the impact of exercise on cancer incidence and ACM in 60,045 adults without a history of cancer. The PLCO dataset addresses the highlighted limitations by providing uniform assessment of exercise exposure, uniform cancer screening (in those allocated to the screening intervention arm), and long follow-up with rigorous ascertainment and adjudication of all incident cancers and cause of death.

*Correspondence: jonesl3@mskcc.org.

DECLARATION OF INTERESTS

L.W.J. – stock ownership in Pacylex, Inc. and Illumisonics, Inc.

J.A.L. – salary support from American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange Biopharma Collaborative (GENIE BPC).

P.C.B. – scientific advisory boards for Sage Bionetworks, BioSymetrics Inc. and Intersect Diagnostics Inc.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2023.12.007.

PLCO was a nationwide, prospective study evaluating the effects of annual screening (intervention) or usual care (control) on cancer mortality. At enrollment, intervention participants completed a questionnaire including assessment of vigorous exercise. To approximate the national definition of vigorous exercise (i.e., ≥75 min per week), 32,930 (55%) were classified as exercisers (≥2 h per week) and 27,115 (45%) as non-exercisers (0 to 1 h per week) (Table S1). Dose response was assessed according to: (1) 0 to 1 h per week (n = 27,115; 45%), (2) 2 to 3 h per week (n = 18,882; 31%), and (3) ≥4 h per week (n = 14,048; 23%). Participants were contacted annually to ascertain and confirm cancer diagnoses and deaths, supplemented by the National Death Index. The trial also used an endpoint adjudication process to assign the cause of death in a uniform and unbiased manner. The last follow-up for cancer ascertainment in the PLCO was conducted in 2017.

The primary endpoint was cancer incidence. Secondary endpoints were cancer site-specific incidence and ACM. Age was used as the timescale for all time-to-event analyses, and participants entered the risk set at the time of Dietary Questionnaire completion to account for the delayed entry criteria. The cumulative incidence of cancer was estimated using the Aalen-Johanssen method. A Cox proportional hazards model was used to estimate the cause-specific hazard of cancer, for any cancer and for the 17 cancer types with ≥100 events (male breast and biliary cancer were ineligible). For cause-specific analyses, individuals dying without cancer or alive at the end of follow-up were censored. We utilized interaction terms to test whether the impact of exercise on cancer incidence differed based on body mass index (BMI), sex, alcohol use, age, smoking history, and comorbidity history. To examine whether the relationship between exercise and cancer incidence influenced ACM, an interaction term between exercise and cancer status was included in a Cox proportinal hazards model, where cancer status was modeled as a time-varying covariate. Covariates significant in univariable Cox regression analyses at a threshold of $p \leq 0.2$ were included in multivariable models. In analyses of the three-level exercise classification, global p values were used to assess whether cancer incidence varied by exercise dose. Proportional hazards assumptions were assessed using weighted score tests and by visual inspection of survival curves by exercise status.[5] Cumulative incidence estimates at 70 years of age alongside multivariable adjusted cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs) are presented. Analyses were performed in R version 4.1.2.

The median time between completion of the exercise survey (study entry) and last follow-up among participants alive at the end of the study period was 18 years (IQR, 15 to 20 years). During this period, 15,954 first incident invasive cancers were diagnosed. At age 70, the estimated cumulative incidence of any incident cancer was 21% (95% CI, 21% to 22%) for exercisers and 22% (95% CI, 21% to 23%) for non-exercisers (Figure S1A). Exercisers had a lower hazard of any cancer than non-exercisers in a multivariable analysis adjusted for age at the time of Dietary Questionnaire completion, PLCO enrollment year, sex, race/ethnicity, smoking pack-years, alcohol (g/day), BMI, and comorbidity history at the time of PLCO enrollment (HR 0.97, 95% CI, 0.94 to 1.00, p = 0.07). The interaction between exercise and sex was significant, with exercise protective for females (HR 0.93, 95% CI, 0.87 to 0.98) but not for males (HR 1.00, 95% CI, 0.95 to 1.05).

For individual cancers, exercisers had a 26% lower risk of head and neck cancer (HR 0.74, 95% CI, 0.59 to 0.94, p = 0.01), 20% lower risk of lung cancer (HR 0.80, 95% CI, 0.72 to 0.88, p < 0.001), and 11% lower risk of breast cancer (HR 0.89, 95% CI, 0.82 to 0.98, p = 0.01) compared with non-exercisers. Conversely, exercisers had a 20% increased risk of melanoma (HR 1.20, 95% CI, 1.05 to 1.37, p = 0.006) and 12% higher risk of prostate cancer (HR 1.12, 95% CI, 1.05 to 1.20, p < 0.001) compared to non-exercisers (Figure S1B).

The inverse relationship between exercise and risk varied by dose (Figures S1C and S1D). For head and neck cancer, 2–3 h per week was associated with a 21% reduction (HR 0.79, 95% CI, 0.61 to 1.03), whereas ≥ 4 h per week was associated with a 31% risk reduction (HR 0.69, 95% CI, 0.51 to 0.93) compared with 0–1 h per week (p = 0.03). For lung cancer, 2–3 h per week was associated with a 19% reduction (HR 0.81, 95% CI, 0.72 to 0.92) whereas ≥ 4 h per week was associated with a 23% risk reduction (HR 0.77, 95% CI, 0.68 to 0.88) compared to 0–1 h per week (p < 0.001). For breast cancer, compared to 0–1 h per week, 2–3 h per week was associated with 2% lower risk (HR 0.98, 95% CI, 0.89 to 1.08) whereas ≥ 4 h per week was associated with a 23% risk reduction (HR 0.77, 95% CI, 0.69 to 0.87) (p < 0.001) (Figure S1C). For prostate cancer, compared with 0–1 h per week, 2–3 h per week was associated with 5% increased risk (HR 1.05, 95% CI, 0.98 to 1.13) whereas ≥ 4 h per week was associated with a 22% increased risk (HR 1.22, 95% CI, 1.13 to 1.32) (p < 0.001). For melanoma, 2–3 h per week was associated with a 22% increased risk (HR 1.22, 95% CI 1.05, 1.41), while ≥4 h per week was associated with an 18% increased risk (HR 1.18, 95% CI 1.00, 1.39) (p = 0.02) (Figure S1D).

During follow-up, a total of 16,271 deaths from any cause were documented. For individuals not diagnosed with cancer, exercisers had a 19% lower hazard of ACM than non-exercisers (HR 0.81, 95% CI, 0.76 to 0.86). Among individuals diagnosed with any cancer, exercisers had a 17% lower hazard of ACM than non-exercisers (HR 0.83, 95% CI, 0.78 to 0.88).

Consistent with our observations, in a pooled analysis of 1.44 million participants, Moore et al.[6] reported high exercise (at the 90th percentile of study participants) associated with significantly lower risk of breast, lung, and head and neck cancer and significantly higher risk of prostate cancer and melanoma, compared to low exercise (10th percentile of study participants). The associations between exercise dose and cancer incidence observed in our study among these cancer sites lend further credence to a potential causal relationship. Moore et al. found no associations between exercise and ovarian and pancreatic cancer, consistent with our results.[6] The PAGAC[1] also found strong evidence for exercise and reduced risks of bladder, colon, endometrial, renal, and gastric cancers, as well as esophageal adenocarcinoma, findings not replicated in our analysis. This may result from the small number of events, although at least 100 events were observed for each cancer site, and HR estimates were generally close to 1.0.

From a clinical perspective, our findings raise the notion for exercise recommendations to be integrated into cancer screening visits.[7] For individuals without cancer, exercise may decrease the risk of other causes of mortality (e.g., cardiovascular disease and other cancers) leading to an ACM benefit. Among those in whom a malignant lesion is detected,

post-diagnosis exercise associates with significant reductions in cancer mortality in select early-stage cancers[8] as well as reductions in cardiovascular among cancer survivors.[9,10]

Limitations of this study include exercise assessment by a single self-reported item of vigorous exercise only; misclassification is expected due to upgrading of lower-intensity exercise to vigorous. Second, exercise was only measured at PLCO baseline entry and therefore may not be a valid proxy for exercise at the time of tumor initiation and progression. A “call to action” is required for prospective studies leveraging wearable devices permitting longitudinal, serial, or “near continuous” evaluation of physical activity during cancer pathogenesis. Additionally, observational studies are susceptible to residual confounding. Although we adjusted all analyses for available clinical covariates, the contribution of unobserved confounding cannot be disregarded. Finally, results should be interpreted in the context of the hypothesis-generating nature of this study, with consideration given to the fact that analyses were not adjusted for multiple testing.

In conclusion, the association between vigorous exercise and incident cancer risk varied as a function of cancer type but lowered the hazard of ACM regardless of cancer status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

J.A.L., J.M.S., T.T., C.S.M., and L.W.J. are supported by the Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748). P.C.B. is supported by the University of California Los Angeles Cancer Center Support Grant (P30 CA016042).

A special thanks to the National Cancer Institute for granting access to the data collected by the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Cancer incidence data have been provided by the Colorado Central Cancer Registry, District of Columbia Cancer Registry, Georgia Cancer Registry, Hawaii Cancer Registry, Cancer Data Registry of Idaho, Minnesota Cancer Surveillance System, Missouri Cancer Registry, Nevada Central Cancer Registry, Pennsylvania Cancer Registry, Texas Cancer Registry, Virginia Cancer Registry, and Wisconsin Cancer Reporting System. All are supported in part by funds from the Center for Disease Control and Prevention, National Program for Central Registries, local states, or by the National Cancer Institute, Surveillance, Epidemiology, and End Results program. The results reported here and the conclusions derived are the sole responsibility of the authors.

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