Cancer Epidemiology 56 (2018) 67–74

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Effect of a 12-month exercise intervention on leukocyte telomere length: Results from the ALPHA Trial

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ARTICLE INFO

Keywords:
Telomeres
Exercise
Physical activity
Postmenopausal
Cancer
Randomized trial

ABSTRACT

Background: Short telomeres may indicate a higher risk of cancer and other chronic diseases. Some observational studies show positive associations between leukocyte telomere length (LTL) and physical activity levels. We hypothesized, therefore, that exercise may be one strategy for slowing telomere attrition.

Methods: We conducted an ancillary analysis of blood from a year-long, two-centred, two-armed (1:1) randomized controlled trial of aerobic exercise versus usual inactivity. The analysis included 212 physically inactive, disease-free, non-smoking, postmenopausal women (n = 99 exercisers, n = 113 controls) in Alberta, Canada (2003–2006). The exercise prescription was aerobic exercise five days/week (supervised three days/week), 45 min/session, achieving 70–80% heart rate reserve. Baseline and 12-month LTL were analyzed using quantitative real-time polymerase chain reactions (qPCR). The primary statistical analysis was intention-to-treat, comparing the ratio of mean LTLs (12-months:baseline) for exercisers versus controls from a general linear model. Secondary analyses included a per-protocol analysis (≥90% adherence) and analyses stratified by baseline LTL, age, body mass index, and fitness level, respectively.

Results: Participants were overweight at baseline (mean BMI = 29 kg/m^2). The primary analysis showed no evidence that LTL change differed between groups (12-month mean LTL change for the exercise group: −13% (95% CI: −32%, 11%) versus controls: −8% (95%CI: −27%, 15%); treatment effect ratio (TER, Exercise/Control) = 0.95 (95% CI: 0.68, 1.32). Per-protocol results were similar (TER = 0.87, 95% CI: 0.59, 1.30). In stratified models, TERs ranged from 0.68 to 1.35 across strata and *P*-interaction > 0.05).

Conclusion: We found no evidence to suggest that one year of aerobic exercise alters telomere attrition significantly in healthy postmenopausal women.

1. Introduction

In Canada in 2017, nearly half of Canadians were expected to develop cancer over a lifetime, most after age 50, and cancer was the leading cause of death [1]. Physical inactivity is a known, modifiable risk factor for cancer [2]. A recent pooled analysis of 1.44 million men and women estimated that women reporting high versus low levels of leisure-time physical activity experienced lower risks of 13 types of cancer [3]. Despite strong epidemiologic evidence of an association, the biologic mechanisms are not well understood.

One hypothesized mechanism relates to telomere length. Telomeres are nucleoprotein structures located at the ends of chromosomes that

Abbreviations: ALPHA, Alberta Physical Activity and Breast Cancer Prevention; BMI, body mass index; CT, computed tomography; DXA, dual x-ray absorptiometry; LTL, leukocyte telomere length; qPCR, quantitative real-time polymerase chain reaction; T/S, relative leukocyte telomere length expressed as a ratio of two quantitative PCR products: leukocyte telomere length (T) and a single-copy, beta-globin gene (36B4) reference standard (S)

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https://doi.org/10.1016/j.canep.2018.07.012
Received 19 January 2018; Received in revised form 19 July 2018; Accepted 20 July 2018
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protect cells from chromosomal instability and shorten naturally with every cellular division in normal cells. Telomere attrition reflects cellular aging, cellular damage, chronological age [4], and has been linked to cancer susceptibility. Over time, telomeres can become critically shortened and dysfunctional. If important cell cycle checkpoint genes are compromised, premalignant cells may continue to grow, eventually leading to genomic instability and potentially cancer [5]. Genetic determinants of telomere length (e.g., variants of the *TERT* gene which encodes telomerase, a reverse transcriptase enzyme that maintains telomere length) have been associated with cancer risk [6–9]. Observational studies show that shorter leukocyte telomere length (LTL) may be associated with higher risks of cancer [10–12], type 2 diabetes [13], and all-cause mortality [14].

A healthy lifestyle may decrease telomere attrition by increasing telomerase activity or slowing cell turnover [15,16]. A systematic review of 37 epidemiologic studies relating physical activity to telomere length showed inconsistent results with evidence of a significant positive association in 15 studies (longer telomeres were associated with higher activity levels) [17]. However most of these studies were not prospective designs, lacked adjustment for important confounders, and may have been inadequately powered to detect associations; moreover, inter-study heterogeneity was high. Recently, cross-sectional analyses from the National Health and Nutrition Examination Survey (NHANES, 1999–2002) in the U.S. showed significant positive associations between longer LTL and vigorous [18] or moderate-vigorous-intensity activity [19] as well as total activity and movement behaviours [20,21].

To strengthen the epidemiologic evidence on this topic, we examined the effect of exercise on LTL in a year-long, randomized controlled exercise trial called the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial. Participants were 320 cancer-free, physically inactive postmenopausal women. Our analysis of LTL stemmed from the ALPHA Trial and focused on a subset of women (274/320) with baseline and 12-month blood samples available for LTL analysis. We hypothesized that women assigned to exercise would experience less telomere attrition than women assigned to a no-exercise control group.

2. Methods

Methods for the ALPHA Trial are published elsewhere [22]. The ALPHA Trial was a two-centred, two-armed (1:1) randomized controlled trial (RCT) conducted in healthy postmenopausal women living in Calgary and Edmonton, Alberta, Canada. Recruitment ran from May, 2003–June, 2006 and 12-month follow-up ended in 2007. Analysis of LTL was done October–December, 2015. Research ethics boards at the Alberta Cancer Board and Universities of Calgary and Alberta approved the trial protocol. The Conjoint Health Research Ethics Board at the University of Calgary and the Health Research Ethics Board of Alberta Health Services approved the LTL analysis protocol. All participants provided written informed consent.

2.1. Participants

Recruitment and eligibility criteria in the ALPHA Trial were described previously [22]. Some noteworthy eligibility criteria were: 50–74 years old, postmenopausal, body mass index (BMI) 22–40 kg/m^2, non-smoker, < 14 alcoholic drinks/week, no previous cancer diagnosis or major co-morbidities, normal fasting glucose and serum cholesterol. All participants were inactive (exercised < 90 min/week or, if 90–120 min/week, had a VO_{2max} level < 34 mL/kg/min) and resided in Calgary or Edmonton.

2.2. Intervention

A statistician used a random number program in S-plus® to assign women to the two intervention arms using a center- and BMI-stratified blocked randomization design. Group assignments were stored in numbered, sealed envelopes until the time of individual random allocation when a Study Coordinator opened an envelope.

For women allocated to exercise, we prescribed aerobic exercise for at least 45 min, five days/week for one year. Three sessions/week were facility-based with on-site ALPHA Trial exercise trainers and two sessions/week were unsupervised. Participants wore heart rate monitors (Polar® A3) to target exercise intensities at 70–80% of heart rate reserve. The prescription increased gradually in months 0–3 and was then maintained in months 4–12. Adherence was monitored by participants and trainers using weekly exercise logs. We asked the control group to maintain their usual lifestyle.

2.3. Health assessments

We assessed demographics and health histories using self-administered questionnaires at baseline. Mental health was a score derived from five items on the Medical Outcomes Study short form survey (SF-36) [23] about feelings of nervousness, depression, peacefulness, happiness or calm in the past four weeks. Additional measures at baseline and 12 months included: self-reported past year diet [24] and physical activity [25], physical fitness (estimated $\dot{V}O_{2max}$ from a modified Balke treadmill protocol for submaximal exercise intensities), and duplicate anthropometric measurements using standardized methods. A certified Exercise Physiologist performed fitness testing and anthropometry. Total body fat was measured using whole body dual X-ray absorptiometry (DXA) by ALPHA Trial staff in Calgary and by University of Alberta staff in Edmonton. We later calculated percent body fat as 100% × (fat mass/(fat mass + lean mass)). Abdominal fat was measured using computed tomography (CT) scans by staff at the Alberta Cancer Board in Calgary or the Cross Cancer Institute in Edmonton [26]. The study radiologist was blinded to randomization group when reviewing CT scans.

2.4. Blood assays

A phlebotomist collected fasting blood, taken at least 24 h post-exercise, at baseline and 12 months. Blood samples were collected, processed, and stored within 12 h of collection and then shipped and stored in −86 °C freezers until the time of assay.

Nucleic acid extraction was done by personnel at the Translational Laboratories at the Tom Baker Cancer Center. All laboratory analysts were blinded to study identification number and randomization group. Buffy coat aliquots were thawed at room temperature and proprietary nucleic acid stabilizer (Solution R, DNA Genotek, Ottawa, Ontario) was added to each sample (1:1) to preserve RNA integrity. The extraction was automated on the Hamilton STARlet (Hamilton Robotics Inc., Reno, USA) using a Macherey-Nagel NucleoMag Blood 200 µl kit (Macherey-Nagel GmbH & Co. KG, Düren, Germany). DNA was eluted in nuclease-free water and quantified using a Qubit dsDNA HS Assay Kit measured on the Qubit 2.0 Fluorometer (ThermoFisher Scientific Inc., Waltham, USA). DNA quantification was performed using the NanoDrop 2000C (Thermo Fischer, MA, USA) and 384-well plates (Applied Biosystems: Life Technologies, MicroAmp® Optical 384-well Reaction Plate with Barcode).

All LTL analyses were conducted in Dr Beattie's laboratory at the University of Calgary. Briefly, we used high-throughput analysis using quantitative real time polymerase chain reaction (qPCR). Sample reactions were set up in triplicate using the EpMotion 5075 (Eppendorf, USA), containing 20 ng of template DNA, Power SYBR Green PCR Master mix (Life Technologies, NY, USA), and primers for telomeres or the single copy gene, ribosomal acidic protein 36B4. Fluorescent signal detection was monitored and quantified as per manufacturer's directions using Quant Studio 06 Flex machine (Life Technologies, NY, USA). qPCR cycling conditions and primer sequences used were as previously

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