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The association between benzo[a]pyrene-DNA adducts and body mass index, calorie intake and physical activity

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Abstract
Prior work suggests that body size and fat content may influence carcinogen-DNA adduct levels measured in white blood cells. Here we consider energy balance more broadly by assessing the impact of body mass index (BMI), physical activity and calorie intake on the presence of benzo[a]pyrene-DNA (BP-DNA) adducts in white blood cell DNA. Our cross-sectional study employed subjects from a separately conducted intervention trial. Physical activity and food intake data were collected at 12 and 15 months of follow-up, respectively. BP-DNA adducts were measured by high-performance liquid chromatography (HPLC) in white blood cell samples collected at 12 months of follow-up. Complete data on all variables were available from 143 subjects. Logistic regression showed that BMI was inversely associated with the presence of detectable adducts (OR = 0.90, $p = 0.02$), and that hours of moderate-intensity physical activity were positively associated with the presence of detectable adducts (OR = 1.04, $p = 0.04$). These results provide further evidence that body fat content influences carcinogen-DNA adduct levels, probably by altering the distribution of the lipophilic parent compound.

Keywords: *Body mass index (BMI), physical activity, carcinogen-DNA adducts, obesity, cancer*

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Introduction

Carcinogen-DNA adducts are thought to represent the biologically effective dose of an exposure to a mutagenic carcinogen (Perera & Weinstein 1982, Rothman et al. 1995). That is, measured levels of adducts represent the dose of carcinogen that has been absorbed from the external environment, has escaped detoxification, has been bound to DNA, and has not been removed through DNA repair (Perera & Weinstein 1982, Rothman et al. 1995). There is a great deal of hope that carcinogen-DNA adducts will be useful biomarkers in epidemiologic studies seeking to link exposures to xenobiotics to later cancer development (Perera & Weinstein 1982, Rothman et al. 1995, Veglia et al. 2003). However, there is a great deal of intra- and inter-individual

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variability in adduct levels, with much of the inter-individual variability thought to relate to differences in exposure and polymorphisms in metabolic and DNA repair genes (Dickey et al. 1997). In addition, factors that impact other toxicological parameters, such as the distribution of the parent compound and its metabolites, may influence adduct levels.

Godschalk and colleagues have shown that increased body mass index (BMI) is associated with lower carcinogen-DNA adduct levels in peripheral mononuclear white blood cells (Godschalk et al. 2002). Additionally, they showed that the half-life of adducts in white blood cells is longer in heavier individuals who quit smoking compared to lighter individuals who quit smoking (Godschalk et al. 2002). The authors suggest that these findings might explain the association between lower BMI and lung cancer risk. These findings also have important implications for a number of published case–control studies of carcinogen-DNA adducts and cancers where blood samples were drawn from cases at the time of diagnosis or after diagnosis (Gammon et al. 2002b, Peluso et al. 2000, Rundle 2000, Tang et al. 1995, Vulimiri et al. 2000). If adduct levels are related to BMI, disease-related changes in body weight or body fat stores may influence adduct levels and the findings of these studies.

Godschalk and colleagues suggested that the mechanism underlying their results was that the parent compounds of the bulky aromatic adducts measured in their study were lipid-soluble and were sequestered in fat stores, making them unavailable to form adducts (Godschalk et al. 2002). Then when exposure was removed, the compounds were released from the fat stores, prolonging the half-life of the adducts in the heavier individuals (Godschalk et al. 2002). Supporting this idea is the observation of high levels of lipophilic carcinogens in fat biopsies (Obana et al. 1981). Alternately, increased BMI results from a positive energy balance – i.e. increased calorie intake and decreased physical activity – and it is possible that these determinants of BMI also impact adduct levels. Physical activity has been shown to be associated with increased activity for several enzymes that metabolise polycyclic aromatic hydrocarbons (PAH) (Duncan et al. 1997, Evelo et al. 1992, Mauriz et al. 2000), and yet strenuous activity has been shown to deplete metabolic cofactors, such as glutathione (Duthie et al. 1990, Ji 1995, Ji et al. 1998). In addition, physical activity may impact the circulation and distribution of parent compounds or reactive intermediates (Persky et al. 2003, Ylitalo 1991). Additional biological pathways linking antecedents of BMI and adduct levels would generate confounding relationships exaggerating or diluting the apparent effect of BMI seen by Godschalk and colleagues.

The analyses reported here were initiated to confirm the results of Godschalk and colleagues and to consider more directly the role of energy balance on adduct formation.

Materials and methods

Cross-sectional analyses of benzo[a]pyrene-DNA (BP-DNA) adducts, BMI, physical activity and calorie intake were conducted in a population taking part in a randomised double-blind, placebo-controlled study of whether antioxidant micronutrient supplementation reduces genetic damage induced by cigarette smoking. From 1997 to 2000, smokers ($n = 320$) were randomized to receive treatment with 500 mg of vitamin C and 400 IU of vitamin E daily or placebo. Men and women aged 18 years and older who attended the New York State Psychiatric Institute Smoking Clinic or who

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responded to a newspaper advertisement were recruited to participate in the chemoprevention trial. Subjects were determined eligible to participate if they smoked more than ten cigarettes per day, had no prior history of cancer or liver disease, had not taken vitamin supplements within the past year, had normal liver enzyme function tests, lived at a permanent address, owned a telephone, were willing to participate for the total duration of the trial (24 months), returned 1 month after the baseline visit, and completed the placebo run-in. Participants received monetary compensation for their participation. Written informed consent was obtained from all subjects. Consent forms and recruitment procedures were approved by the Institutional Review Boards (IRBs) of Columbia Presbyterian Medical Center (CPMC), the Herbert Irving Cancer Center and the New York State Psychiatric Institute. The cohort was followed for 2 years, during which time the intervention arm received vitamin treatment for 15 months and then placebo for another 9 months.

At baseline, the study subjects completed extensive questionnaires on demographic and lifestyle characteristics. Study subjects visited the CPMC at 3-month intervals and gave blood samples and filled out study questionnaires. At the 12-month time point, study subjects completed the Paffenbarger Physical Activity Questionnaire, and at the 15-month time point, study subjects completed the Block 95 Food Frequency Questionnaire. Of the 320 subjects who entered the cohort, 180 remained at the 12-month time point and had white blood cell DNA analysed for BP-DNA adducts. Of these subjects, 158 (68 women and 90 men) had also completed the physical activity questionnaire administered at the 12-month time point. Of the 158 subjects, data on dietary intake at 15 months of follow-up were available from 146 subjects. BMI data presented here are based on weight data from the 12-month time point. If weight data were unavailable from the 12-month time point, weight data from the closest visit were used. A total of 143 subjects had data on BMI, physical activity, and calorie intake; statistical analyses were conducted on these 143 subjects.

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Laboratory analyses

Mononuclear white blood cell DNA samples were analysed for BP-DNA adduct levels by high-performance liquid chromatography (HPLC) as described previously (Mooney et al. 2005).

Statistical analyses

BP-DNA adduct data were dichotomised into detectable and non-detectable categories using the detection limit of the HPLC protocol. The adduct data were treated in this way because in the literature on the association between adducts levels and cancer risk the adduct data are typically dichotomised into high and low categories of adducts and the use of the detection limit as the cut point is common (Gammon et al. 2004, Gammon et al. 2002b, Peluso et al. 2005b, Sun et al. 2001). Separate logistic regression models were used to determine whether BMI, physical activity and calorie intake were associated with detectable levels of BP-DNA adducts. Analyses controlled for age, gender, cigarettes smoked per day at the 12-month visit, laboratory batch and race/ethnicity (African-American, Caucasian, Hispanic and other). 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. These measures were chosen a priori because past work has suggested that the effect

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of increasing durations of activity might differ depending on intensity level (Rundle 2005, Rundle et al. 2005) Hours of moderate and vigorous activity were entered into the initial model together. BMI, hours of moderate activity, hours of vigorous activity and calorie intake were entered into the model as continuous variables. Finally, a model was implemented that included predictor variables for BMI, of moderate activity, hours of vigorous activity and calorie intake.

Results

Table I shows the demographic characteristics of the study population and the percentage of each demographic group that had detectable B[a]P-DNA adduct levels. The population is racially/ethnically diverse, and has a poor socio-economic status with a high prevalence of overweight and obesity. Overall, 87% of the subjects had detectable B[a]P-DNA adducts. Table II provides descriptive data for the energy balance measures, BMI, hours of moderate and vigorous intensity physical activity per week and calorie intake. Table III shows the results of logistic regression analyses predicting the presence of detectable BP-DNA adducts. When entered into the model without measures of physical activity and calorie intake (model 1), increasing BMI was inversely associated with the presence of detectable BP-DNA adducts (OR = 0.90, $p = 0.02$). Associations with hours of moderate activity and hours of vigorous activity were assessed together (model 2), and hours of moderate activity were found to be positively associated with the presence of BP-DNA adducts (OR = 1.05, $p = 0.04$), while hours of vigorous activity were unassociated with the presence of BP-DNA adducts (OR = 0.98, $p = 0.16$). When calorie intake was assessed alone (model 3) it was unassociated with the presence of BP-DNA adducts (OR = 1, $p = 0.59$).

Table I. Demographic characteristics of the sample and percentage of each demographic group with detectable benzo[a]pyrene (B[a]P) adducts.

Demographic characteristics	Percentage of sample ($n = 143$)	% of category with detectable adducts
Age group (years)		
<36	31.3	84.4
36–43	34.7	86.0
≥44	34.0	89.8
Gender		
Male	55.9	85.7
Female	44.1	88.3
Race/ethnicity		
African-American	47.5	82.9
Caucasian	36.7	90.2
Hispanic	13.0	89.5
Other	2.8	100.0
Income		
<10 000	42.2	82.0
10 000–20 000	23.3	97.0
21 000–31 000	18.3	88.5
31 000–40 000	7.8	84.6
41 000+	8.3	81.8

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Table II. Descriptive statistics of the energy balance variables.

Energy balance variables	Mean	SD	Inter-quartile range
Body mass index (BMI)	26.8	5.6	22.95–29.53
Hours of moderate physical activity week^{-1}	25.1	15.1	14.0–32.0
Hours of vigorous physical activity week^{-1}	14.7	14.3	2.0–22.0
Calorie intake day^{-1}	2521.0	1476.6	1608.50–2940.70

$^{-1}$physical activity per week.

Model 4 considers BMI, calorie intake and physical activity simultaneously, and thus the effect shown for each variable is mutually controlling for the effect of the other variables. In this model, BMI remained inversely associated with the presence of detectable adducts (OR = 0.90, $p = 0.02$) and hours of moderate activity per week were positively associated with the presence of BP-DNA adducts, although now with only borderline statistical significance (OR = 1.04, $p = 0.07$). Analyses of variance inflation factors and eigenvalues in the final model suggested that potential colinearity between the energy balance variables was not appreciable and did not impact the analyses (Kleinbaum et al. 1988).

Discussion

This work supports the finding of Godschalk and colleagues that increased body size is associated with lower carcinogen-DNA adduct levels. The results reported here also extend this work by more fully assessing the roles of calorie intake and physical activity, factors that determine energy balance. The findings for moderate activity in the model that assessed activity alone are consistent with the results from the model that considered BMI alone, i.e. increased hours of moderate activity, which are

Table III. Results[a] of logistic regression analyses of body mass index (BMI), physical activity and calorie intake and the presence of detectable benzo[a]pyrene-DNA (BP-DNA) adduct levels.

	Model 1 OR, p value ($n = 143$)	Model 2 OR, p value ($n = 143$)	Model 3 OR, p value ($n = 143$)	Model 4 OR, p value ($n = 143$)
BMI	0.90 (0.82–0.99), $p = 0.02$	–	–	0.90 (0.82–0.99), $p = 0.02$
Hours of moderate physical activity week^{-1}	–	1.05 (1.00–1.09), $p = 0.04$	–	1.04 (1.00–1.09), $p = 0.07$
Hours of vigorous physical activity week^{-1}	–	0.98 (0.94–1.01), $p = 0.16$	–	0.97 (0.94–1.01), $p = 0.12$
Calorie intake day^{-1}	–	–	1.00 (1.00–1.00), $p = 0.59$	1.00 (1.00–1.00), $p = 0.63$

[a]Models 1–3 respectively assess the association between detectable B[a]P-DNA adducts and BMI alone, hours of moderate and vigorous intensity physical activity together and calorie intake alone. Model 4 assesses the joint associations between detectable adduct levels and BMI, hours of moderate and vigorous intensity physical activity and calorie intake, with each OR mutually adjusted for the effects of the other three energy balance variable. Each model controls for age, gender, race/ethnicity, cigarettes smoked/day and analytical batch.

$^{-1}$physical activity per week.

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expected to be associated with lower BMI, were associated with the presence of detectable BP-DNA adducts. However, the final model suggests that the effects of increasing levels of moderate physical activity are not mediated through lower BMI. The association between hours of moderate physical activity and the presence of adducts remained after control for BMI.

BMI is well correlated with body fat content, particularly in individuals who are not engaged in vigorous training regimes, and judging from the responses on the physical activity questionnaire, few if any of the respondents were training at that level (Deurenberg et al. 2001, Fernandez et al. 2003, Gallagher et al. 2000, Jackson et al. 2002). This work supports the idea that increased body fat impacts adduct levels, probably by affecting the distribution of the carcinogen. The parent compound to BP-DNA adducts, benzo[a]pyrene, is highly lipid-soluble and can deposit in fat stores, removing it from circulation (Godschalk et al. 2002, Obana et al. 1981). The OR for BMI may appear modest but one must consider the range of BMI which is 16.1–45.0 and that the OR represents the effect of a one unit change in BMI. The analyses also suggest that hours of moderate physical activity may have an effect on adduct levels that is independent of any effect of activity on BMI. Activity may affect systemic circulation of carcinogens and reactive metabolites through the blood stream, hydration and solubility of the parent compound, or metabolic pathways. Again, the OR for hours of moderate activity is small, but represents the effect of a one hour per week difference, for a variable that has a range of 77 units.

Past work has suggested that physical activity may increase PAH detoxification through induction of phase II metabolic enzymes (Duncan et al. 1997, Evelo et al. 1992) and by increasing the level of co-factors involved in metabolism (Rundle et al. 2005). Yet research on drug metabolism suggests that exercise may induce p450 metabolism and increase the level of reactive intermediates (Mauriz et al. 2000). Physical activity also causes changes in other pharmacokinetic parameters that may alter the distribution, metabolism and elimination of B[a]P (Dossing 1985, Lenz et al. 2004, Persky et al. 2003, Ylitalo 1991). Exercise increases muscular blood flow and decreases adipose blood flow, potentially altering the distribution of xenobiotics (Dossing 1985, Ylitalo 1991). Exercise also reduces blood flow to the liver, potentially lowering the rate of xenobiotic metabolism, and it reduces urine excretion rates by reducing renal plasma flow and it lowers urine pH, effects that may reduce the urinary excretion of xenobiotics (Persky et al. 2003, Ylitalo 1991). Changes in toxicokinetic parameters associated with physical activity may yield longer half-lives for B[a]P and its reactive metabolites, and could alter adduct levels independent of the effects of physical activity on body fat. It is unclear why the association between physical activity and the presence of detectable adducts was observed for hours of moderate but not for hours of vigorous activity. However, it has been observed with other biomarkers that the effects of physical activity depend on the context of activity, whether physical activity is conducted as part of regular exercise or in sporadic bouts, whether it is conducted at moderate or vigorous levels and whether exhaustion results from the activity (Rundle 2005, Rundle et al. 2005). There is some evidence that the effect of exercise on renal function varies depending on the duration and intensity of the exercise, suggesting that toxicokinetic parameters may be influenced by the context of activity (Poortmans et al. 1996, Touchberry et al. 2004).

This work and that of Godschalk is important in relation to a number of case–control studies of carcinogen-DNA adducts and cancer. These studies have enrolled

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cases at the time of diagnosis or after treatment for cancer and measured carcinogen-DNA adducts in white blood cell samples drawn at that time (Gammon et al. 2002b, Hou et al. 1999, Peluso et al. 2000, Popp et al. 1993, Tang et al. 1995, Vulimiri et al. 2000). For instance in the Long Island Breast Cancer Study, adducts were measured in blood samples drawn from cases on average 96 days after diagnosis with 23% of the samples collected after chemotherapy (Gammon et al. 2002a). However, preclinical symptoms of cancer and the subsequent treatment of cancer can cause both weight gain and loss depending on the disease and treatment. Weight loss is often seen at clinical presentation of lung cancer (Hamilton & Sharp 2004, Hamilton et al. 2005) and a published review of all lung cancers occurring in New Hampshire and Vermont from 1973 to 1976 found that 46% of cases clinically presented with weight loss (Chute et al. 1985). It is possible that such weight loss would influence whether or not detectable levels of adducts are observed among cases since unmetabolised or partially metabolised carcinogens may return to systemic circulation as fat deposits diminish. In breast cancer, treatment with adjuvant chemotherapy often leads to weight gain (Grunfeld et al. 2005, Schwartz 2000) and particularly to increases in percent body fat (Freedman et al. 2004, Ingram & Brown 2004). Such concerns highlight the advantages of prospective studies of carcinogen-DNA adducts where disease processes are much more unlikely to impact the level of the biomarker (Peluso et al. 2005a, Qian et al. 1994, Tang et al. 2001). Likewise, studies of adduct levels and stage of disease and other measures of severity of disease are likely to be influenced by changes in body fat stores.

In conclusion, this work provides further evidence that body fat content influences carcinogen DNA adduct levels in white blood cell DNA and suggests that physical activity may also influence adduct levels. Epidemiologic studies involving adduct measures should carefully consider the possibility that disease-associated changes in body fat stores may influence adduct levels.

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