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ORIGINAL ARTICLE

Physical activity and lung cancer among non-smokers: a pilot molecular epidemiological study within EPIC

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Abstract

The association between physical activity, potential intermediate biomarkers and lung cancer risk was investigated in a study of 230 cases and 648 controls nested within the European Prospective Investigation of Cancer and Nutrition. Data on white blood cell aromatic-DNA adducts by ^{32}P-post-labelling and glutathione (GSH) in red blood cells were available from a subset of cases and controls. Compared with the first quartile, the fourth quartile of recreational physical activity was associated with a lower lung cancer risk (odds ratio (OR) 0.56, 95% confidence interval (CI) 0.35–0.90), higher GSH levels (+1.87 μmol GSH g^{-1}

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haemoglobin, $p = 0.04$) but not with the presence of high levels of adducts (OR 1.05, 95% CI 0.38–2.86). Despite being associated with recreational physical activity, in these small-scale pilot analyses GSH levels were not associated with lung cancer risk (OR 0.95, 95% CI 0.84–1.07 per unit increase in GSH levels). Household and occupational activity was not associated with lung cancer risk or biomarker levels.

Keywords: *Physical activity; lung cancer; biomarkers; molecular epidemiology*

Introduction

In 2006 in Europe lung cancer represented 12.1% (386 300 cases) of all incident cancer and it was the leading cause of cancer death (Ferlay et al. 2007). Several studies have suggested that increased physical activity is protective against lung cancer (Kubik et al. 2007, Lee & Paffenbarger 1994, Lee et al. 1999, Leitzmann et al. 2009, Mao et al. 2003, Severson et al. 1989, Sinner et al. 2006, Sprague et al. 2008, Thune & Lund 1997, Yun et al. 2008). As there are few prevention programmes for ex-smokers, the most interesting data from a public health perspective are on associations between physical activity among ex-smokers and future lung cancer risk. Two reports from the Harvard Alumni Study saw reductions in lung cancer risk among physically active subjects who were non- and ex-smokers while two studies have found physical activity to be protective among ex-smokers but not non-smokers (Lee & Paffenbarger 1994, Lee et al. 1999, Leitzmann et al. 2009, Sinner et al. 2006). However, in a hospital-based case–control study in Prague, physical activity was not associated with lung cancer risk in non-smokers and long-term ex-smokers (Kubik et al. 2007).

It has been recommended that biomarker studies be conducted of possible mechanisms through which physical activity might exert protective effects on cancer outcomes (Hoffman-Goetz et al. 1998, McTiernan et al. 1998, Thune 2000). Several mechanisms have been proposed to explain the observed protective effects of physical activity, including increased endogenous antioxidant defences which are particularly relevant for ex-smokers, as oxidative stress promotes tumour growth (Cerutti 1985, Frenkel 1992, Rundle 2005). Glutathione (GSH) is an endogenous antioxidant found in exceptionally high concentrations in respiratory tract lining fluid and is a cofactor in the glutathione peroxidase-mediated detoxification of reactive oxygen species and is a cofactor in the glutathione *S*-transferase-mediated detoxification of carcinogens (Figure 1) (Bartsch et al. 1991, Boehme et al. 1992, Cantin et al. 1987, Jernstrom et al. 1982, Kelly 1999). Glutathione levels have also been shown to be positively associated with increased moderate intensity physical activity and to increase with exercise training (Evelo et al. 1992, Karolkiewicz et al. 2003, Michelet et al. 1995, Robertson et al. 1991, Rundle et al. 2005a). As such, activity-induced increases in GSH have been proposed as a mechanism through which physical activity might influence cancer risk (Rundle et al. 2005a). Additionally several studies have investigated whether carcinogen-DNA adducts, typically bulky aromatic adducts thought to be derived from cigarette smoke, are associated with lung cancer risk (Bak et al. 2006, Peluso et al. 2005b, Tang et al. 2001, 1998, Veglia et al. 2008, 2003). In general, positive associations between increased adduct levels and lung cancer risk have been observed among current smokers (Veglia et al. 2008, 2003); however in one study the strongest association was found among never-smokers (Peluso et al. 2005b). Physical activity has been associated with increases in enzymatic systems that detoxify chemical carcinogens and protect the lungs (Duncan et al. 1997, Rundle et al. 2005a) suggesting another mechanism through which physical activity may be protective.

An important issue arises when analysing data from recent ex-smokers; the decision to quit smoking may be

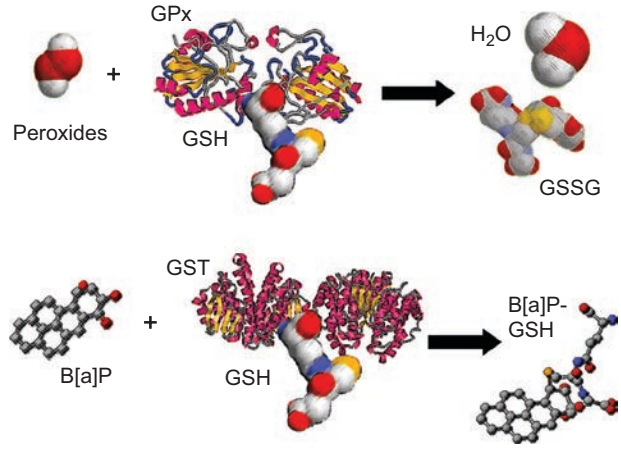

Figure 1. Pathways through which glutathione (GSH) is hypothesized to reduce lung cancer risk. GSH is a cofactor in the glutathione peroxidase (GPx)-mediated detoxification of hydroperoxides and is oxidized to glutathione disulfide (GSSG). Additionally, GSH is a conjugating group for the glutathione transferase (GST)-mediated detoxification of chemical carcinogens, here illustrated with GSH being conjugated to benzo[a]pyrene to create a water soluble metabolite.

linked to changes in physical activity and health status. Several studies of smokers have shown that increased stage of change for smoking cessation is associated with increased physical activity and with stage of change for exercise adoption and that readiness for physical activity is inversely associated with cigarettes smoked per day (Boyle et al. 2000, Doherty et al. 1998, Emmons et al. 1994, Garrett et al. 2004). In some people smoking cessation may be associated with the adoption of healthier lifestyle practices (Kawada 2004, Tang et al. 1997). However, many smokers quit smoking because of declining health which may also impact physical activity patterns in the years around the time of smoking cessation (Fishman et al. 2003, Halpern & Warner 1994, Joseph et al. 2005, Twardella et al. 2006, Wagner et al. 1995). Thus among some recent quitters health status may be causally associated with smoking status, and with past smoking behaviour and recent physical activity patterns. In other recent quitters, the decision to quit smoking may be associated with the decision to adopt exercise and both decisions may be associated with the extent of past daily smoking. Such patterns of variables that may simultaneously act with mediating and confounding effects may bias the results of analyses and such a bias cannot be addressed by standard multivariate approaches (Robins 1989, Robins et al. 2000).

Analyses of lung cancer risk and physical activity have been conducted in the overall European Prospective Investigation of Cancer and Nutrition (EPIC) cohort and no overall protective effect was observed (Steindorf et al. 2006). Here we focus on never-smokers and individuals who quit smoking 10 or more years before entering the cohort, thus minimizing the potential for smoking cessation in recent quitters being associated with changes in lifestyle that might bias study results. This issue has not been addressed previously in studies of physical activity and lung cancer. We also incorporate biomarker analyses into an epidemiological study of physical activity and cancer and report on pilot analyses of physical activity, GSH levels in red blood cells and carcinogen-DNA adducts in white blood cells.

Materials and methods

Study design

Gen-Air is a case–control study nested within the EPIC cohort designed to study the relationship between smoking-related cancers and air pollution and environmental tobacco smoke, and has been described extensively elsewhere (Airoldi et al. 2005, Peluso et al. 2005a, b). Follow-up in EPIC was based on population cancer registries in seven of the participating countries: Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the UK. In France, Germany and Greece, a combination of methods was used, including health insurance records, cancer and pathology registries, and active follow-up through study participants and their next of kin. Follow-up was virtually 100% complete. Individuals who were non-smokers at enrolment into EPIC or who were ex-smokers at enrolment and quit smoking 10 years or more prior to enrolment were eligible for inclusion in Gen-Air. For analyses of questionnaire data up to three controls per case were matched on gender, age (± 5 years), smoking status (never or former smoker), country of recruitment and follow-up time. The study was designed to have two of these controls per case be subjects from whom blood samples were available for biomarker analyses. Mean follow-up was 89 months (minimum, 51 months; maximum, 123 months). A total of 269 incident lung cancer cases were eligible for inclusion in Gen-Air and 255 of these subjects could be matched to controls. Complete physical activity data were available from 230 cases and 648 matched controls.

At baseline enrolment into the EPIC cohort, past week physical activity data were obtained via in-person or self-administered interviews using a standardized questionnaire that has been extensively described elsewhere (Haftenberger et al. 2002, Steindorf et al. 2006). Data were gathered on the frequency and duration of non-occupational physical activities including housework, home repair (do-it-yourself), gardening, stair climbing, walking, cycling and sports. Metabolic equivalent (MET) values were assigned to each reported activity to weight the activities by intensity level and MET-h weekly of activity were calculated (Ainsworth et al. 2000, Steindorf et al. 2006). Housework, home repair, gardening and stair climbing were combined to estimate household activity. Recreational activity was calculated as the sum of walking, cycling and sports activities. EPIC respondents categorized themselves as having sedentary, standing, manual, heavy manual or no occupation. A precursor to the EPIC physical activity questionnaire was tested for reliability and validity in Dutch study subjects (Pols et al. 1997). Compared with the final EPIC protocol, the validity study used different wording for the questions and a different approach for weighting the activities for energy expenditure, and so the validity study is not completely congruent with the physical activity analyses conducted with EPIC data (Pols et al. 1997). To provide further information on the relative validity of the physical activity measures in the population included in Gen-Air, analyses were conducted to determine whether increasing recreational, household and occupational activity were associated with body mass index (BMI). These analyses do not provide a measure of absolute validity the way a comparison to a criterion measure of energy expenditure would, but are useful for providing a sense of the construct validity of physical activity questionnaires

(Alfano et al. 2004, Bowles et al. 2004, DeVellis 1991, Jacobs et al. 1993, Washburn et al. 1991).

Laboratory analyses

Glutathione levels

Blood samples were collected at baseline enrolment into the EPIC cohort. GSH levels were measured in the red blood cell samples that remained after prior analyses of 4-aminobiphenyl-haemoglobin adducts (51 lung cancer cases and 110 matched controls) (Airoldi et al. 2005). Study subjects were randomly selected for inclusion in the 4-aminobiphenyl adduct study. Availability of biological samples for the GSH analyses was not associated with any of the physical activity variables, age at recruitment into EPIC, smoking status or years of smoking. Of the subjects with available samples physical activity data were only available from 43 cases and 92 controls. Total GSH levels, the sum of reduced and non-reduced GSH, were measured in red blood cell samples using a 5,5'-dithiobis-(2-nitrobenzenoic acid) colorimetric assay as described previously (Richie et al. 1996, Rundle et al. 2005a). Haemoglobin levels were measured using Drabkin's reagent and results are expressed as μmol of GSH g^{-1} haemoglobin (Hb) to control for potential differences in red blood cell concentrations across samples and reported as GSH/Hb (Fairbanks & Klee 1987).

Carcinogen-DNA adducts

Carcinogen-DNA adduct data were available from prior analyses of Gen-Air study subjects (Peluso et al. 2005b). Blood samples for these analyses were available to Gen-Air from all EPIC centres except Malmo, and DNA samples were available from 68% of the study subjects. Carcinogen-DNA adduct levels were measured in white blood cells collected from the study subjects at enrolment into EPIC using the 32^{P} post-labelling assay as previously described (Peluso et al. 2005b). Briefly, DNA samples were treated with nuclease P1 and labelled with 25–50 μCi carrier-free [γ-^{32}P] ATP (3000 Ci $mmol^{-1}$ l^{-1}). Separation of adduct species was conducted by two dimensional chromatography and adduct levels were quantified by Cerenkov counting or storage phosphorimaging techniques (Peluso et al. 2005b).

Statistical analyses

Conditional logistical regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between lung cancer risk and physical activity. Quartile cut points were calculated for increasing levels of recreational and household activity based on the distribution of activity levels in the controls, and dummy variables for the quartiles were entered into the statistical model. For occupational activity the sitting category was used as the referent and dummy variables were created to indicate categories of occupational activity. Standing, manual and heavy manual occupations were combined because of the low numbers of cases in each of the respective categories. Analyses simultaneously considered the effects of increasing activity in the separate domains of recreational, household and occupational activity.

The initial conditional logistic regression analyses controlled for gender, age category, country and smoking status through the individual matching and further analyses also controlled for smoking duration. For the purposes of classifying subjects on smoking status, cigarette, cigar and pipe smoking were treated as equivalent and likewise data on cigarettes, pipes and cigars were used to calculate duration of smoking. Data on number of cigarettes smoked per day was not commonly available in the dataset for these ex-smokers and pack-years of smoking could not be calculated. Years of smoking was entered into the models as a continuous variable and never-smokers were assigned a value of zero. Data on passive smoke exposure at work or at home were not collected at all of the EPIC sites; only 59 of the cases with physical activity data also had data on passive smoke exposure. Thus, it was not possible to adequately control for passive smoke exposure. Education level, BMI, total calorie intake and servings of fruits and vegetables were also evaluated as potential confounders.

Conditional logistic regression analyses were used to determine whether increasing GSH levels in red blood cells were protective against lung cancer. Because of the small number of cases and controls included in these pilot analyses, GSH levels were analysed as a continuous variable and then again separately analysed as a dichotomous variable using the median level in the controls as the cut point to designate high and low levels.

Analyses of associations between physical activity categories and BMI and GSH levels among controls were conduced using generalized estimating equations (GEE) (Rundle et al. 2005b). Adjusted means and 95% CI were calculated for BMI and GSH level by physical activity quartile categories. The association between categories of physical activity and aromatic-DNA adduct levels in white blood cells was also assessed. As is common the adduct data were not normally distributed and 15% of subjects had adduct levels below the detection limit of the post-labelling assay. As such mathematical transformations of the data did no improve the distribution of the continuous data for analytical purposes. Thus, the data were dichotomized into high and low adduct level groups using the median value in the controls as the cut-off point. The association between physical activity categories and the presence of high aromatic-DNA adduct levels in white blood cells was assessed using GEE

and results are reported as the OR and corresponding 95% CI. *p*-Values were calculated comparing the mean BMI, GSH level and odds of high adduct levels in each ascending physical activity quartile category compared with the lowest.

Results

Table 1 provides descriptive statistics on the demographics and physical activity levels of the 230 lung cancer cases and 648 individually matched controls. Table 2 shows the results for conditional logistic regression analyses of physical activity categories and lung cancer with results for each domain of activity mutually adjusted for the effects of the other domains. In analyses that considered the matching variables as potential confounders and in analyses that further controlled for years of smoking, increasing levels of recreational physical activity were significantly protective against lung cancer. Increasing levels of household activity were non-significantly positively associated with lung cancer risk. Compared with sedentary occupations, jobs that required physical activity were not associated with lung cancer, nor was being unemployed. Further control for BMI, education, energy intake and consumption of fruits and vegetables did not substantially alter the results observed in the initial conditional logistic regression model. In analyses of the subset of 59 cases and 216 controls for whom passive smoke exposure data were available recreational physical activity was not significantly associated with lung cancer risk and further control for passive smoke exposure did not appreciably alter the OR estimates. However, due to the small sample size the models appeared quite unstable and it was not possible to evaluate fully potential confounding by passive smoke exposure.

Table 1. Demographic, smoking and physical activity characteristics of cases and controls.

	Cases (n = 230)	Controls (n = 648)
Categorical variables, n (%)		
Gender		
Male	72 (31)	207 (32)
Female	158 (69)	441 (68)
Smoking status		
Never	124 (54)	348 (54)
Ex-smoker	106 (46)	300 (46)
Occupational physical activity		
Sitting	36 (16)	112 (17)
Standing	44 (19)	129 (20)
Manual/heavy	10 (4)	32 (5)
Unemployed	140 (61)	375 (58)
Continuous variables, mean (SD), *n*		
Age at recruitment (years)	60.30 (8.96), 230	60.33 (8.98), 648
Body mass index (kg m^{-2})	25.64 (4.03), 230	25.45 (4.11), 648
Years of smoking among ex-smokers	24.26 (11.68), 102	22.22 (11.43), 285
Years since quitting smoking among ex-smokers	20.66 (7.92), 106	22.38 (9.97), 300
Recreational physical activity (MET-h weekly)	26.88 (23.68), 230	30.12 (25.17), 648
Household physical activity (MET-h weekly)	49.16 (35.84) 230	47.00 (36.82), 648

MET, metabolic equivalent.

Table 3 presents the results of analyses separately for never-smokers and long-term ex-smokers. Among never-smokers those in the third and fourth quartile of recreational activity were at non-significantly lower risk, while household activity was significantly associated with increased risk. Among ex-smokers each category of recreational physical activity above the reference category had a rate ratio of around 0.50, suggesting a protective effect but no dose–response related to increasing activity above the reference category. Occupational activity remained unassociated with lung cancer regardless of smoking status.

Table 4 presents the results of analyses of BMI, GSH/ Hb levels in red blood cells and high adduct aromatic-DNA adduct levels in white blood cells and categories of physical activity among controls. Increasing recreational activity was significantly associated with lower BMI (p_{trend} = 0.02), while household and occupational activity were not. Increasing recreational physical activity was positively associated with GSH/Hb levels, while household activity was not. Occupational activity was not associated with GSH/Hb but compared with subjects engaged in sitting occupations, unemployed subjects have significantly lower GSH/Hb levels. Increasing levels of GSH/Hb were not associated with lung cancer case–control status, OR 0.95 (95% CI 0.84–1.07) per unit GSH/Hb and OR 0.95 (95% CI 0.43–2.09) comparing high with low levels of GSH/Hb. There were no apparent associations between the presence of aromatic-DNA adducts and physical activity categories, although increasing BMI was inversely associated with the presence of high adduct levels (beta = -0.07, p = 0.05).

As household activity was not associated with BMI and appeared to be positively associated with lung cancer risk, separate post hoc analyses were conducted of the component physical activity measures that comprise household activity (housework, home repair (do-it-yourself), gardening and stair climbing). Except for stair climbing, increasing activity in each of these areas was modestly, positively, but not significantly, associated with lung cancer risk. Among ex-smokers the positive association between gardening and lung cancer approached statistical significance, p_{trend} = 0.07 (details not shown).

Discussion

Preventing the initiation of smoking and promoting smoking cessation remain the primary means of preventing lung cancer. However there are few prevention programmes available to never- or ex-smokers, and so the possibility that physical activity prevents lung cancer in these groups is of tremendous public health

Table 2. Odds ratios (OR) for physical activity[a] and lung cancer.

	Model 1[b] (n = 878)		Model 2[c] (n = 847)	
	OR	95% CI	OR	95% CI
Recreational (MET-h weekly)				
0–12.00	1		1	
>12.00–24.00	0.75	(0.49–1.15)	0.77	(0.50–1.19)
>24.00–39.00	0.59	(0.37–0.92)	0.58	(0.37–0.93)
>39.00	0.60	(0.37–0.95)	0.56	(0.35–0.90)
p_{trend}		0.02		0.01
Household (MET-h weekly)				
0–19.00	1		1	
>19.00–36.50	1.05	(0.66–1.67)	1.07	(0.66–1.71)
>36.50–63.30	1.10	(0.69–1.76)	1.08	(0.67–1.75)
>63.30	1.53	(0.91–2.56)	1.55	(0.91–2.63)
p_{trend}		0.13		0.14
Occupational				
Sitting	1		1	
Standing/manual/heavy	0.99	(0.58–1.70)	1.03	(0.60–1.79)
Unemployed	1.24	(0.72–2.16)	1.25	(0.72–2.18)
Year of smoking		NA	1.04	(1.01–1.08)

[a]Results for recreational, household and occupational activity mutually adjusted for each other domain of activity.
[b]Model 1 controls for matching variables. [c]Model 2 controls for matching variables and total years of smoking.
MET, metabolic equivalent; CI, confidence interval.

Table 3. Odds ratios (OR) for physical activity[a] and lung cancer by smoking status.

	Never-smoker		Ex-smoker			
	Model 1[b]		Model 1[b]		Model 2[c]	
	(n = 472)		(n = 406)		(n = 387)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Recreational (MET-h weekly)						
0–12.00	1		1		1	
>12.00–24.00	1.16	(0.66–2.05)	0.42	(0.21–0.84)	0.43	(0.21–0.89)
>24.00–39.00	0.64	(0.35–1.17)	0.58	(0.29–1.18)	0.57	(0.27–1.18)
>39.00	0.73	(0.39–1.38)	0.46	(0.23–0.92)	0.41	(0.20–0.84)
p_{trend}		0.17		0.08		0.04
Household (MET-h weekly)						
0–19.00	1		1		1	
>19.00–36.50	1.29	(0.68–2.45)	0.96	(0.47–1.96)	1.01	(0.48–2.13)
>36.50–63.30	1.41	(0.71–2.79)	0.93	(0.46–1.85)	0.90	(0.43–1.86)
>63.30	2.50	(1.18–5.37)	1.03	(0.49–2.14)	1.03	(0.46–2.19)
p_{trend}		0.02		0.97		0.94
Occupational						
Sitting	1		1		1	
Standing/manual/heavy	0.96	(0.47–1.96)	0.83	(0.35–1.96)	0.90	(0.37–2.19)
Unemployed	1.04	(0.50–2.17)	1.43	(0.61–3.34)	1.47	(0.61–3.53)
Years of smoking	NA	NA	NA	NA	1.04	(1.003–1.07)

[a]Results for recreational, household and occupational activity mutually adjusted for each other domain of activity.
[b]Model 1 controls for matching variables.
[c]Model 2 controls for matching variables and total years of smoking.
MET, metabolic equivalent.

interest (Lee et al. 1999, Mao et al. 2003). Although not initially designed to investigate the role of physical activity, the Gen-Air study, with its focus on never- and long-term ex-smokers and the availability of biological samples, presents an interesting context in which to study physical activity (Peluso et al. 2005a). This the first study to incorporate intermediate biomarker analyses into a prospective analysis of physical activity and cancer and the first analysis of blood GSH levels and lung cancer risk. A previous report from the entire cohort found no overall protective effect, and no protective effects by smoking status (Steindorf et al. 2006). The major difference between these two analyses is the restriction of ex-smokers to those who had quit smoking 10 years or more prior to entry into EPIC and may explain the differences in results. As noted in the Introduction, smoking cessation is associated in variable and complex ways with changes in other lifestyle risk factors including physical activity. There is evidence that among some ex-smokers quitting is associated with increases in physical activity, while among others cessation is prompted by declining health, which also impacts the ability to engage in activity. The restriction of ex-smoking cases to those who quit 10 or more years prior to entry into EPIC reduces the possibility that activity patterns measured at entry into the cohort are associated with the decision to quit and with health status at the time of quitting.

The analyses presented here provide further evidence that recreational activity is protective against lung cancer risk in ex- and non-smokers. To place the results in context 30 MET-h of recreational activity is equivalent to 5 h of cycling. These results are consistent with those from the Harvard Alumni Study, the Canadian National Enhanced Cancer Surveillance System study and the Iowa Women's Health Study (Lee et al. 1999, Mao et al. 2003, Sinner et al. 2006). Physical activity can induce endogenous antioxidant defences which can reduce the damage caused by episodes of oxidative stress (Miyazaki et al. 2001); theoretically this response could protect against both initiation and promotion caused by oxidative stress (Cerutti 1985, Frenkel 1992). However in Gen-Air household activity was positively associated with risk and in some analyses this association was statistically significant, whereas occupational activity was not associated with risk. Again to place these results in context, 30 MET-h of household activity is equivalent to 10 h of housework. Steindorf and colleagues have analysed the association between physical activity and lung cancer risk in the EPIC cohort, which partially overlaps with Gen-Air (Steindorf et al. 2006). They did not observe an inverse association between lung cancer risk and recreational or household physical activity. Some reductions were found with sports in males, cycling in females and non-occupational vigorous physical activity. For occupational physical activity, lung cancer risks were increased for unemployed men and men with standing occupations.

The divergent results for recreational and household activity may be construed as calling into question whether energy expenditure through physical activity is biologically protective against lung cancer. A priori one would not expect to observe associations between

Table 4. Associations between physical activity[a] and body mass index (BMI), glutathione (GSH) and carcinogen-DNA adducts among controls.

	BMI[b] (n = 648) Adjusted mean (95% CI)	GSH/Hb[c] (n = 92) Adjusted mean (95% CI)	Carcinogen-DNA adduct (n = 208) Levels above the median[d] OR (95% CI)
Recreational (MET-h weekly)			
0–12.00	25.93 (25.19–26.67)	8.16 (7.33–8.99)	Ref
>12.00–24.00	25.64 (25.03–26.25)p = 0.52	8.92 (7.40–10.44)p = 0.39	1.31 (0.46–3.67)p = 0.61
>24.00–39.00	25.27 (24.68–25.86)p = 0.15	8.94 (7.95–9.99)p = 0.23	1.38 (0.49–3.94)p = 0.54
>39.00	24.90 (24.32–25.48)p = 0.03	10.03 (8.41–11.65)p = 0.04	1.05 (0.38–2.86)p = 0.93
Household (MET-h weekly)			
0–19.00	25.17 (24.60–25.74)	9.73 (7.71–11.75)	Ref
>19.00–36.50	24.95 (24.28–25.63)p = 0.61	8.35 (7.45–9.27)p = 0.36	1.48 (0.54–4.06)p = 0.44
> 36.50–63.30	25.46 (24.88–26.04)p = 0.48	8.84 (7.78–9.91)p = 0.10	1.84 (0.69–4.90)p = 0.22
> 63.30	26.16 (25.38–26.95)p = 0.05	9.58 (8.35–10.81)p = 0.89	0.94 (0.37–2.41)p = 0.90
Occupational			
Sitting	25.25 (24.49–26.01)	10.49 (9.25–11.72)	Ref
Standing/manual/heavy	25.02 (24.40–25.65)p = 0.63	9.35 (7.91–10.78)p = 0.19	0.90 (0.33–2.47)p = 0.84
Unemployed	25.68 (25.20–26.16)p = 0.37	8.20 (7.21–9.18)p <0.01	1.30 (0.57–2.92)p = 0.53

[a]Results for recreational, household and occupational activity mutually adjusted for each other domain of activity.
[b]Adjusted for gender and smoking status.
[c]Adjusted for gender, age at recruitment, energy intake, and fruit and vegetable consumption.
[d]Adjusted for laboratory batch, age at recruitment, BMI and gender.
MET, metabolic equivalent.

increased activity and risk that differ by domain of activity. However, it is possible that the questions on recreational and household activity are not equivalently valid measures of their respective domains of physical activity. Consistent with this possibility is the observation that BMI significantly decreases with increasing levels of recreational activity among controls but is not consistently associated with household activity. Another possibility is that given the relatively short duration of follow-up, subjects with low engagement in recreational physical activity were less active in this domain because of subclinical disease symptoms. The design reduces biases that might occur if decisions to quit smoking were associated with activity patterns measured at baseline. However, it does not address the possibility that at baseline cases were expressing symptoms related to lung cancer or other co-morbid conditions that influenced their activity levels. It is possible for instance that those with poor health did not engage in recreation but did engage in more hours of lower intensity household activity, explaining the divergent results for recreational and household activity.

It is unclear why household activity appears to be detrimental and particularly so among never-smokers, although the results among the never-smokers may just be an artifact of the modest sample size. The measurement of household activity does present more challenges than the measurement of recreational activity and the lack of association between BMI and household activity suggests that this measure may be less valid. However, measurement error would explain null results but not the increased risk observed here. Separate analyses of housework, home repair (do-it-yourself) and gardening, three of the four measures that comprise total household activity, showed similar associations with lung cancer risk. It is possible that the questions regarding household activity tap into a socioeconomic related effect not controlled for by education or that there are exposures associated with gardening, do-it-yourself projects and housework that are detrimental. In this case the questions may be measuring unknown factors related to risk that are associated with doing household work.

Past studies of occupational activity have generally shown null findings (Colbert et al. 2002, Dosemeci et al. 1993, Paffenbarger et al. 1987, Severson et al. 1989, Steenland et al. 1995, Thune & Lund 1997), although a few have found elevated risks of lung cancer with increased occupational physical activity (Bak et al. 2005, Brownson et al. 1991, Steindorf et al. 2006). In the Danish component of EPIC, lung cancer was significantly increased for men and women reporting standing occupations, but not for light activity or heavy activity occupations (Bak et al. 2005). In earlier analyses of the entire EPIC cohort, risk of lung cancer was elevated for unemployed men and for men who reported standing occupations (Steindorf et al. 2006). One difficulty in analysing the data on occupational activity is that the questionnaire collected data on occupational activity at enrolment into the cohort, and more than half of the subjects were not employed. The analyses of occupational activity is also complicated by the possibility that increased activity on the job may be associated with industrial occupations that increase ones risk for lung cancer. Thus any putative benefit of occupational physical activity may be obscured by occupational exposures. Again this may be another instance where the questionnaire data on physical activity not only taps into the construct of physical activity but other processes as well. However, further control for employment in at risk occupations did not alter these results.

The biomarker data may further illuminate the results of the questionnaire data on physical activity. GSH is an important endogenous antioxidant that detoxifies reactive oxygen species thought to act both as tumour initiators and promoters (Cerutti 1985, Frenkel 1992). Furthermore, as a cofactor of glutathione transferases, GSH plays an important role in detoxifying chemical carcinogens (Bartsch et al. 1991, Jernstrom et al. 1982). Relevant to the work presented here, GSH levels have been shown to be positively associated with physical activity (Karolkiewicz et al. 2003, Robertson et al. 1991, Rundle et al. 2005a) and to increase with physical training (Evelo et al. 1992). The associations between GSH levels and recreational activity among controls parallel those seen between recreational physical activity and lung cancer risk, while household activity is not associated with GSH. This suggests that the questions on recreational activity are measuring physical activity-related behaviour that is having a physiological effect while the questions on household activity may not be. Again this is consistent with the observation that recreational activity is associated with BMI while household activity is not. Among those employed, occupational activity is not associated with GSH level; however those unemployed have significantly lower levels of GSH that those in sedentary jobs. These analyses controlled for age and past research has shown that for any given age being unemployed is associated with lower health status (Arrighi & Hertz-Picciotto 1994, Richardson et al. 2004), and GSH levels have been seen to be lower in those with poorer general health (Julius et al. 1994, Nuttall et al. 1998). Thus lower GSH levels seen among the unemployed may reflect the general lower health status common to this group. As described above, there are good biological reasons to expect GSH to be protective against lung cancer, however GSH levels were not associated with lung cancer risk, although the sample size was small in these pilot analyses.

A prior report from Gen-Air has shown that the presence of carcinogen-DNA adducts was associated with lung cancer risk (Peluso et al. 2005b). Past studies have shown increases in UDP-glucuronosyl transferase and glutathione *S*-transferases activities associated with running (Duncan et al. 1997, Evelo et al. 1992). However contrary to expectations, a past analysis of physical activity found that increased hours of moderate intensity physical activity was positively associated with the presence of BP-DNA adducts (Rundle et al. 2007). Also of relevance to energy balance are the findings that increased BMI is associated with lower carcinogen-DNA adducts and among ex-smokers with a longer half-life of carcinogen-DNA adducts in white blood cells (Godschalk et al. 2002, Rundle et al. 2007). In the analyses presented here physical activity was not associated with the presence of high levels of carcinogen-DNA adducts in white blood cells, suggesting that any effect of activity on lung cancer risk is not mediated by altering the amount of genetic damage caused by chemical carcinogens. However, increasing BMI was inversely associated with the presence of high levels of carcinogen DNA adducts among controls.

These results provide further evidence that recreational activity is associated with lower risk of lung cancer among non- and ex-smokers. This has particularly important implications for ex-smokers, who remain at high risk for lung cancer and after quitting have few options for further lowering their risk. The restriction of the study to long-term ex-smokers reduces methodological issues associated with studying physical activity in ex-smokers; however further follow-up of the cohort is required to rule out other ways in which reverse causality can arise. In addition, because of the limited data collected in EPIC it was not possible to control for passive smoke exposure; it is possible that those who are more recreationally active have lower exposure to passive smoke. The biomarker and BMI analyses suggest that the data do reflect patterns of recreational physical activity that are having physiological consequences and thus lend weight to the findings on lung cancer risk. This research adds to the existing literature suggesting that physical activity programmes may be useful as an adjunct of smoking prevention and cessation in preventing lung cancer.

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