Benzo(a)pyrene Diol Epoxide-induced Chromosomal Aberrations and Risk of Lung Cancer

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ABSTRACT

Benzo(a)pyrene is considered a classic DNA-damaging carcinogen and is one of a multitude of polycyclic aromatic hydrocarbons commonly found in tobacco smoke and in the ambient environment. In this report, we describe the characteristics of chromosomal aberrations induced in vitro by activated benzo(a)pyrene diol epoxide (BPDE) in lymphocyte cultures of 172 normal individuals ages 19—95 years and present the analysis of a pilot case-control study of 33 lung cancer patients and 96 selected controls without history of cancer and frequency matched on age (50—85 years) to the cases. The BPDE-induced chromosomal aberrations were predominantly single chromatid breaks, with few isochromatid breaks or exchange figures. In the 172 normal subjects, the frequencies of both spontaneous and BPDE-induced chromatid breaks were not correlated with age, sex, ethnicity, or tobacco use. However, the frequency of BPDE-induced chromatid breaks was significantly correlated with the frequency of spontaneous chromatid breaks (r = 0.19, P < 0.05). In addition, Hispanics had significantly higher mean BPDE-induced chromatid breaks than did non-Hispanic whites (P < 0.01). From the case-control analyses, the frequency of BPDE-induced chromosomal aberrations was significantly higher in cases (mean, 0.67 breaks/cell) than in controls (mean, 0.41 breaks/cell; P < 0.0001). An adjusted odds ratio of 6.53 (95% confidence interval, 3.74—11.4) for lung cancer was associated with increased frequency of these chromosomal aberrations. The higher rate of BPDE-induced chromosomal aberrations may be due to inefficient DNA repair. These findings warrant additional molecular epidemiological studies. The BPDE mutagen sensitivity assay will facilitate epidemiological studies of genetic susceptibility to smoking-related cancers.

INTRODUCTION

It has been estimated that 169,900 new cases of lung cancer and 158,700 deaths from lung cancer will occur in the United States in 1996 (1). To date, cigarette smoking has been consistently identified as the major risk factor for lung cancer (2—4). One of the polycyclic aromatic hydrocarbons, B(a)P, is considered a classic DNA-damaging carcinogen (5) and is commonly found in tobacco smoke and in the ambient environment. The parent compound B(a)P is relatively nontoxic, but its bioactivation in vivo by cytochrome P450 and per-oxidases generates highly toxic electrophilic and free radical reactive intermediates, such as BPDE, that can irreversibly damage DNA by covalent binding or oxidation (6—9). Because not all exposed individuals develop cancer, genetically determined host factors may contribute to predisposition to DNA damage and therefore modulate risk of lung cancer in smokers (10).

Molecular epidemiological studies using immunoassays with antibodies against BPDE-modified DNA have documented that smokers often have higher polycyclic aromatic hydrocarbon-DNA adduct levels than do nonsmokers (11—13). The levels of DNA adducts detected in nonneoplastic surgical lung parenchymal samples (14) and alveolar macrophages (15) are also higher in smokers than in ex-smokers, indicating that tobacco exposure is a source of BPDE. Frequent mutations found in the p53 gene suggest that this gene may be one of the targets involved in carcinogenesis (16, 17). Molecular sequencing analysis has consistently shown a high frequency of p53 G to T transversion mutations in murine skin tumors induced by B(a)P (18) and in tobacco-related human cancers, including lung cancer (19, 20), head and neck cancers (21), and esophageal carcinomas (22, 23), suggesting an association with exposure to specific mutagens such as B(a)P in tobacco smoke (24, 25).

It has been demonstrated that BPDE-induced DNA adducts are repaired by the nucleotide excision repair pathway (26, 27). The premutagenic lesions induced by BPDE are repaired more efficiently in the transcribed strand than in the untranscribed strand of the hypoxanthine-guanine phosphoribosyltransferase gene, suggesting that BPDE-DNA adducts may block the transcription of essential genes (28) and cause changes in the chromatin structure (29). We recently demonstrated a correlation between DNA repair capacity and in vitro-induced chromosomal aberrations in lymphoblastoid cell lines (30), which supports the hypothesis that reduced DNA repair capacity is one of the factors responsible for increased mutagen-induced chromosomal breakage in human lymphocytes. However, few studies have evaluated in vitro BPDE-induced chromosomal aberrations in human lymphocytes. In this report, we describe the frequency of in vitro BPDE-induced chromosomal aberrations in human peripheral lymphocytes from normal individuals and present the preliminary findings of a pilot case-control study of lung cancer.

MATERIALS AND METHODS

Chemicals and Reagents. BPDE (NCI L0137, 99% purity) was purchased from Midwest Research Institute (Kansas City, MO) as a white powder and was completely dissolved in tetrahydrofuran (Sigma Chemical Co., St. Louis, MO). The stock concentration (1 mm; i.e., 0.3 mg/ml) was further diluted for the working solution, which was prepared once in a dark room, aliquoted into microcentrifuge tubes, and kept at −20°C without exposure to air or light.

Cell Lines. Four EBV-immortalized human lymphoblastoid cell lines from the Human Genetic Mutant Cell Repositories (Camden, NJ) were used: two apparently normal cell lines, GM00892B and GM00831A, and two XP cell lines, GM02345B (XP-A) and GM02246B (XP-C), with deficient nucleotide excision repair. We used these two types of cell lines to test the sensitivity and specificity of the effect of BPDE in terms of DNA repair-related chromosomal aberrations. All of the cells were cultured in T-25 flasks at 37°C in a 5% CO2 atmosphere in the standard medium RPMI 1640 (Life Technologies, Inc., Grand Island, NY) supplemented with 15% fetal bovine serum (Life Technologies, Inc.).

Flow Cytometry Analysis. The effect of BPDE treatment on the cell cycle was evaluated using flow cytometry (31) to assess whether BPDE had different genotoxic effects on cells with different repair capacities. Briefly, treated and untreated cells were washed twice with PBS and fixed in ice-cold 70% ethanol for at least 30 min. A suspension containing approximately 2 X 10⁶ fixed cells was then centrifuged, and the supernatant was removed by aspiration. The cells were resuspended with a vortex mixer in 1 ml propidium iodide staining solution (50 μg/ml propidium iodide and 100 units/ml RNase A). After 30 min
of incubation at room temperature, the cells were analyzed using flow cytometry (Profile Coulter, Miami, FL) to determine the fractions of cells in the G1, S-phase, and G2 + M.

**Study Subjects.** The 33 cases included in this report were a subset of patients from an ongoing molecular epidemiological study of lung cancer. The histopathological types of tumors included 2 large cell carcinomas, 4 non-small cell carcinomas, 3 small cell carcinomas, 12 squamous cell carcinomas, 7 adenocarcinomas, and 5 unspecified tumors. The 172 apparently healthy subjects included in this report were randomly recruited from community centers, cancer screening programs, and The University of Texas M. D. Anderson Cancer Center blood drives. Each subject completed a short questionnaire that elicited information about demographic variables and smoking history. The exclusion criteria were previous chemotherapy or radiotherapy for cancer, recent infections, and recent blood transfusion. Ten ml of blood from each subject was drawn into a heparinized Vacutainer (Becton Dickinson, Franklin Lakes, NJ). From each sample, two short-term cultures were established and maintained under conditions similar to those used for the lymphoblastoid cell lines except for supplementation with 20% fetal bovine serum and a final concentration of 112.5 µg/ml phytohemagglutinin (Murex Diagnostics, Norcross, GA).

**Quantitation of Chromosomal Aberrations.** We followed the published protocol for the mutagen sensitivity assay using bleomycin (32) with minor modifications for BPDE. For each sample, 1 ml of whole blood was first inoculated into each of two T-25 flasks containing 9 ml of culture medium with phytohemagglutinin, and the caps were tightened and incubated at 37°C for 72 h. At approximately 67 h of incubation, one set of cultures was treated with BPDE for another 5 h. The 5-h treatment was chosen to avoid BPDE-related cytotoxicity due to prolonged (i.e., 24 h) treatment and to allow a workable timetable and evaluation of chromosomal damage in metaphases related to DNA damage that escaped repair in G2. During the last hour, the cultures were treated with Colcemid at a final concentration of 0.04 µg/ml (Life Technologies, Inc.) to induce mitotic arrest. The cells were then harvested by using published chromosome harvesting procedures (32), i.e., the cells were treated with a hypotonic KCl (60 mM) solution for 15 min, fixed, washed with a freshly prepared mixture of meibanyl:acetic acid (3;1; v:v), and then dried on wet slides. Slides of each culture were stained with 4% Giemsa (Biomedical Specialties, Santa Monica, CA) for approximately 7 min to visualize the chromosomes without banding. The slides from untreated and treated cultures were coded, mixed, and evaluated with a Nikon Labophot-2 photomicroscope (Nikon Inc. Instrument Group, Melville, NY). For each culture, chromosomal breakage in 50 well-spread full metaphases was counted. This number has been statistically shown to be as efficient as 100 metaphases and provides an acceptable level of reliability (33). The chromosomal breaks were counted by following published criteria (34): each simple chromatid break was scored as one break, and each isochromatid break set and each exchange figure (including interstitial deletion) were regarded as two breaks.

**Host-Cell Reactivation Assay.** The cellular DNA repair capacity of the cell lines was measured using the host-cell reactivation assay as described elsewhere (35). Purified plasmid (pCMVcat; 5 kb) was dissolved in Tris-EDTA buffer (pH 7.9) at a concentration of 500 µg/ml, and 1-ml aliquots of the solution were placed in microcentrifuge tubes. For BPDE treatment, the working solution was added to the tubes to final concentrations of 0, 30, 60, or 90 µM for 3 h in a dark room. These treatments were performed in one batch for all CAT assays. After treatment, the plasmids were precipitated three times with 70% ethanol and then dissolved in Tris-EDTA buffer at a final concentration of 50 µg/ml (stock solution) and assessed for confomational changes with 0.8% agarose gel electrophoresis. The cells were transfected with either treated or untreated (control) plasmid (approximately 0.25 µg/pmlasmid/2 x 10⁶ cells for each determination) using the diethylaminoethyl-dextran procedure (36). The transfections were performed in triplicate for each dose; CAT gene expression (or the DNA repair capacity) was measured as described previously (37).

**Statistical Analysis.** The number of chromatid breaks was first analyzed as a continuous variable. Student’s t test was used to compare the differences in the means of the number of breaks between groups. Correlation analyses were performed for dose-rate relationship in the induced chromatid breaks, the tertile of controls’ b/c was also used to create the tertile variable. Tobacco use was defined as the following: those who smoked more than 100 cigarettes in their lifetime were ever-users and others were nonusers. Among ever-users, those who had quit smoking for more than 1 year were former users and others were current users. For logistic regression analysis, the variable tobacco use was recoded as a dummy variable (0.0 = nonuser, 0.1 = former user, and 1.0 = current user). A similar approach was applied to the variable of ethnicity (0.0 = non-Hispanic whites, 0.1 = Hispanics, and 1.0 = African Americans) and the tertile variable (0.0 < 0.26 b/c (lower); 0.1 = 0.26—0.45 b/c (middle); 1.0 > 0.45 b/c (upper)). All of the statistical analyses were performed using Statistical Analysis System software (Version 6; SAS Institute, Inc., Cary, NC).

**RESULTS**

**Cytotoxicity and Genotoxicity.** A solvent control test was conducted by treating the cell lines with different concentrations of tetrahydrofuran and counting the induced chromosomal breaks. The results showed that tetrahydrofuran at concentrations up to 0.5% (v/v), which was greater than the final concentration (0.1% v/v) used for BPDE treatment, did not increase the number of de novo chromosomal breaks (data not shown). This number was in the range of that observed in a larger sample (n = 182) of spontaneous chromosomal breaks (0—0.12 b/c) of untreated lymphocytes (32).

The results of cell-cycle analysis indicated that treated cells had an arrest (increased percentage of cells) in the S-phase as compared to untreated cells. BPDE doses up to 0.18 µM did not cause significant differences in the arrest between repair-proficient and -deficient cells (data not shown), suggesting that this dose did not have differential cytotoxicity or genotoxicity in these cell lines. To determine the optimal dose of BPDE for induced chromosomal aberration in peripheral lymphocytes, dose-response curves were first established for the selected lymphoblast cell lines with different DNA repair capacities (Fig. 1A). Doses greater than 0.2 µM either killed cells or greatly reduced the number of mitotic figures, leaving few metaphases (i.e., <50) for evaluation. The dose of 0.18 µM BPDE was adequate to produce differential dose-response curves for repair-proficient and -deficient cell lines (Fig. 1B) with different DNA repair capacities. It is evident that BPDE-induced chromosomal aberrations were more frequent in XP cell lines than in normal cell lines, because XP cells are deficient in the nucleotide excision repair system (27) by which BPDE-DNA adducts are repaired (26). Furthermore, the levels of BPDE-induced chromosomal breaks were inversely correlated with the capacity to repair BPDE-induced damage to DNA in the four cell lines, suggesting that the lower the DNA repair capacity, the higher the frequency of BPDE-induced chromosomal aberrations.

**Characteristics of Spontaneous and Induced Chromosomal Aberrations in Healthy Subjects.** A dose of BPDE as high as 4 µM, as determined from initial experiments on five blood samples (data not shown), induced a similar frequency of chromosomal aberrations in normal peripheral lymphocytes to that induced by 0.18 µM BPDE in normal lymphoblastoid cell lines. This optimal dose (4 µM BPDE) was then applied to the blood samples of the 172 apparently healthy subjects. To evaluate the types of aberrations, chromosomal breakage was recorded for each metaphase examined 5 h after BPDE treatment. Of 3363 chromosomal aberrations in the 8600 metaphases, 92.7% and 7.1% of the observed aberrations were single chromatid breaks and isochromatid breaks, respectively. Only a small number of exchange figures (0.2%) was observed, which enhanced the accuracy of quantitating total chromatid breaks, because exchanged figures are subject to misclassification error.

**REFERENCES**

Fig. 1. A, repair response to BPDE-induced damage of plasmids in cells proficient or deficient in nucleotide excision repair. The dose-response curves of XP cells and normal cells are well separated for the doses of BPDE in the range of 30–90 μM. There was a more than 10-fold difference between XP-A and normal cells. (Note: the y axis is a logarithmic scale.) B, BPDE-induced chromosomal breakage. XP-A cells are the most sensitive to BPDE treatment, being twice as sensitive as normal cells. Points, means of two independent experiments.

Table 1 Distribution of mean BPDE-induced chromosomal breakage by selected host factors in normal individuals

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) (n = 172)</th>
<th>Mean b/c ± SD</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;50 yr)</td>
<td>71 (41)</td>
<td>0.37 ± 0.19</td>
<td>0.368</td>
</tr>
<tr>
<td>Age (≥50 yr)</td>
<td>101 (59)</td>
<td>0.40 ± 0.23</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57 (33)</td>
<td>0.37 ± 0.20</td>
<td>0.933</td>
</tr>
<tr>
<td>Male</td>
<td>115 (67)</td>
<td>0.40 ± 0.23</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>85 (49)</td>
<td>0.36 ± 0.17</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>68 (40)</td>
<td>0.43 ± 0.23</td>
<td>0.006</td>
</tr>
<tr>
<td>African American</td>
<td>19 (11)</td>
<td>0.35 ± 0.30</td>
<td>0.844</td>
</tr>
<tr>
<td>Tobacco use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>79 (46)</td>
<td>0.41 ± 0.21</td>
<td>0.607</td>
</tr>
<tr>
<td>Former</td>
<td>53 (31)</td>
<td>0.39 ± 0.23</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>40 (23)</td>
<td>0.37 ± 0.21</td>
<td>0.328</td>
</tr>
</tbody>
</table>

*From two-sided t test analysis.

Of the 172 apparently healthy subjects, whose ages ranged from 19 to 95 years, 59% of the subjects were more than 50 years old, 67% were men, and 49% were non-Hispanic whites (Table 1). The overall distribution of spontaneous (untreated) chromosomal breaks was approximately normal, with a range of 0–0.08 b/c and only a few (about 4%) observations skewed to high values (>0.06 b/c; Fig. 2A), whereas BPDE-induced chromosomal breaks varied between 0.2 and 1.4 b/c, which is a 7-fold range (Fig. 2B). The mean frequency of spontaneous chromatid breaks did not differ by age, sex, or tobacco use, nor did the mean frequency of BPDE-induced chromosomal aberrations (Table 1). Hispanics exhibited more b/c than both non-Hispanic whites and African Americans, although the differences were significantly different only for non-Hispanic whites (P < 0.006) and not for African Americans because of the relatively small sample size (Table 1). Correlation analyses showed that the frequencies of both spontaneous chromatid breaks and BPDE-induced chromatid breaks were not correlated with age, sex, ethnicity, or tobacco use. However, the frequency of BPDE-induced chromatid breaks was significantly correlated with the frequency of spontaneous chromatid breaks (r = 0.19, P < 0.05).

Case-Control Analysis. Ninety-six controls were selected from the 172 apparently healthy subjects for case-control analysis. The mean age was 67.0 for cases and 64.2 for controls. This difference was not statistically significant (P > 0.05; Table 2). The mean values of spontaneous chromatid breaks were higher in cases (mean, 0.025) than in controls (mean, 0.019), but the difference was also not statistically significant (P > 0.05). However, the mean values of BPDE-induced chromatid breaks were significantly higher in cases (mean,
0.67 ± 0.39) than in controls (mean, 0.41 ± 0.24, P < 0.0001; Table 2). It is apparent that younger cases were more likely to have a higher mean frequency of BPDE-induced chromosomal breakage (0.81 b/c) than either controls of the same ages (0.38 b/c) or older cases (0.60 b/c; Table 2). Since the frequency matching on age between cases and controls was not complete, i.e., older, male, or African American cases were more likely included in the analysis (Table 3), these variables were adjusted for using logistic regression analyses. Because of the lack of correlation between the frequency of BPDE-induced chromosomal breakage and these host factors, the adjustment did not show substantial differences between the estimates of crude and adjusted ORs for these host factors (Table 3). After adjustment for age, sex, ethnicity, and mutagen sensitivity, tobacco use was still a strong risk factor for lung cancer with increased ORs associated with both former (OR, 14.5) and current (OR, 13.8) users. After adjustment for age, sex, ethnicity, and tobacco use, a significantly increased OR (6.53; 95% CI, 14.5–93.0) was noted compared to those in the lower tertile, indicating that sensitivity to BPDE is an independent risk factor for lung cancer. No further interaction between smoking and sensitivity to BPDE was evaluated because of the small numbers of cases in each group.

### DISCUSSION

We have established laboratory procedures for measuring the frequency of BPDE-induced chromosomal aberrations using a mutagen sensitivity assay (32). In addition to our previously published study using bleomycin as the test agent (38), the pilot case-control study of lung cancer reported here has demonstrated that this assay is also useful in evaluating genetic susceptibility to smoking-related cancers. The findings suggest that inherited sensitivity to BPDE may have contributed to increased risk of lung cancer in both the former and current smokers included in the analysis.

BPDE-induced adducts are repaired mainly by nucleotide excision repair (26). XP cells, which are deficient in nucleotide excision repair, cannot repair damage induced by BPDE (35). It is likely that inefficient nucleotide excision repair is one of the underlying molecular mechanisms for the increased frequency of induced aberrations (30). Inefficient DNA repair of BPDE adducts has been associated with formation of mutation hotspots in essential genes (25). Deficient preferential repair and strand-specific repair of lesions induced by BPDE may be responsible for changes in chromatin structure (25, 29), because unrepairred adducts are probably more sensitive to endogenous enzymatic cleavage, which may produce chromatid breaks. It has been demonstrated that mononuclear cells, including lymphocytes, are a valid surrogate tissue for estimating the burden of DNA adducts in the lung (39); therefore, measuring sensitivity to BPDE in lymphocytes should provide valid estimates for lung sensitivity. Some other cytotoxic effects that cause oxidative damage to DNA, such as impaired clearance of free radicals (40), may also play a role in the formation of chromatid breaks. However, the exact molecular mechanisms underlying the sensitivity to BPDE measured as chromatid breaks remain unclear and warrant further investigation.

Mutagen sensitivity is considered a useful biomarker for cancer susceptibility (41). For example, increased in vitro sensitivity to bleomycin has been associated with increased risk not only of primary lung cancer and aerodigestive cancers (38, 42, 43) but also of multiple cancers in patients with initial aerodigestive tract cancers (44). In general, induced mutagen sensitivity is not dependent on age (41, 42), although age has an effect on DNA repair capacity (37), suggesting that other mechanisms in addition to DNA repair may contribute to chromosomal breakage. The frequency of chromosomal aberrations or chromatid breaks measured using the mutagen sensitivity assay is a nonspecific marker for cancer susceptibility, but the assay also has the flexibility to assess cancer risk related to exposures to different carcinogens. Although DNA repair capacity correlates with in vitro mutagen sensitivity to the same type of mutagens (30), DNA damage caused by different types of mutagens may be repaired by different repair pathways that reflect the different molecular mechanisms of carcinogenesis. These pathways include recombination repair of damage induced by bleomycin, which causes DNA strand breaks, and nucleotide excision repair of damage induced by BPDE, which causes bulky lesions in DNA (27). Therefore, use of different types of mutagens in the mutagen sensitivity assay may help identify the biological mechanisms underlying different molecular mechanisms of carcinogenesis.

It is concluded that the BPDE mutagen sensitivity assay will facilitate epidemiological studies of smoking-related cancers and improve the precision of risk assessment. However, the preliminary findings in this report need further verification in a larger case-control study of lung cancer that will allow analysis of the interaction between smoking and sensitivity to BPDE. The ethnic difference in BPDE-induced mutagen sensitivity is of interest and also warrants further investigation.

### Table 3 Characteristics of lung cancer cases and controls and logistic regression analysis for adjusted ORs and CI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR (CI)</th>
<th>Adjusted OR (CI)</th>
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</thead>
<tbody>
<tr>
<td>Age (range, 50–85)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;65 yr</td>
<td>11</td>
<td>50</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>22</td>
<td>46</td>
<td>2.17 (0.95–4.97)</td>
<td>3.03 (0.98–9.32)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>8</td>
<td>29</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>67</td>
<td>1.35 (0.55–3.35)</td>
<td>1.15 (0.35–3.76)</td>
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<tr>
<td>Ethnicity</td>
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<tr>
<td>Non-Hispanic</td>
<td>7</td>
<td>27</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11</td>
<td>53</td>
<td>0.80 (0.28–2.30)</td>
<td>0.38 (0.24–0.59)</td>
</tr>
<tr>
<td>African American</td>
<td>15</td>
<td>36</td>
<td>3.62 (1.21–10.8)</td>
<td>2.70 (0.64–11.4)</td>
</tr>
<tr>
<td>Tobacco use</td>
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<tr>
<td>None</td>
<td>2</td>
<td>40</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Former</td>
<td>15</td>
<td>33</td>
<td>9.09 (1.94–42.3)</td>
<td>14.5 (2.65–74.6)</td>
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<tr>
<td>Current</td>
<td>16</td>
<td>23</td>
<td>13.9 (2.93–66.0)</td>
<td>13.8 (2.47–76.8)</td>
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<tr>
<td>Mutagen sensitivity (tertile of controls)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.26 b/c</td>
<td>4</td>
<td>28</td>
<td>1.00</td>
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<tr>
<td>0.26–0.45 b/c</td>
<td>8</td>
<td>35</td>
<td>1.60 (0.44–5.87)</td>
<td>2.26 (0.53–9.67)</td>
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<tr>
<td>&gt;0.45 b/c</td>
<td>21</td>
<td>33</td>
<td>4.45 (1.37–14.5)</td>
<td>8.37 (2.06–33.9)</td>
</tr>
</tbody>
</table>

*Adjusted in a logistical regression model including age, sex, ethnicity, smoking status, and mutagen sensitivity.
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