Null Results in Brief

Lack of Association Between Physical Activity in Smokers and Plasma Glutathione Peroxidase Levels

Andrew Rundle,[1] Catherine Richards,[1] Deliang Tang,[2] and Frederica Perera[2]

Departments of [1]Epidemiology, and [2]Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York

Introduction

One proposed mechanism for the protective effect of physical activity on cancer development is through increasing endogenous antioxidant enzyme systems such as glutathione peroxidase (GPX; ref. 1). GPX reduces hydrogen and lipid peroxides to less toxic hydroxy fatty acids using glutathione as a reducing agent, and these compounds play a major role in defending the body against reactive oxygen species(2). Several exercise training studies have found that GPX activity increases in response to training, and that GPX declines in response to detraining (3-7). However, because most population-based physical activity interventions aim to increase levels of activities in the low to moderate exertion range, such as promoting walking, it is important to understand associations between biomarkers and variation in activity for levels of activity that are lower than those used in exercise training trials (8). There is very little data on whether variation in GPX levels is associated with variation in physical activity achieved through everyday activity conducted outside of the clinical trial setting. One cross-sectional study of women found that whole-blood GPX activity was positively associated with total leisure and household activity (9).

Materials and Methods

A cross-sectional analysis of physical activity was conducted in a population taking part in a randomized double-blind placebo-controlled study of antioxidant micronutrient supplementation and genetic damage from cigarette smoke. The characteristics of this study population have been extensively described elsewhere (10, 11). At the 12-month follow-up in the trial study, subjects completed the Paffenbarger Physical Activity Questionnaire. Written informed consent was obtained from all subjects. Consent forms and recruitment procedures were approved by the Institutional Review Boards of Columbia Presbyterian Medical Center, the Herbert Irving Cancer Center, and the New York State Psychiatric Institute.

Plasma levels of extracellular GPx (eGPx) in samples from month 12 were analyzed using the Calbiochem, Inc. ELISA kit. The ELISA kits used standard 96-well plates, and to reduce variability, duplicate samples were run on each plate and the mean of the two aliquots was used as the measurement of eGPx concentration.

Statistical Analyses. Linear regression models were used to determine whether physical activity was associated with increased levels of eGPX. Physical activity was considered as hours of activity per week engaged in at a moderate intensity and hours of activity per week engaged in at a vigorous intensity, and the total MET-hours per week of activity, which includes light, moderate, and vigorous activity. Hours of moderate and vigorous activity were analyzed together, and total MET-hours per week of physical activity was considered in a separate model. Hours of moderate and vigorous activity were divided by 5, and regression coefficients represent the change in eGPx concentration per 5 h of activity. MET-hours of activity were divided by 15 to represent 5 h of light to moderate activity per week, and the regression coefficients represent the change in eGPx concentration per 15 Met-hours per week. Each of the two models controlled for age, gender, race/ethnicity, cigarettes smoked per day at the 12-mo visit, laboratory batch, and treatment group. The coefficients, 95% confidence intervals, and *P* values are presented for each of the models predicting eGPX.

Results

Data on physical activity and plasma levels of eGPx were available from 174 study subjects. Table 1 shows the descriptive characteristics of the study subjects included in the analysis.

Table 2 shows univariate and multivariate results for the linear regression analysis of moderate and vigorous physical activity and eGPX; no associations were apparent in either model. Table 2 also shows the results for the univariate and multivariate results for the linear regression analysis of MET-hours per week of physical activity and eGPX; no associations were apparent in either model.

Cancer Epidemiol Biomarkers Prev 2008;17(4):1004–6

Received 8/6/07; revised 11/3/07; accepted 2/8/08.

Grant support: National Cancer Institute (K07 CA92348 and M01RR000645-320825).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Andrew Rundle, 722 West 168th Street, Room 730, New York, NY 10040. Phone: 212-305-7619. E-mail: Agr3@columbia.edu

Copyright © 2008 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-07-0721

Downloaded from http://aacrjournals.org/cebp/article-pdf/17/4/1004/2267698/1004.pdf by guest on 21 February 2024

Table 1. Descriptive characteristics of the study population

Categorical variables		Continuous variables	
	n (%)		Mean (SD)
Gender			
Male	100 (57.5)	Age	38.9 (10.3)
Female	74 (42.5)	Cigarettes per day	16.6 (10.9)
Race/ethnicity		GPX in plasma	24.1 (7.6)
Caucasian	63 (36.2)	H of moderate activity per wk	24.8 (15.8)
Hispanic	23 (13.2)	H of vigorous activity/wk	15.5 (15.8)
African American	82 (47.1)	MET-h of activity per wk	454.6 (133.0)
Other	6 (3.4)		
Treatment			
Antioxidant micronutrient group	80 (46.0)		
Placebo group	94 (54.0)		

Discussion

Numerous mechanistic hypotheses have been suggested for the protective effects of physical activity on cancer risk, including reducing oxidative stress through increases in endogenous antioxidant enzyme systems(1). eGPX is one of at least four genetically distinct forms of the antioxidant GPx enzyme family and is found in plasma and respiratory tract lining fluid (12, 13). Under oxidative stress conditions, such as during smoking, the eGPX concentrations in the lung increase, in what is believed to be a protective response (14-16). Several clinical exercise training trials have suggested that increased physical activity is associated with increased GPx levels. However, most population-based activity interventions, such increasing walking, involve promoting increases in light to moderate activity (8). Past work has suggested that activity-induced biological changes that are hypothesized to influence cancer risk vary depending on the context of activity, with one important factor being the extent of exertion (1).

Covas and colleagues (9) conducted analyses of an individual's daily activity patterns and found that higher levels of high intensity leisure time activity and total leisure time activity plus household activity were associated with increased levels of whole blood GPx activity. The analyses presented here measured plasma eGPx protein levels and, so, are not directly analogous to this past work. However, it has been shown that the eGPx activity of a sample is proportional to the protein concentration (17, 18). It is possible that the previous results represent an effect of activity on intracellular RBC GPx activity and not plasma eGPx activity.

The study presented here was sufficiently powered to observe effects on the scale observed by Covas and in other reports (19). However, it was not powered to detect associations of the small magnitude actually observed; in the multivariate model, the *post hoc* power to detect the β for weekly physical activity was 8%, and in the multivariate model, the power to detect the observed βs for vigorous and moderate activity the power was 8% and 0%, respectively. The R^2 for the overall model was 0.17, mainly due to associations with the demographic variables, and the overall model had >95% power to observe a R^2 of this magnitude. Past work with this study population and these activity measures has shown associations between activity and body mass index, blood pressure, and blood glutathione levels, suggesting that the measure has construct validity (10, 20). It is possible that other, unknown, demographic, or life-style differences between the populations account for the differences in findings.

These data suggest that plasma GPx levels are not associated with variation in everyday physical activity levels observed in the community. These findings suggest that increases in GPx-related antioxidant capacity are not likely to occur due to modest increases in activity that are likely to result for population level public health campaigns. It seems that sustained exercise training programs may be required to effect GPx levels.

Table 2. Results of linear regression analyses of physical activity and eGPx

	H of moderate and vigorous activity per wk					
	Univariate (n = 174)			Multivariate* (n = 174)		
	β (SE)	95% CI	*P*	*β* (SE)	95% CI	*P*
Moderate activity (per 5 h)	−0.16 (0.19)	−0.52-0 21	0.40	−0.01 (0.19)	−0.39-0.37	0.95
Vigorous activity (per 5 h)	0.01 (0.18)	−0.36-0.37	0.97	0.10 (0.20)	−0.29-0.49	0.61
	Total activity per wk					
Total activity (per 15 MET-h)†	−0.02 (0.07)	−0.15-0.11	0.82	0.04 (0.07)	−0.10-0.18	0.60

Abbreviation: 95% CI, 95% confidence interval.
*Adjusted for age, sex, race, cigarette smoking, treatment group, and ELISA plate.
†Per 15 MET-hours, equivalent to 5 h of light to moderate activity per week.

Downloaded from http://aacrjournals.org/cebp/article-pdf/17/4/1004/2267698/1004.pdf by guest on 21 February 2024

References

1. Rundle A. The molecular epidemiology of physical activity and cancer. Cancer Epidemiol Biomarkers and Prev 2005;14:227–36.
2. Rahman Q, Abidi P, Farrukh A, et al. Glutathione redox system in oxidative lung injury. Crit Rev Toxicol 1999;29:543–68.
3. Miyazaki H, Oh-ishi S, Ookawara T, et al. Strenuous endurance training in humans reduces oxidative stress following exhausting exercise. Eur J Appl Physiol 2001;84:1–6.
4. Kedziora J, Buczynski A. Antioxidative enzymes activities and lipid peroxidation indicators in blood platelets during bed rest. Int J Occup Med Environ Health 1996;9:45–51.
5. Francisco Javier O, Manuel R, Manuel RR. Regular physical activity increases glutathione peroxidase activity in adolescents with Down syndrome. Clin J Sport Med 2006;16:355–6.
6. Elosua R, Molina L, Fito M, et al. Response of oxidative stress biomarkers to a 16-week aerobic physical activity program, and to acute physical activity, in healthy young men and women. Atherosclerosis 2003;167:327–34.
7. Fatouros IG, Jamurtas AZ, Villiotou V, et al. Oxidative stress responses in older men during endurance training and detraining. Med Sci Sports Exer 2004;36:2065–72.
8. Wyatt HR, Peters JC, Reed GW, Barry M, Hill JO. A Colorado statewide survey of walking and its relation to excessive weight. Med Sci Sports Exer 2005;37:724–30.
9. Covas MI, Elosua R, Fito M, Alcantara M, Coca L, Marrugat J. Relationship between physical activity and oxidative stress biomarkers in women. Med Sci Sports Exer 2002;34:814–9.
10. Rundle A, Orjuela M, Mooney L, et al. Moderate physical activity is associated with increased blood levels of glutathione among smokers. Biomarkers 2005;10:3390–400.
11. Rundle A, Madsen A, Orjuela M, et al. The association between benzo[a]pyrene-DNA adducts and body mass index, calorie intake and physical activity. Biomarkers 2007;12:123–32.
12. Avissar N, Finkelstein J, Horowitz S, et al. Extracellular glutathione peroxidase in human lung epithelial lining fluid and in lung cells. Am J Physiol 1996;270:L173–82.
13. Kim K, Whitin J, Sukhova N, Cohen H. Increase in extracellular glutatione peroxidase in plasma and lungs of mice exposed to hyperoxia. Pediatr Res 1999;46:715–21.
14. Comhair S, Thomassen M, Erzurum S. Differential induction of extracellular peroxidase and nitirc oxide synthase 2 in airways of healthy individuals exposed to 100% O2 or cigarette smoke. Am J Respir Cell Mol Biol 2000;23:350–4.
15. Hilbert J, Mohsenin V. Adaptation of lung antioxidants to cigarette smoking in humans. Chest 1996;110:916–20.
16. Comhair S, Lewis M, Bhathena P, Hammel J, Erzurum S. Increased glutathione and glutathione peroxidase in lungs of individuals with chronic beryllium disease. Am J Respir Crit Care Med 1999;159:1824–9.
17. Yamamoto Y, Takekoshi Y, Itami N, et al. Enzyme-linked immunosorbent assay for extracellular glutathione peroxidase in serum of normal individuals and patients with renal failure on hemodialysis. Clin Chim Acta 1995;236:93–9.
18. Suemizu H, Yoshimura S, Tada N, Watanabe K, Moriuchi T. Production and characterization of two monoclonal antibodies to human glutathione peroxidase. Hybridoma 1992;11:795–801.
19. Robertson J, Maughan R, Duthie G, Morrice P. Increased blood antioxidant systems of runners in response to training load. Clin Sci (Lond) 1991;80:611–8.
20. Rundle A, Hagins M, Orjuela M, Mooney L, Kim M, Perera F. Traditional physical activity indexes derived from the Harvard alumni activity survey have low construct validity in a lower income, urban population. J Urban Health 2007;84(5):722–32. Epub 2007 Jul 2.

Downloaded from http://aacrjournals.org/cebp/article-pdf/17/4/1004/2267698/1004.pdf by guest on 21 February 2024