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

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Keywords

Physical activity; anti-oxidant

Introduction

One proposed mechanism for physical activity's protective effect on cancer development is through increasing endogenous antioxidant enzyme systems, such as glutathione peroxidase (GPX) (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 de-training (3-7). However, since 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 IRBs of Columbia Presbyterian Medical Center (CPMC), the Herbert Irving Cancer Center, and the New York State Psychiatric Institute.

Plasma levels of extra-cellular GPx (eGPx) in samples from month 12 were analyzed using the Calbiochem, Inc ELISA kit (San Diego, CA. Cat. # 353918). The ELISA kits used

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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/week of activity, which includes light, moderate and vigorous activity. Hours of moderate and vigorous activity were analyzed together and total MET-hours/week of physical activity was considered in a separate model. Hours of moderate and vigorous activity were multiplied by five and regression coefficients represent the change in eGPx concentration per five hours of activity. Met*hours of activity were multiplied by 15 to represent 5 hours 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 month 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/week of physical activity and eGPx; no associations were apparent in either model.

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). Extra-cellular GPx 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 conducted analyses of 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 (9). 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 previously results represent an effect of activity on intra-cellular red blood cell 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 beta for weekly physical activity was 8% and in the multivariate model the power to detect the observed betas 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 greater than 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 lifestyle 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 appears that sustained exercise training programs may be required to impact GPx levels.

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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)	Hrs of moderate activity/week	24.8, 15.8
Hispanic	23 (13.2)	Hrs of vigorous activity/week	15.5, 15.8
African American	82 (47.1)	MET*hrs of activity/week	454.6, 133.0
Other	6 (3.4)		
Treatment			
Antioxidant			
Micronutrient			
group	80 (46.0)		
Placebo group	94 (54.0)		

Table 2
Results of Linear Regression Analyses of Physical Activity and eGPx

	Hours of Moderate and Vigorous Activity per Week					
	Uni-variate (n=174)			Multi-variate* (n=174)		
	β (SE)	95 % CI	P-value	β (SE)	95 % CI	P-value
Moderate activity (per 5 hours)	-0.16 (0.19)	(-0.52, 0.21)	0.40	-0.01 (0.19)	(-0.39, 0.37)	0.95
Vigorous activity (per 5 hours)	0.01 (0.18)	(-0.36, 0.37)	0.97	0.10 (0.20)	(-0.29, 0.49)	0.61
Total Activity per Week						
	Uni-variate (n=174)			Multi-variate* (n=174)		
	β (SE)	95 % CI	P-value	β (SE)	95 % CI	P-value
Total activity (per 15 MET [‡] hours) [‡]	-0.02 (0.07)	(-0.15, 0.11)	0.82	0.04 (0.07)	(-0.10, 0.18)	0.60

* adjusted for age, sex, race, cigarette smoking, treatment group, ELISA plate
[‡]per 15 MET[‡]hours, equivalent to 5 hours of light to moderate activity per week