Short Communication

White Blood Cell DNA Adducts, Smoking, and NAT2 and GSTM1 Genotypes in Bladder Cancer: A Case-Control Study

Marco Peluso, Luisa Airoldi, Munnia Armelle, Tiziana Martone, Renato Coda, Christian Malaveille, Giuseppe Giacomelli, Carlo Terrone, Giovanni Casetta, and Paolo Vineis

Abstract

We conducted a case-control study on 114 bladder cancer patients and 46 hospital controls. DNA adducts were measured in WBCs by 32P postlabeling and showed no association with smoking habits and the glutathione-S-transferase M1 genotype. A strong association between adduct levels and the N-acetyltransferase (NAT2) genotype was found ($P = 0.0002$). The NAT2 genotype was associated in a nonstatistically significant way to the case-control status (odds ratio, 1.6; 95% confidence interval, 0.8–3.2). In a logistic regression model, the log of DNA adduct levels was associated in a highly significant way to the risk of bladder cancer (regression coefficient, 0.75; $P = 0.0006$), independently of smoking habits. Using the median of DNA adducts (RAL, 0.3) as a cutoff point, the odds ratio for the risk of bladder cancer was 4.1 (age-adjusted; 95% confidence interval, 1.9–9.0). Our study suggests that sources other than tobacco smoke contribute to the formation of aromatic DNA adducts in WBCs. The role of WBC-DNA adducts in predicting bladder cancer is still to be clarified.

Introduction

Cigarette smoking is an established cause of urinary bladder cancer, accounting for at least 50% of the bladder cancers in Western populations (1). Epidemiological studies conducted in Italy (2, 3), Argentina (4), and France (5) have shown that smokers of black (air-cured) tobacco have a higher risk of bladder cancer than smokers of blond (flue-cured) tobacco. Arylamines, including ABP (2) and 2-naphthylamine, have been found in cigarette smoke and have been recognized as human and animal bladder carcinogens (1, 6); in addition, the condensate of smoke from black (air-cured) tobacco has been shown to contain higher concentrations of the same carcinogens (7).

To ascertain the role of arylamines in the induction of bladder cancer in smokers and to assess the contribution of the metabolic phenotype to cancer risk, studies of molecular epidemiology have been conducted. In a previous investigation, we found that the levels of the ABP-hemoglobin adduct were approximately five times higher in smokers of black tobacco and three times higher in smokers of blond tobacco than in nonsmokers (8), in accordance with the risks of bladder cancer reported in epidemiological studies (3, 4, 5). For several carcinogens, hemoglobin adducts represent a marker of their internal dose (9). The magnitude of increased risk of bladder cancer among smokers of the two tobacco types, as compared with nonsmokers, was proportional to the concentrations of ABP-hemoglobin adducts, consistent with an etiological role of arylamines in tobacco-induced bladder cancer. In another investigation (10) by our group, urine from smokers of black tobacco contained approximately twice as many mutagens as did that from blond tobacco smokers, when adjusting for the same nicotine intake.

Arylamines are metabolically activated to electrophilic compounds in the liver via N-hydroxylation. The N-hydroxy derivative either reacts covalently with hemoglobin and other macromolecules or is filtered in the bladder lumen, where it reacts with urothelial DNA. In humans, N-hydroxylation is catalyzed by cytochrome P450 IA2 (11). The detoxification reaction competes with N-hydroxylation and proceeds mainly via N-acetylation, catalyzed by N-acetyltransferase(s) in the liver and other tissues (12–14). N-Acetyltransferase is a non-inducible enzyme under autosomal dominant genetic control. At least two genes are involved, NAT1 and NAT2. A number of investigations have reported that “slow” acetylators are at higher risk of bladder cancer, especially subgroups occupationally exposed to aryl amines (15–19).

We conducted a case-control study in which we have measured DNA adducts in WBCs by the 32P-postlabeling method. The hypotheses underlying the study were: whether the level of DNA adducts is influenced by smoking, particularly of air-cured tobacco; whether the NAT2 and GSTM1 genotypes influence the level of adducts; and whether adducts are related to the case-control status.

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3 The abbreviations used are: ABP, 4-aminobiphenyl; OR, odds ratio; C1, confidence interval; PAH, polycyclic aromatic hydrocarbon; DRZ, diagonal reactive zone.
Subjects and Methods

We conducted a hospital-based, case-control investigation involving four Departments of Urology in two hospitals (Gra- denigo and S. Giovanni Battista) in Torino, Northern Italy. More than one-half of the newly diagnosed bladder cancers occurring in residents of the Torino metropolitan area are treated in such departments. Cases, living in the Torino metropolitan area, were incident (newly diagnosed) cases of bladder cancer with a histologically confirmed diagnosis. They were men, ages 40–74, and treated in such departments in 1994–1996. The identification of cases occurred through daily contacts between a trained interviewer and the urology departments. Histological confirmation was obtained from the pathology departments.

Controls were recruited in the same urology departments and in surgical departments and included benign diagnoses, mainly prostatic hyperplasia and cystitis (all newly diagnosed). All cancers, metabolic diseases, and smoking-related conditions were excluded. Controls were men living in the Torino metropolitan area, ages 40–74.

Cases and controls were interviewed by a trained interviewer before therapy, with a standard questionnaire concerning a detailed history of tobacco smoking (including brands and tobacco type), a simplified 24-h recall for dietary habits, drug use, and occupational history. Because all lived in the Torino metropolitan area, urban/rural differences could not be investigated.

Biological Samples: Collection and Analyses. Before therapy and after informed consent, blood was collected from both cases and controls (40 ml) and immediately centrifuged. Buffy coats were separated from coded blood samples (8 ml) by centrifugation at 800 x g for 45 min, followed by lysis of the contained red cells by suspension in three volumes 0.17 ammonium chloride at 4°C for 10 min and centrifugation at 800 x g for 10 min. The pellet containing WBCs was washed with ammonium chloride and stored at -80°C. WBC DNA was isolated and purified from the stored cell pellets by enzymatic digestion of RNA and proteins followed by phenol/chloroform extractions (20).

WBC DNA samples were digested to 3'-mononucleotides with 0.46 unit of micrococal nuclease (0.312 unit/μl; Sigma Chemical Co., St. Louis, MO) and 0.352 unit of spleen phosphodiesterase (0.058 unit/μl; Sigma) in 17 mM sodium succinate and 8 mM calcium chloride (pH 6.0) at 37°C for 4.5 h (21). DNA hydrolysates were evaporated to dryness and redissolved appropriately. Enrichment of carcinogen-DNA adducts in DNA digests was done by selective destruction of normal nucleotides by nuclease P1 procedure, which involves the addition of tetrabutylammonium chloride at 4°C for 10 min and centrifugation at 800 x g for 45 min, followed by lysis of the contained red cells by suspension in three volumes 0.17 ammonium chloride at 4°C for 10 min and centrifugation at 800 x g for 10 min. The pellet containing WBCs was washed with ammonium chloride and stored at -80°C. WBC DNA was isolated and purified from the stored cell pellets by enzymatic digestion of RNA and proteins followed by phenol/chloroform extractions (20).

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### Table 1

Means, medians, and SE of DNA adducts in the blood cells (RAL × 10^4), by case-control status, smoking habits, and acetylator (NAT2) and GSTM1 genotype.

All men are ages 40–74. Data on 54 subjects, based on butanol extraction before adduct analysis, are shown only in relation to the N-acetyltransferase genotype.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th></th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>Median</td>
<td>SE</td>
<td>Mean</td>
<td>Median</td>
<td>SE</td>
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<tr>
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<td>0.76</td>
<td>0.6</td>
<td>0.16</td>
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<td>0.19</td>
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<tr>
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<td>0.05</td>
<td>8</td>
<td>0.50</td>
<td>0.3</td>
</tr>
<tr>
<td>Current smokers</td>
<td>64</td>
<td>0.60</td>
<td>0.4</td>
<td>0.07</td>
<td>13</td>
<td>0.31</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>112</strong></td>
<td><strong>0.56</strong></td>
<td><strong>0.4</strong></td>
<td><strong>0.08</strong></td>
<td><strong>46</strong></td>
<td><strong>0.29</strong></td>
<td><strong>0.1</strong></td>
</tr>
</tbody>
</table>

P (Kruskal-Wallis test) = 0.09

Current and ex-smokers:

<table>
<thead>
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<th>Type of tobacco smoked throughout life</th>
<th>Cases</th>
<th></th>
<th></th>
<th>Controls</th>
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<tbody>
<tr>
<td>Blue-cured tobacco</td>
<td>38</td>
<td>0.65</td>
<td>0.4</td>
<td>0.1</td>
<td>10</td>
<td>0.40</td>
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<td>Mixed tobacco</td>
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<td>0.41</td>
<td>0.3</td>
<td>0.05</td>
<td>11</td>
<td>0.36</td>
<td>0.3</td>
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<tr>
<td>Air-cured tobacco</td>
<td>17</td>
<td>0.59</td>
<td>0.5</td>
<td>0.14</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>96</strong></td>
<td><strong>0.50</strong></td>
<td><strong>0.4</strong></td>
<td><strong>0.08</strong></td>
<td><strong>21</strong></td>
<td><strong>0.29</strong></td>
<td><strong>0.1</strong></td>
</tr>
</tbody>
</table>

P (Kruskal-Wallis test) = 0.11

### Acetylator genotype (NAT2)

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<tr>
<th></th>
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<th>Rapid</th>
<th></th>
<th></th>
<th>Totals</th>
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<td></td>
<td>n</td>
<td>Mean</td>
<td>Median</td>
<td>SE</td>
<td>n</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Cases</td>
<td>76</td>
<td>0.66</td>
<td>0.5</td>
<td>0.07</td>
<td>38</td>
<td>0.38</td>
<td>0.26</td>
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<tr>
<td>Controls</td>
<td>26</td>
<td>0.39</td>
<td>0.18</td>
<td>0.10</td>
<td>20</td>
<td>0.13</td>
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P (Kruskal-Wallis test) = 0.0002

### GSTM1 genotype

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<th>Totals</th>
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</thead>
<tbody>
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<td>n</td>
<td>Mean</td>
<td>Median</td>
<td>SE</td>
<td>n</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Cases</td>
<td>59</td>
<td>0.60</td>
<td>0.44</td>
<td>0.07</td>
<td>55</td>
<td>0.54</td>
<td>0.4</td>
</tr>
<tr>
<td>Controls</td>
<td>27</td>
<td>0.27</td>
<td>0.17</td>
<td>0.06</td>
<td>19</td>
<td>0.29</td>
<td>0.17</td>
</tr>
</tbody>
</table>

P (Kruskal-Wallis test) = 0.90

### Acetylator genotype (NAT2)\(^a\)

<table>
<thead>
<tr>
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<th>Slow</th>
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<th></th>
<th>Rapid</th>
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<th></th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>Median</td>
<td>SE</td>
<td>n</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Cases</td>
<td>27</td>
<td>0.62</td>
<td>0.65</td>
<td>0.09</td>
<td>12</td>
<td>0.33</td>
<td>0.25</td>
</tr>
<tr>
<td>Controls</td>
<td>8</td>
<td>0.39</td>
<td>0.2</td>
<td>0.19</td>
<td>7</td>
<td>0.35</td>
<td>0.1</td>
</tr>
</tbody>
</table>

P (Kruskal-Wallis test) = 0.09

\(^a\) Two missing values.

\(^b\) Butanol extraction.

ers were 2 (5%), former smokers 20 (47.5%), and current smokers 20 (47.5%). These cases did not differ from the others in terms of clinical or pathological characteristics.

Twenty-four cases and 8 controls had worked in high-risk occupations (dyes, rubber, painting, truck driving, and textiles; OR, 1.45; 95% CI, 0.5–3.9; occupations with uncertain exposure were excluded from the reference category). Among these, 10 cases and 1 control were judged to be at very high risk (occupations in rubber, dye, or painting; OR, 5.6; 95% CI, 0.6–48).

Table 1 shows mean and median levels of DNA adducts in blood cells according to case-control status, smoking (including type of tobacco), and NAT2 or GSTM1 genotypes. There is no clearcut difference between nonsmokers, ex-smokers, or current smokers for DNA adducts. In cases, nonsmokers had higher levels of adducts than smokers. No evident association is present with the type of tobacco smoked. The vast majority of the subjects had retired from work several years before recruitment; therefore, an analysis of adducts by recent occupation could not be made.

A rather strong association was found between the case/control status and the level of adducts. According to nonparametric analysis, P was 0.0001. A strong statistical association was found also with the NAT2 genotype (Table 1; P = 0.0002), whereas the GSTM1 genotype was not associated with adduct levels. As far as NAT2 is concerned, butanol extraction did not change the estimates sensibly, in comparison with nuclease P1 extraction (Table 1): this suggests that DNA adducts may have an aromatic structure.

There was no association between the histological grade (invasiveness) of the tumors and adducts levels (median adducts: 0.43 in grade 1; 0.4 in grade 2; and 0.48 in grade 3).

According to multivariate analysis (Table 2), the concentration of adducts was strongly associated with the NAT2 genotype (model 1). Using the number of cigarettes smoked, both as a continuous and as a dummy variable, smoking was not a predictor of the logarithm of the concentration of adducts (models 1 and 2). Also, interactive terms between levels of smoking and the NAT2 genotype did not contribute significantly to the model (model 3). Instead, the introduction of the case/control status contributed in a statistically significant way to the concentration of adducts (model 4).
Short Communication: Adducts, Smoking, and Genotypes in Bladder Cancer

Table 2  Multivariate models: dependent variable log (DNA adducts) (RAL × 10^4)

<table>
<thead>
<tr>
<th>Model</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model I</td>
<td>Age (continuous)</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td>No. of cigarettes/day (continuous)</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Acetylator genotype (NAT2)</td>
<td>3.1</td>
</tr>
<tr>
<td>Model II</td>
<td>No. of cigarettes/day*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–10</td>
<td>−0.4</td>
</tr>
<tr>
<td></td>
<td>10–20</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>20–30</td>
<td>−0.45</td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Acetylator genotype (NAT2)</td>
<td>3.0</td>
</tr>
<tr>
<td>Model III</td>
<td>No. of cigarettes/day*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–10</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>10–20</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>20–30</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Acetylator genotype (NAT2)</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Interactive terms</td>
<td></td>
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<tr>
<td></td>
<td>1–10 cigarettes/day *NAT2</td>
<td>−0.7</td>
</tr>
<tr>
<td></td>
<td>10–20 cigarettes/day *NAT2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>20–30 cigarettes/day *NAT2</td>
<td>−0.9</td>
</tr>
<tr>
<td></td>
<td>30+ cigarettes/day *NAT2</td>
<td>−0.6</td>
</tr>
<tr>
<td>Model IV</td>
<td>No. of cigarettes/day*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–10</td>
<td>−0.5</td>
</tr>
<tr>
<td></td>
<td>10–20</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>20–30</td>
<td>−1.1</td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Acetylator genotype (NAT2)</td>
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<tr>
<td></td>
<td>Case/control status</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Table 3  Logistic regression model: dependent variable case-control status All models are age adjusted

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>P</th>
<th>OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model I</td>
<td>Acetylator genotype (slow versus rapid)</td>
<td>0.12</td>
</tr>
<tr>
<td>Model II</td>
<td>Log (DNA adducts)</td>
<td>0.75</td>
</tr>
<tr>
<td>Model III</td>
<td>Acetylator genotype (slow versus rapid)</td>
<td>0.10</td>
</tr>
<tr>
<td>Model III</td>
<td>No. of cigarettes smoked (continuous variable)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Log (DNA adducts)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

* Reference category nonsmokers.

The NAT2 slow genotype, as such, was weakly predictive of the case-control status, with an OR of 1.6 (age-adjusted; 95% CI, 0.8–3.2). According to logistic regression analysis (Table 3), a strong direct association between the logarithm of DNA adducts in blood cells and the risk of bladder cancer was found (continuous measurement: regression coefficient, 0.44; P = 0.0003). When the median of DNA adducts (RAL = 0.3) was used as a cutoff point, the OR was 4.1 (age-adjusted; 95% CI, 1.9–9.0). The inclusion of the NAT2 genotype in the regression model led to an OR for the slow genotype of 1.1 (P = 0.8) instead of 1.6, whereas the association with DNA adducts persisted unchanged (regression coefficient, 0.75; P = 0.0006). The number of cigarettes smoked was a predictor of the case-control status independent of DNA adducts (model 3).

Discussion

As we have suggested in previous investigations, it is likely that bladder cancer induced by tobacco smoke is attributable to arylamines, such as 4-ABP (27). However, tobacco smoke contains other carcinogenic compounds, including PAHs and nitrosonamines (28), many of which are able to form DNA adducts after metabolic activation to electrophilic species (29). We decided to investigate the association between smoking and the risk of bladder cancer further, by examining the levels of tobacco-related adducts in the WBC DNA of 114 bladder cancer cases and 46 referents, using both the nuclease P1 and the butanol extraction methods. The nuclease P1 technique, alone, is able to detect bulky hydrophobic adducts, such as those formed by the PAHs and by some arylamines bound to the exocyclic position of guanine or adenine (30), whereas extraction with butanol is effective for most of the aromatic amines bound to the C-8 position of guanine and some low molecular weight alkylation agents (30).

Our chromatographic results showed a similar qualitative pattern of DNA adducts (DRZ and seven distinct DNA adducts) in the DNA samples of bladder cancer cases and referents. However, the levels and the proportions of the adduct spots were higher in the cases than in the controls. Three specific DNA adducts (nos. 1, 3, and 6) were detected in higher proportions in the group of current smokers than in nonsmokers (data not shown). The DRZ was present in 40–50% of positive current smokers and in lower proportions of positive former smokers or nonsmokers. A similar DNA adduct pattern has already been detected in the lung and in other tissues of cigarette smokers, such as heart, kidney, placenta, nasal mucosa, and ascending aorta (31–33). The DRZ pattern is broadly characteristic of the DNA adducts formed by the aromatic carcinogens present in tobacco smoke and indicates that a part of the WBC DNA adducts of smokers in our study were formed by a complex mixture of such chemicals. The different proportions of specific adduct spots in the positive chromatograms of smokers and nonsmokers may reflect the exposure to cigarette smoke and/or other genotoxic chemicals. Similar results have already been shown in the exfoliated urothelial cells of smokers and nonsmokers (34).

No relationship between the WBC total DNA adduct levels and the smoking status was found either in the cases or in the controls in univariate (nonparametric) and in multivariate analyses (Table 2), using both enhancement techniques. Previous 32P-postlabeling studies have reported conflicting results of the association between the adduct levels in peripheral leukocytes and tobacco smoking (35–40). Discrepancies may depend on the marked interindividual variation in the metabolism of carcinogens, which results in different DNA adduct levels for similar degrees of exposure (41).

The case or control status was associated in a statistically significant way to the DNA adduct levels, independently of the NAT2 genotype (Table 2). Other studies have shown that the DNA adduct levels may be higher in cancer cases than in controls (42–44). The biological reasons for such an association are not known. It is possible that the higher DNA adduct levels in cases represent an artifact due to the metabolic impairment associated with cancer. Alternatively, the association may indicate that persons who form high levels of adducts in...
response to environmental carcinogens have a higher risk of developing cancer than those with lower DNA damage.

The role of genetic polymorphism of enzymes involved in metabolic detoxification of aromatic compounds was analyzed by studying the frequency of GSTM1 and NAT2 genotypes. GSTM1 is a gene polymorphic in humans that contributes to detoxifying several carcinogens, such as the PAHs (45). A weak association between the risk of bladder cancer and the null GSTM1 genotype has been reported from several investigations, with an overall OR (meta-analysis) of 1.4 (45). In our study, the GSTM1 genotype had no effect on DNA adduct levels of WBC-DNA of bladder cancer cases and referents, using both the nuclease P1 and the butanol extraction techniques (Table 1). The lack of effect of the GSTM1 null genotype on DNA adducts has been already reported using both enhancement techniques (37, 46). It is possible that the rate of the GSTM1-related detoxification of aromatic carcinogens is lower in the WBC than in other target tissues, i.e., lung and urinary bladder.

NAT2 is a noninducible hepatic enzyme that deactivates carcinogenic aromatic amines by N-acetylation (45). The activity of arylamines is modulated by the polymorphic N-acetyltransferase; slow acetylators exposed to aromatic amines have a higher risk of bladder cancer (45). Our data clearly show that the N-acetyltransferase genotype was strongly associated with adduct concentration (Tables 1 and 2). In the present study, the bladder cancer patients who were slow acetylators showed higher adduct levels than rapid acetylators, using both the nuclease P1 and the butanol extraction procedures (Table 1). Among the referents, slow acetylators had higher levels of aromatic WBC-DNA adducts than rapid acetylators only when using the nuclease P1 technique (Table 1). No interaction was found between smoking levels and the NAT2 genotype in influencing the adduct levels (Table 2).

The relationship between the NAT2 genotype and DNA adducts has been already described in bus maintenance workers using the nuclease P1 technique, but only in interaction with GSTM1 (47). Lack of a NAT2 effect on DNA adducts has been reported in bus drivers using the butanol extraction technique (36). Our findings seem to suggest that the WBC-DNA adducts that we have measured might be formed by arylamines in the bladder cancer cases, and only by aromatic compounds bound to the exocyclic positions of guanine or adenosine among the referents, as already suggested in a previous study on the influence of GSTM1 and NAT2 upon aromatic DNA adduct levels, using the nuclease P1 technique (47). Clearly, this observation needs confirmatory evidence.

The relationship between the case-control status, NAT2, and DNA adducts in blood cells is rather complex. According to logistic regression analysis (Table 3), a strong direct association between (log) DNA adduct in blood cells and the risk of bladder cancer was found. The inclusion of the NAT2 genotype in the regression model led to an OR for the slow genotype of 1.1 (P = 0.9) instead of 1.6, whereas the association with the DNA adducts persisted unchanged. Also, the inclusion of smoking habits (which were strongly predictive of cancer) did not substantially change the association between the case-control status and DNA adducts.

We can hypothesize, on the basis of our results, that: (a) the level of WBC-DNA adducts is influenced by the NAT2 genotype, suggesting that such adducts are at least in part formed by aromatic compounds; (b) smoking is not predictive of WBC-DNA adducts, whereas it is clearly an independent risk factor for bladder cancer; (c) there are unidentified sources of aromatic compounds, other than smoking, that can explain the WBC-DNA adduct levels; (d) the relationship between NAT2 and the risk of bladder cancer can be, at least in part, mediated by DNA adducts, because such relationship disappears when adjustment for adduct levels is made. Alternative explanations that should be further explored are that: (a) DNA adducts are increased in cancer cases, compared with controls, as a consequence of the cancer process itself; or (b) there is an increased susceptibility of a subgroup of subjects (who are prone to develop cancer) to form adducts for a similar level of environmental exposures (48). Such susceptibility might be related, for example, to the efficiency of DNA repair.

References


White blood cell DNA adducts, smoking, and NAT2 and GSTM1 genotypes in bladder cancer: a case-control study.

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