Association between Carcinogen-DNA Adducts in White Blood Cells and Lung Cancer Risk in the Physicians Health Study

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Abstract

In this matched case-control study nested within the prospective Physicians’ Health Study, we evaluated whether DNA damage in blood samples collected at enrollment significantly predicted risk, consistent with our hypothesis that cases have greater biological susceptibility to polycyclic aromatic hydrocarbons and other aromatic tobacco carcinogens. The subjects were 89 cases of primary lung cancer and 173 controls, all males, matched on smoking, age, and duration of follow-up. Aromatic-DNA adducts were measured in WBCs by the nuclease P1-enhanced 32P-postlabeling method that primarily detects smoking-related adducts. Among current smokers, but not former or nonsmokers, there was a significant increase in mean adduct levels of cases compared with controls (11.04 versus 5.63; P = 0.03). “Healthy” current smokers who had elevated levels of aromatic DNA adducts in WBCs were approximately three times more likely to be diagnosed with lung cancer 1–13 years later than current smokers with lower adduct concentrations (odds ratio, 2.98; 95% confidence interval, 1.05–8.42; P = 0.04). We were not able to discern case-control differences in former smokers and nonsmokers. The findings are of interest because they suggest that individuals who become cases have greater biological susceptibility to tobacco carcinogens, a biological difference, which manifests most clearly while exposure is ongoing.

Introduction

A goal of molecular epidemiology is cancer prevention through the validation of biological markers as early indicators of risk (1). We have conducted a matched case-control study nested within a prospective cohort study, the PHS (2), to determine the relationship between a number of biological markers and risk of developing lung cancer. In this study, we have evaluated whether PAH- and other aromatic-DNA adducts measured in enrollment blood samples from healthy individuals predicted risk among those who were subsequently classified as lung cancer cases (n = 89) or as controls (n = 173). Our hypothesis was that, after controlling for cigarette smoking as the major exposure source, aromatic adducts at baseline would be higher in cases and would significantly predict risk, consistent with the cases having greater biological susceptibility to carcinogens. Our hypothesis was borne out among individuals who were current smokers at time of enrollment, but not in individuals who were not active smokers (former and nonsmokers) at enrollment.

Lung cancer is the leading cause of cancer deaths in the United States in men and women. In 1999, 171,600 new cases were diagnosed (3). Although active cigarette smoking is the major cause of lung cancer, passive smoking, various occupational exposures, and carcinogens found in heavily polluted air are also causally related to lung cancer in humans (4, 5). Tobacco smoke contains over 50 known carcinogens including BaP and other PAHs, aromatic amines such as 4-aminobiphenyl, heterocyclic amines, and the nicotine-derived nitrosamine, 4-(methyl)nitrosamino)-1-(3-pyridyl)-1-butanol (5, 6). In addition to being major carcinogenic constituents of tobacco smoke, PAHs are found in ambient and indoor air because of emissions from vehicles, power plants, industrial sources, cooking, and heating. They are also present in the diet from grilling or broiling of food and from atmospheric deposition (7–9).

Experimental research has demonstrated that PAHs, like many carcinogens, exert their effects by binding covalently to DNA to form adducts that may lead to mutation and, ultimately, to cancer (10–12). Although the relationship between adduct concentrations in blood and target tissues such as the lung has not been conclusively established, a number of molecular epidemiological studies (13, 14) and experimental studies (15) have shown a good correlation between PAH- and aromatic-DNA adducts in blood and lung tissue from the same individuals. Thus, as a biomarker, adducts have the theoretical advantage of reflecting chemical-specific genetic damage that is mechanistically relevant to carcinogenesis. Supporting molecular evidence that DNA damage from PAHs may play an important role in lung cancer has come from the observation that the p53 tumor suppressor gene is mutated in 40–50% of lung tumors, and the pattern of p53 mutations is consistent with the type of DNA adducts and mutations induced experimentally by BaP (16).

Carcinogen-DNA adducts, including aromatic adducts such as PAH-DNA, can be quantitated in human tissue by the 32P-postlabeling method (9, 17), by immunoperoxidase (18, 19), and by physical/chemical methods (20). Although not all of the studies have been consistent, a number have found a higher prevalence or elevated concentrations of these PAH/aromatic-DNA adducts in WBCs or lung tissue of cancer cases compared with controls (13, 18, 20, 21) of smokers compared with nonsmokers (22–26) and of smokers sampled before and after smoking cessation (27). These earlier findings suggested that the propensity to activate and bind carcinogens to DNA might be a risk factor in lung cancer.

Materials and Methods

The Parent (PHS) Study. In the present nested case-control study, a panel of biological markers was measured in baseline blood samples that were collected at the onset of the PHS (2). The PHS was a randomized trial of the effect of aspirin on cardiovascular mortality and the effect of β-carotene on...
Cancer incidence. This investigation was conducted among 22,071 United States male physicians, nearly all of whom were Caucasian. Subjects with a history of cancer (except for nonmelanoma skin cancer) were excluded from the study. The overall smoking distribution in the PHS was 39% ex-smokers, 11% current smokers, and 50% nonsmokers. All of the subjects were asked to donate a blood sample at initial enrollment and roughly 75% complied. There were no notable differences between the “blood subgroup” and the whole cohort with respect to demographics. There was virtually no loss to follow-up of the cohort; 100% were followed up for vital status, and >99% followed up for nonfatal outcomes. It is likely that few, if any, cases were missed given the nature of the population and the tracking system in place. The 89 cases in this study were similar to the cases in the blood subgroup of the entire cohort with respect to standard risk factors (e.g., smoking and age). Between August 1982 and December 1984, 15,700 baseline blood samples (two 4-ml tubes of plasma and one 4-ml tube of whole blood) were collected from the physicians participating in the run-in phase. The samples were coded and stored at −80°C. Of the 15,700 samples collected, 14,916 were from subjects who subsequently entered the PHS study and were randomly assigned to one of four groups (aspirin and β-carotene treatment, aspirin, β-carotene, or neither treatment). The dosage of β-carotene was 30 mg on alternate days and that of aspirin was 325 mg on alternate days, continued for the duration of the study.

Questionnaires regarding their health history were completed by the physicians at entry and at 2, 6, 12, 24, 36, 48, and 60 months. Follow-up after 5 years consisted of yearly questionnaires and postcard inquiries every 6 months regarding heart disease or cancer diagnosis. Smoking history was obtained from each physician at enrollment. This history included smoking status [never, former (had smoked regularly), current (smoking at time of enrollment), and current CPD] as well as status of cigar and pipe smoking.

The Nested Case-Control Study. In addition to the frozen whole blood and plasma specimens, an extensive database was available on each study participant in the nested case-control study, including serial questionnaire data, medical record review, pathology reports, and autopsy reports for the cancer cases. Data on age, tobacco habits, and other variables were extracted from questionnaires.

A total of 89 lung cancer cases were documented over a 13-year period (1982–1995) in the subset of the cohort with blood samples. For the cases, the date of first hospital admission for lung cancer or first documented visit for symptoms related to the diagnosis of lung cancer was regarded as the incident date. The histological type of cancer was obtained by the PHS staff from pathology reports or, for two subjects, from death certificates. Upon identifying each new case, the PHS contacted the patient’s hospital and requested pathology reports, medical records, and samples of lung tumor and tumor-adjacent tissue removed at the time of surgery. Two controls were matched to each incident case at the time of diagnosis. The controls were cohort members without a prior diagnosis of cancer (excluding nonmelanoma skin cancer) before the date of matching. Matching of cases and controls was based on the following criteria: (a) age (± 1 year); (b) length of follow-up to diagnosis of case (± 6 months); (c) smoking status at enrollment: never used tobacco regularly, former smoker, current smoker; and (d) CPD (1–19, 20–39, 40+) for current smokers only.

A prior study had observed seasonal variation in DNA binding, possibly related to seasonal fluctuations in aryl hydrocarbon hydroxylase activity, with aryl hydrocarbon hydroxylase activity higher in July-October compared with November–June (13, 28). In the present study, cases and controls were not matched on season of blood drawing because most of the samples were drawn during the months of July through October. Cigarette smoking data and adduct data were not available for one case and two controls and two cases and 13 controls, respectively.

Analysis of Aromatic/Hydrophobic-DNA Adducts. Whole blood aliquots were shipped by the PHS investigators to Columbia University, where DNA from total WBCs was isolated by the standard chloroform DNA extraction procedure. The DNA was sent to the Institute of Cancer Research (Belmont, United Kingdom) for analysis of aromatic adducts by nuclease P1-enhanced 32P-postlabeling as described previously (26). All of the analyses were carried out on coded samples, and all of the investigators were blinded as to case/control and treatment status. Samples from cases and controls were handled identically, shipped in the same batch, and assayed in the same analytical batch. The order of analysis was randomly determined within each case-control triad. Specimens were analyzed in triplicate on different days, and the mean adduct level was determined for each individual. For each batch of samples run sequentially, a positive control, consisting of BaP-modified or benzo[g]chrysene-modified DNA, was included.

In general, the 32P-postlabeling method with nuclease P1 digestion is efficient for most PAH adducts but not for many aromatic amine adducts (29). Under controlled conditions using a BaP diol-epoxide-modified DNA, the nuclease P1 enhancement method has been shown to recover 93% of adducts (9). In the present study, total DNA adduct levels were measured in the DRZ area of the TLC plates and were considered to primarily represent PAH-DNA and other aromatic/hydrophobic adducts resistant to nuclease P1 digestion (30, 31). The method provides a summary measure of a complex mixture of adducts present in the postlabeling chromatograms. Prior analyses of various tissues (blood, lung, and cervix) have associated adducts in the DRZ with exposure to tobacco smoke (32).

Statistical Analysis. Biomarker data were log transformed to stabilize the variance and normalize the distribution of DNA adducts. Arithmetic means are presented. ANOVA was applied to determine whether smoking status was associated (at a significance level of P ≥ 0.05) with adduct levels. To take advantage of the dependence between cases and controls in the matched design of this study, the paired t test was used to test for differences in adduct means between cases and controls using the mean of the two controls. To determine the need to control for possible confounding by laboratory variability, batch effects (systematic variation between analytical runs) were assessed by ANOVA and were not statistically significant. To account for matched factors, a conditional logistic model was used to generate ORs and 95% CIs (33). Adducts were considered both as a dichotomous variable (high/low) based on the median level among controls and as a continuous variable. In the latter case, the OR represents the estimated increase in risk of lung cancer associated with a log unit increase in adducts/108 nucleotides.

As described above, in the PHS study, enrollees were randomly assigned to aspirin and β-carotene treatment groups after donating a baseline blood sample. Unlike β-carotene, aspirin has not been reported to affect lung cancer risk (34). Nonetheless, we included each treatment in models that examined the relationship of adducts to cancer risk.

Another consideration was that cases diagnosed early in the study may be prevalent cases and that the presence of preclinical disease may alter biomarkers in unknown ways. Therefore, mean levels of biomarkers for cases and controls were compared by duration of follow-up (<3 years versus ≥3 years) to determine whether there might be an effect of active, though asymptomatic, disease on biomarkers. Separate logistic regression models were run to compare ORs in subjects with a shorter versus a longer duration of follow-up. ORs were calculated for the two major groups: SCLC versus NSCLC. The small number of cases in our population limited the analysis by each histological type.

Results

The cases included 15 SCLCs and 74 NSCLCs. Table 1 provides the distribution of cases by specific histological type. Table 2 shows the distribution of subjects according to age, duration of follow-up, and smoking status. Arithmetic mean levels of aromatic DNA adducts by case/control and smoking status are presented in Table 3. The arithmetic mean for all of the cases was 8.32 adducts/108 nucleotides, compared with 7.39/108 for all of the controls. Among the current

| Table 1 Distribution of lung tumors by histological type |
|----------------|------------------|
| Histological type | N (cases) |
| SCLC             | 15              |
| NSCLC            | 32              |
| Adenocarcinoma   | 19              |
| Squamous cell carcinoma | 3         |
| Adenosquamous     | 3               |
| Bronchoalveolar   | 5               |
| Carcinoma        | 5               |
| Carcinosarcoma   | 2               |
| Large cell carcinoma | 8          |
| Total            | 89              |

4 M. Stampfer, personal communication.
smokers, there was an approximate doubling in arithmetic mean adduct level of the cases compared with the controls (11.04 versus 5.63 adducts/10^8; P = 0.03). No significant case-control difference was seen within the other two smoking categories. By ANOVA, mean adduct concentrations did not differ significantly between smoking categories overall. However, among the cases but not controls, there was a modest but nonsignificant decreasing trend in mean adduct level from current smokers to former smokers to never-smokers (Table 3).

Controlling either for the number of CPD by the current smokers or for cigar and pipe smoking did not materially alter the relationships between cigarette smoking and adducts or between adducts and risk.

By conditional logistic regression, DNA adducts were significantly associated with lung cancer risk among current smokers. The OR for high versus low adducts among current smokers was 2.98 (95% CI, 1.05–8.42; P = 0.04). The OR/log unit increase in adduct concentration was 2.15 (95% CI, 1.00–4.63; P = 0.05). Therefore, for an increase of two log adducts/10^8 nucleotides, the OR would be 4.65 (95% CI, 1.00–21.40; P = 0.05). A similar relationship was not seen among former smokers or never-smokers (see Tables 4 and 5). Tests for interaction between smoking status and carcinogen-DNA adducts (treated as either a dichotomous or a continuous variable) on lung cancer risk were not significant (P < 0.05) when smoking status was entered either as three categories (current, former, never-smokers) or as two categories (current and former smokers combined, never-smokers). Adding β-carotene or aspirin to the model did not materially alter the ORs (OR/log unit increase in adduct concentration for current smokers in the β-carotene treatment group, 2.14; CI, 0.99–4.62; P = 0.05; or for current smokers in the aspirin treatment group, 2.14; CI, 0.97–4.70; P = 0.06). This is consistent with the reported lack of an effect of β-carotene or aspirin on lung cancer risk in this cohort (2).

Mean levels of adducts were not significantly higher among combined cases and controls with greater than 3 years of follow-up (arithmetic means, 8.24 versus 5.46 adducts/10^8). Among current smokers with less than 3 years of follow-up, the OR for the presence of high adduct levels and lung cancer risk was 1.44 (95% CI, 0.19–11.12; P = 0.73; n = 27), whereas the OR was 3.85 (95% CI, 1.07–13.84; P = 0.04; n = 73) for current smokers with 3 to 13 years of follow-up. The OR for continuous adduct levels and lung cancer risk among current smokers with less than 3 years of follow-up was 1.62 (95% CI, 0.29–9.02; P = 0.58; n = 27), whereas the OR was 2.31 (95% CI, 0.96–5.51; P = 0.06; n = 73) for current smokers with greater than 3 years of follow-up.

There were no significant differences between mean levels of adducts in cases with SCLC and NSCLC or between the two corresponding groups of matched controls (Table 6). ORs for either continuous or dichotomous adducts did not vary by histological group or type.

### Discussion

In this nested case-control study, our original hypothesis (that after controlling for smoking, adducts would predict future case-control status) was borne out among the current smokers, but not in former smokers and never-smokers. We found that "healthy" current smokers who had high levels of aromatic DNA adducts in WBCs were approximately three times more likely to be diagnosed with lung cancer 1–13 years later than current smokers with low concentrations of this biomarker. When adducts were considered on a continuous log scale, the increased risk/log unit increase in adducts (e.g., from 4.06–11.04/10^8 nucleotides in arithmetic scale) was approximately 2-fold. Thus, an increase of two log adducts/10^8 nucleotides would be associated with an estimated 4.6-fold higher risk of lung cancer. Among the current smokers, adducts were more predictive of lung cancer as the time interval between blood sample collection and diagnosis increased from <3 years to 3–13 years. The ORs for adducts and lung cancer did not vary by major histological group (SCLC versus NSCLC) or by the major histological types (SCLC, squamous cell, adenocarcinoma).

However, these analyses had low statistical power.

The hypothesis that PAH adducts and other aromatic adducts in WBCs would predict lung cancer risk is biologically plausible for a number of reasons. First, adducts are on the pathway to mutation and cancer (1, 10–12, 19, 20, 35). Second, previous findings from human (14, 21) and experimental (15) studies indicate that WBC adducts measured by the same 32P-postlabeling procedure are correlated with those in lung tissue. Using this method to analyze samples from

### Table 2

<table>
<thead>
<tr>
<th>All</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>262 (100%)</td>
<td>89 (34.0%)</td>
<td>173 (66.0%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61.84 ± 7.73</td>
<td>61.92 ± 7.72</td>
</tr>
<tr>
<td>Current smokers</td>
<td>103 (39.3%)</td>
<td>36 (40.4%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>28.14 ± 12.41 (101)</td>
<td>29.37 ± 12.84 (35)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>108 (41.2%)</td>
<td>36 (40.4%)</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>48 (18.3%)</td>
<td>16 (18.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.1%)</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

*Two controls matched to each case. Cases and controls also matched on duration of follow-up (time between enrollment and diagnosis of case, which ranged from 1–13 years).

**Mean ± SD (n) for current smokers. Data is not available for two subjects.

### Table 4

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>β</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH-DNA</td>
<td>1.09</td>
<td>2.98 (1.05–8.42)</td>
<td>0.04</td>
</tr>
<tr>
<td>Current</td>
<td>0.26</td>
<td>1.30 (0.51–3.29)</td>
<td>0.58</td>
</tr>
<tr>
<td>Former</td>
<td>–0.65</td>
<td>0.52 (0.12–2.32)</td>
<td>0.39</td>
</tr>
<tr>
<td>Never</td>
<td>0.47</td>
<td>1.59 (0.88–2.90)</td>
<td>0.12</td>
</tr>
<tr>
<td>All</td>
<td>0.21</td>
<td>1.23 (0.85–1.78)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Based on median PAH/aromatic adduct levels in controls.

### Table 3

<table>
<thead>
<tr>
<th>Current smokers</th>
<th>Former smokers</th>
<th>Never-smokers</th>
<th>Total</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>11.04 ± 4.03 (36)</td>
<td>7.04 ± 1.46 (35)</td>
<td>4.96 ± 0.64 (15)</td>
<td>8.32 ± 1.78 (87)</td>
</tr>
<tr>
<td>Controls</td>
<td>5.63 ± 0.53 (64)</td>
<td>9.84 ± 2.41 (64)</td>
<td>6.23 ± 1.19 (30)</td>
<td>7.39 ± 1.02 (160)</td>
</tr>
<tr>
<td>Total</td>
<td>7.58 ± 1.50 (100)</td>
<td>8.85 ± 1.64 (99)</td>
<td>5.81 ± 0.82 (45)</td>
<td>7.72 ± 0.91 (244)</td>
</tr>
<tr>
<td>Paired t-test</td>
<td>0.03</td>
<td>0.81</td>
<td>0.66</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*P* by two-tailed ANOVA for differences across strata of smoking levels.
**Arithmetic mean ± SE (n).
* Cigarette smoking data and adduct data were not available for one case and two controls and two cases and 13 controls, respectively.
**Paired t-test. See “statistical methods” in text.
patients undergoing surgery for lung cancer, Wiencke et al. (21) noted a major adduct in WBCs and in noninvolved lung tissue that cochromatographed with radiolabeled (+)-anti-BaP diol-epoxide-N2-deoxyguanosine. They found a significant correlation between DNA adduct levels in the mononuclear WBCs and lung tissue (14). Similarly, in an earlier study using an immunoassay to detect PAH-DNA adducts, Tang et al. (13) found a significant correlation between DNA adducts in WBCs and lung tissue from the same subjects. Third, biological plausibility is also supported by considerable evidence that certain individuals are inherently more susceptible to genetic damage and cancer from environmental exposures such as tobacco smoke (1, 36–38, 46). Molecular epidemiological research has demonstrated significant interindividual variation in carcinogen-DNA binding among subjects with comparable exposure, suggesting that DNA adducts have the potential to identify persons with an enhanced response because of the nature of their metabolic/detoxification and DNA repair pathways (25, 36, 39–43). Moreover, a number of studies have shown a relationship between cancer at various sites and mutagen sensitivity, tested by measuring induction of DNA adducts (44).

Although not all of the case-control studies have been consistent, a number using ELISA or high-performance liquid chromatography/fluorimetry to measure PAH-DNA adducts have reported that DNA adducts are elevated in WBCs or lung tissue of lung cancer cases (13, 18, 20, 24, 45). They found a significant correlation within a prospective cohort design. However, there are a number of limitations. Given the nature of the 32P-postlabeling method, we are unable to specify the exact composition of the adducts for subtype analysis. Furthermore, we did not have data on changes in smoking after enrollment. It is possible that this may have biased our results toward the null because controls with high enrollment levels of adducts may have subsequently reduced both their adduct levels and lung cancer risk by quitting. Although it is unlikely that unmeasured differences in smoking habits (brand, number of puffs, and so forth) might explain our results, we were only able to control for differences in CPD. The limited number of cases precludes definitive conclusions regarding biomarker-disease relationships by histological type of cancer. Finally, we did not have serial samples drawn at sufficiently frequent intervals to determine the operative stage for the biomarker (e.g., whether adducts are early or late events or a combination). For example, we cannot necessarily assume that biomarkers measured in men at older ages are representative of those present at earlier ages when, presumably, critical initiating events would have occurred. This is particularly true for individuals whose environmental exposure has changed significantly over time, as in former smokers. However, there is substantial evidence that adduct measures can serve as general indices of individual ecogenetic response to environmental carcinogens and can distinguish constitutionally “high responders” from “low responders” (12, 25, 35, 40, 42). These high responders may have increased activation via P450 enzymes, decreased detoxification via the glutathione S-transferase pathway, and/or decreased DNA repair that are shared by lymphocytes and lung. It is possible that, in this relatively small number of subjects, the case-control difference was clearly evident only in the presence of ongoing challenge via active smoking. This may explain why the current smokers among the controls have lower levels than current smoker cases and why current smoker controls had lower adduct levels than former smoker controls.

In the present study in which we have controlled for differences in the major carcinogenic exposure detected by the assay (i.e., PAH and other aromatics in tobacco smoke) among current smokers but not among former and never-smokers, elevated PAH-DNA and other aromatic/hydrophobic carcinogen-DNA adducts in WBCs were significant predictors of lung cancer risk.

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Table 6 PAH/aromatic-DNA adducts (per 10⁸ nucleotides) in WBCs of cases and their corresponding controls stratified by histological category

<table>
<thead>
<tr>
<th></th>
<th>Small cell</th>
<th>Adenocarcinoma</th>
<th>Squamous cell</th>
<th>Total</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>6.43 ± 1.20 (15)</td>
<td>10.39 ± 4.54 (30)</td>
<td>5.48 ± 0.74 (19)</td>
<td>8.32 ± 1.78 (87)</td>
<td>0.52</td>
</tr>
<tr>
<td>Controls</td>
<td>12.53 ± 4.77 (26)</td>
<td>7.31 ± 1.47 (57)</td>
<td>5.86 ± 1.77 (34)</td>
<td>7.39 ± 1.02 (160)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total</td>
<td>10.30 ± 3.07 (41)</td>
<td>8.38 ± 1.83 (87)</td>
<td>5.72 ± 1.16 (53)</td>
<td>7.72 ± 0.91 (244)</td>
<td></td>
</tr>
</tbody>
</table>

* P by ANOVA across histological categories.

** Arithmetic mean ± SE (n).
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