Path Analysis of Biomarkers of Exposure and Early Biological Effects among Coke-Oven Workers Exposed to Polycyclic Aromatic Hydrocarbons

Li Qiu,1 Shuguang Leng,2 Zhongxu Wang,2 Yufei Dai,2 Yuxin Zheng,2 and Zengzhen Wang1

1Department of Epidemiology and Statistics, School of Public Health, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China; and 2National Institute for Occupational Health and Poison Control, Chinese Center for Disease Control and Prevention, Beijing, China

Abstract

Many host factors or biomarkers are involved in the process of early DNA damage induced by occupational exposure to polycyclic aromatic hydrocarbons (PAH) as seen in coke-oven workers. This paper aimed to identify complicated causal interrelationship of various biomarkers using the path analysis. In this analysis, we included 235 subjects (166 coke-oven workers and 69 nonexposed controls) whose data on the comet assay (e.g., Olive tail moment) and cytogenetic analysis of peripheral blood lymphocytes as well as urinary 1-hydroxypyrene (1-OHP) were available. The path analysis showed that coke-oven exposure and tobacco smoke were both significant predictors of the concentrations of urinary 1-OHP (P < 0.05), with a coefficient of determination of 0.75. The factors having significant influence on the Olive tail moment were in the following order: urinary 1-OHP > XRCCI-exon 9 variant genotype > ERCC2-exon 10 variant genotype > XRCCI-exon 6 variant genotype, with a coefficient of determination of 0.22. The variables of relative importance in influencing on cytokinesis-block micronucleus frequencies were in the following order: coke-oven exposure > urinary 1-OHP > age > mEH3 variant genotype > ERCC2-exon 10 variant genotype > XRCCI-exon 6 variant genotype, with a coefficient of determination of 0.27. These results indicated that exogenous agents, especially the coke-oven exposure, played a more important role than the genotypes in the induction of early genetic damage. In conclusion, the path analysis seemed to be an alternative statistical approach for the ascertainment of complicated association among related biomarkers for the assessment of occupational exposure. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1193–9)

Introduction

Polycyclic aromatic hydrocarbons (PAH) are an established carcinogen that has been extensively investigated to date. Recently, there is an increasing interest in using biomarkers for exposure to PAHs and early biological effects such as DNA damages caused by carcinogens like PAHs in the risk assessment (1-5), thanks to the rapid development of molecular biological monitoring techniques. It is well known that many factors can contribute to carcinogenesis in humans. In molecular epidemiology studies, biological effects are more frequently measured by biomarkers, which are divided into three categories: measures of internal dose, early biological response, and host susceptibility (6, 7). Many studies have found the associations between PAH environmental exposure, whose internal dose is usually quantified by 1-hydroxypyrene (1-OHP) in urine, and an increase in the levels of carcinogen-DNA adducts, sister chromatid exchange, and chromosomal aberrations (8-12). In addition, environmental exposure interacts intricately with environmental responsive genes and some known behavioral factors such as tobacco smoking and alcohol consumption (13-15).

Therefore, the early genotoxic damage to human cells results from an interaction between extrinsic and endogenous factors. At the same time, there exist complicated interactions among various additional unknown factors. It has been recommended that combinations of biomarkers (e.g., those for internal dose, adducts, metabolic phenotype, and DNA repair capacity) are needed to assess individual risk of diseases (16). To address the complicated interrelationship among various biomarkers in response to exposure to PAHs, such as seen in coke-oven workers, we used the path analysis to reveal any causal associations between DNA damage or chromosomal aberrations in peripheral blood lymphocytes from coke-oven workers and environmental exposure to PAHs in a clearer and more visualized way. To accomplish this, we used published data on the comet assay and cytokinesis-block micronucleus (CBMN) assay to evaluate levels of DNA and chromosomal damage in peripheral blood lymphocytes, respectively. Both urinary 1-OHP and genetic damage were analyzed in relation to genotypes of metabolic genes or DNA repair genes. We included three biomarkers, urinary 1-OHP as the internal dose of exposure to PAHs, the Olive tail moment and frequencies of micronucleus as the early biological effects, and genotype data on CYP1A1, mEH3, mEH4, GSTT, GSTP1, and XRCCI gene and XPD as the susceptibility markers.

Path analysis was first developed by Sewall Wright in the 1920s for the use in quantitative genetic studies and later was gradually adopted by social sciences, ecology, psychology, and economics (17, 18), as well as health sciences (19, 20), in which the interaction mechanisms were not well understood in the presence of known risk factors, such as epidemiologic studies of chronic illness. The path analysis helps understand comparative strengths of direct and indirect relationships among a set of variables of interest. In this analysis, a network of causes and effects is seen as a series of steps in a path with a coefficient assigned to each step to quantify their interrelationships (21). With the advances of path analysis methodology, this method has been used more extensively in different fields (22-26). Santos et al. first applied the path analysis to elucidate...
a biochemical pathway of carotenoid and had obtained some interesting results (25). Their work again showed the efficacy of path analysis for identifying key compounds in complex pathways.

In this report, we tested our hypothesis that the path analysis may also be an effective tool to identify the main risk factors of earlier biological effects induced by PAHs exposure, and the information produced by such an analysis could provide insights into the PAHs metabolic pathway in humans. The hypothesized model was based on the shown facts of previous studies, intending to reveal the causal relationship of selected variables rather than simple correlation.

Materials and Methods

Study Population and Sample Collection. The details of subject recruitment and blood sample procurement of this cross-sectional study were previously described (27). Briefly, 166 coke-oven workers exposed to PAHs at workplaces and 69 medical staffs without work-related PAH exposure were enrolled in this study as the exposed and nonexposure groups, respectively. Exclusion criteria for participation in the study included recent treatment with mutagenic agents (such as X-ray), chronic conditions (such as autoimmune diseases), and recent acute infections that required medications (such as antibiotics). All participants were then interviewed by an occupational physician using a questionnaire including demographic information, smoking history, alcohol consumption, history of occupational exposure, and personal medical history after informed consents were obtained. Individuals who had smoked >100 cigarettes in their lifetime were considered as smokers. Among these smokers, individuals who still smoked when interviewed were classified as current smokers and were asked for further detailed smoking-related information, including age at onset of smoking and duration of smoking; the others were classified as former smokers; however, their complete smoking history was not available. Individuals who drank more than twice a week in the last 6 months were classified as alcohol users. Biological samples, including shift-end urine and venous blood, were obtained from each subject.

PAH Exposure Assessment. PAH exposure assessment was also previously described (27). Briefly, the air concentrations of benzene-soluble matter and particulate-phase benzo(a)pyrene in the working environment of coke-oven workers and non–coke-oven workers were sampled ~1.5 months before urine and blood sample collection and were analyzed according to the Occupational Safety and Health Administration method no. 58 (28). The excretion of urinary 1-OHP as the internal dose of personal recent PAH exposure was measured according to the method of Jongeneelen et al. (29), with some modifications (30). Measurements below the limit of detection (LOD) were replaced with LOD/√2 before statistical analysis (31). The urinary 1-OHP concentrations were corrected by urinary creatinine and presented as μmol mol⁻¹ creatinine.

Comet Assay in Peripheral Blood Lymphocyte. The detailed procedure of comet assay was previously described (32). In short, the blood samples for alkaline comet assay were stored at 4°C after venipuncture for no more than 1 h before the separation of lymphocytes. Lymphocytes were separated from ~1 mL heparinized whole blood and suspended in 500 μL ice-cold PBS. The comet assay was done immediately after lymphocyte separation according to Singh et al. (33), with minor modifications. Slides were examined with Olympus IX 50 microscope equipped with a 100-W mercury lamp and WG filter block. Measurements were made using an image analysis system (version 1.0, IMI comet assay software, China). More than 100 cells per subject were scored (50 cells for each of the two replicate slides). Olive tail moment were calculated. For each subject, the arithmetic mean of Olive tail moment of 100 cells was presented as DNA damage level in the following statistical analysis.

CBMN Assay Using Peripheral Blood Lymphocytes. The CBMN assay was done according to the standard method as previously described (34, 35). Standard scoring criteria for selecting binucleated cells and identifying a micronucleus were adopted (34, 36). All slides were coded and scored blindly by an experienced scorer. Total MN (the frequency of micronuclei per 1,000 binucleated lymphocytes) and MNed cells (the frequency of micronucleated cells per 1,000 binucleated lymphocytes) were scored as chromosomal damage indexes.

Genotyping. DNA was isolated from the whole blood using a standard method (37). The Ile/Val polymorphism in exon 7 of the CYP1A1 was analyzed according to the method of Hayashi et al. (38). Analysis of the GSTT1 polymorphism resulting in an Ile/Val substitution at residue 105 in exon 5 was done as described by Saarikoski et al. (39). Genotypes of GSTT1 were determined by a modified multiplex PCR method with β-globin as positive control (40, 41). The Tyr/His polymorphism at residue 113 in exon 3 and His/Arg polymorphism at residue 139 in exon 4 of mEH was analyzed as described by Zhou et al. (42). Three single nucleotide polymorphisms in XRCC1 gene, including C26304T (Arg194Trp), G27466A (Arg269His), and G28152A (Arg99Gln) were detected using the method of PCR–restriction fragment length polymorphism (43-45). The G23591A (Asp312Asn) and A35931C (Lys119Gln) polymorphisms of ERCC2 gene were determined according to published protocols (43). All genotypes were evaluated and agreed upon by at least two persons independently. Ten percent of DNA samples were genotyped a second time, and the concordance was 100%.

Statistical Analysis. Path analysis, an extension of the regression model, was used in this study. A path coefficient, represented as p_{ij}, is a standardized regression coefficient indicating the direct effect of variable i on variable j. Accordingly, in a multivariate regression system, it is a partial regression coefficient controlling for other prior variables. Basically, whenever a causal, rather than spurious or coincidental, correlation among a set of variables is suspected, the path analysis is strongly suggested to be done, especially when there is a possibility to sort out the sequence of variables or when it is necessary to distinguish the spurious effect by an intervening factor from the observed relationships (46).

The path analysis has several advantages. First of all, it allows for effect decomposition because the total causal effect is the sum of the values of all the paths from i to j. The indirect effect, measuring the effect of the intervening variables, is the total causal effect minus the direct effect. A second advantage of path analysis is shown by path diagram, which explains the hypothetical causality graphically. It runs through from the left to the right, with the exogenous variables or independent variables on the extreme left and the dependent or endogenous variables (the model tries to explain) on the right side. The relationship between two variables is represented by a straight line or curve with arrows in both extremities with the size of the correlation proportional to the width of the line.

Before performing the path analysis, a number of assumptions need to be checked (47). Among these assumptions, sample size and selection criteria to include variables in the models are the most important. As Kline (48) recommended, 10 times as many cases as parameters were needed to assess significance. If the ratio of the number of cases to the number of parameters was below 5, the model with great possibility to be estimated would be unstable (49). For this study, the number of the parameters to be estimated was 24. Conceptually, an adequate sample size should be >240. However,
The basic characteristics of coke-oven workers and controls were very close to those described previously (27), and all variables used in this analysis are listed in Table 1. In brief, the distributions of age, sex, and alcohol consumption were similar between the two groups (P = 0.29, P = 0.16, and P = 0.19, respectively), except the proportion of current smokers and the number of cigarettes smoked per day, both of which were higher in coke-oven workers than in controls (64.46% versus 36.23%, P < 0.01 and 8.22 ± 7.18 cigarettes/day versus 4.88 ± 7.58 cigarettes/day, P < 0.01).

Indexes used for the overall test of the model were as follows: GFI = 0.9910; AGFI = 0.9320; χ²/df = 12.0433; RMSEA = 0.0042; 90% confidence interval = 0, 0.0718; NFI = 0.9835; and the ratio of χ²/df is < 0.05. Taken together, these indexes showed the good fitness of the model.

Table 1. List of variables included in this paper

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Connotation</th>
<th>Value assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log_Hydcre</td>
<td>Ln-transformed urinary 1-OHP</td>
<td>Numerical type</td>
</tr>
<tr>
<td>Log_olive</td>
<td>Ln-transformed olive tail moment</td>
<td>Numerical type</td>
</tr>
<tr>
<td>Log_mni</td>
<td>Ln-transformed CBMN frequencies</td>
<td>Numerical type</td>
</tr>
<tr>
<td>Cokework</td>
<td>Coke-oven worker or not</td>
<td>0, non–coke-oven worker; 1, coke-oven worker</td>
</tr>
<tr>
<td>Tobacco smoke</td>
<td>Smoke status 0, no; 1, yes</td>
<td></td>
</tr>
<tr>
<td>Cigarettes</td>
<td>Rating of cigarettes per day</td>
<td>1–19 cigarettes/day ≥ 20 cigarettes/day</td>
</tr>
<tr>
<td>Age</td>
<td>Rating of age 0, to &lt; 35 y 1, 35–44 y 2, to &gt; 44 y</td>
<td></td>
</tr>
<tr>
<td>mEH3</td>
<td>His113Tyr polymorphism in exon 3 0, w/w*; 1, m/m</td>
<td></td>
</tr>
<tr>
<td>CYP1A1</td>
<td>Ile462Val polymorphism in exon 7 0, w/w; 1, m/m</td>
<td></td>
</tr>
<tr>
<td>GSTP1</td>
<td>Ile60 polymorphism in exon 5 0, w/w; 1, m/m</td>
<td></td>
</tr>
<tr>
<td>XRCC1-exon 6</td>
<td>Arg134Tyr polymorphism 0, w/w; 1, m/m</td>
<td></td>
</tr>
<tr>
<td>XRCC1-exon 9</td>
<td>Arg283His polymorphism 0, w/w; 1, m/m</td>
<td></td>
</tr>
<tr>
<td>ERCC2-exon 10</td>
<td>Asp312Asn polymorphism 0, w/w; 1, m/m</td>
<td></td>
</tr>
</tbody>
</table>

*W, wild-type allele; m, mutation allele.

Table 2. Standardized coefficients and parameter test for the path analysis model of urinary 1-OHP (R² = 0.7489)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cokework</th>
<th>Tobacco smoke</th>
<th>Age</th>
<th>CYP1A1</th>
<th>mEH3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard coefficient</td>
<td>0.8253</td>
<td>0.1444</td>
<td>-0.0582</td>
<td>0.0368</td>
<td>0.0453</td>
</tr>
<tr>
<td>SE</td>
<td>0.0364</td>
<td>0.0363</td>
<td>0.0359</td>
<td>0.0334</td>
<td>0.0314</td>
</tr>
<tr>
<td>t value</td>
<td>22.6971*</td>
<td>3.9743*</td>
<td>-1.6216</td>
<td>1.0398</td>
<td>1.2768</td>
</tr>
</tbody>
</table>

*p < 0.05.
Olive tail moment was statistically significant. Their importance was ranked as follows: urinary 1-OHP concentration > XRCC1-exon 9 variant genotypes > ERCC2-exon 10 variant genotypes > XRCC1-exon 6 variant genotypes. The $R^2$ of the equation was 0.22. That is, the variables in the model accounted for 22% of the total variance.

Table 4 shows that the variables, including coke-oven exposure, age, and mEH3 variant genotypes, significantly influenced the levels of CBMN frequency. Their preference ordering was as follows: coke-oven exposure > urinary 1-OHP concentration > age > mEH3 variant genotypes > ERCC2-exon 10 variant genotypes > XRCC1-exon 6 variant genotypes. The $R^2$ of the equation was 0.27, indicating that 27% of the total variance for this model was explained by these variables.

The effective decompositions of different variables associated with either Olive tail moment or frequencies of CBMN were presented in Table 5. As it was shown in Table 5, the variables, including coke-oven exposure, age, and mEH3 variant genotypes, not only had direct effects on Olive tail moment but also had indirect effects on Olive tail moment by the pathway of urinary 1-OHP. The total causal effect was decomposed into a direct effect and an indirect effect. For example, the direct effect of mEH3 variant genotypes on the Olive tail comet was $-0.0315$. In comparison, the total indirect effect was only $+0.0148$. So, the total causal effect of mEH3 variant genotypes was $+0.0315 + 0.0148 = 0.0463$. Likewise, as listed in Table 5, the variables that exerted both direct effects and indirect effects on CBMN frequencies were coke-oven exposure, age, and mEH3 variant genotypes. The GSTP1 variant genotype had a direct effect on CBMN frequencies.

Lines presented the path equations for the three variables (Log_Hydcre, Log_olive, and Log_mni) given by

\[
\text{Log}\_\text{Hydcre} = 0.8253 \times \text{cokework} + 0.1444 \times \text{smoke} + 0.0368 \times \text{CYPIA1} + 0.0453 \times m\text{EH3} - 0.0582 \times \text{age} + 0.5011
\]

\[
\text{Log}\_\text{olive} = 0.3266 \times \text{Log}\_\text{ohp1} + 0.0303 \times \text{cokework} + 0.0463 \times \text{cigarettes} + 0.0335 \times \text{age} - 0.0315 \times m\text{EH3} + 0.2012 \times \text{XRCC1} - \text{exon9} + 0.1195 \times \text{ERCC2} - \text{exon10} + 0.1061 \times \text{XRCC1} - \text{exon6} + 0.8855
\]
It is interesting to have a look at the effect of the \( mEH3 \) genotype on CBMN frequencies where the \( mEH3 \) variant genotype exerted a direct protective effect and had an indirect risk effect by the pathway mediated by urinary 1-OHP. This was consistent with the conclusion drawn by Leng et al. that genetic polymorphism of the \( mEH \) gene was a susceptibility biomarker in the metabolic process of PAHs (54). In Leng’s other two published studies (27, 55), they found that individuals with \( mEH3 \) variant genotypes had lower frequencies of CBMN. As we know, the microsomal epoxide hydrolase (\( mEH \)) can convert \( 7,8 \)-diol of benzo(a)pyrene to more water-soluble \( 7,8 \)-dihydrodiols, which is further activated by phase 1 enzymes to form the ultimate carcinogenic diol epoxide. When genetic variation takes place at the H113Y site of the \( mEH \) gene, the enzyme activity is reduced (56), which, on one hand, brings the reduction of the chance for epoxide to transform to dihydrodiols and, on the other hand, increases the probability for epoxide to become 1-hydroxypyrene. In addition, due to its involvement in the formation of ultimate carcinogens, the reduction of ultimate carcinogens further lessens the genetic damage. This biological plausibility indicates that the proposed model is somewhat compatible to the data.

The path analysis also showed that after repeated selection, the variant genotypes of these three DNA repair enzyme genes (i.e., \( XRCC1 \)-exon 6, \( XRCC1 \)-exon 9, and \( ERCC2 \)-exon10) stayed in the path model ultimately, and they were all statistically significant. As shown in Leng’s study (32), subjects with \( XRCC1 \)-exon 9 heterozygous genotypes had a longer Olive tail moment compared with those with wild-type genotype on \( mEH3 \) and \( XRCC1 \)-exon 6, \( XRCC1 \)-exon 9, and \( ERCC2 \)-exon 10 genotype were also studied, but their relations to Olive tail moment were not evident. However, a study conducted by Cheng et al. (57) showed that the Olive tail moment was significantly higher in subjects with \( XRCC1 \) His\(^{280} \) allele than those with the Arg\(^{280} \) allele. In Leng’s other study (58), they identified the association between the \( XRCC1 \)-exon 6 polymorphism and the frequencies of CBMN. Therefore, the consistency within these studies also suggests that the path model built fits to the data, although our findings need to be verified in larger studies and several conflicting studies on the XPD gene (59-61) that we should be aware of.

An indication of the appropriateness of causal diagrams is given by the coefficient of determination (\( R^2 \)) and path significance values. According to Hatcher (51), it is generally accepted that, when \( R^2 \) is >60%, a relatively large percentage of the variance can be explained by a causal model. In our path analysis, the \( R^2 \) value for the urinary 1-OHP-dependent variable was 75%, suggesting that this model explained a considerable portion of the total variance of this dependent variable. However, the \( R^2 \) value for the Olive tail moment and CBMN frequencies was only 22% and 27%, respectively, exhibiting a poor fitness of the models. This is a limitation of this study.

In summary, the path model in this report illuminated the relative importance of environmental factors and genetic polymorphisms in terms of their effects on DNA or chromosome damage that was not described in previous studies (27, 32, 52-55). Either the coke-oven exposure or its internal dose of urinary 1-OHP had a main effect on Olive tail moment and CBMN frequencies, suggesting the predominance of environmental factors in inducing genetic damage. Thus, we should put more weight on the improvement of occupation environmental conditions to reduce the exposure. Alternatively, we could as well identify the most susceptible by screening for specific genotypes of candidate genes. Compared with previous studies (27, 32, 52-55), the path analysis helped figure out the interactions between different factors clearly, exhibiting the multistages from PAHs exposure to genetic damage. However, a more integrated and coherent way of analyzing the data was

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**Table 5. Effect decompositions for Olive tail moment and CBMN frequencies**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olive tail moment</th>
<th></th>
<th></th>
<th>CBMN</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direct</td>
<td>Indirect</td>
<td>Total</td>
<td></td>
<td>Direct</td>
<td>Indirect</td>
</tr>
<tr>
<td>Cokework</td>
<td>0.0039</td>
<td>0.2696</td>
<td>0.2999</td>
<td></td>
<td>0.2423</td>
<td>0.1576</td>
</tr>
<tr>
<td>Smoke</td>
<td>—</td>
<td>0.0472</td>
<td>0.0472</td>
<td></td>
<td>—</td>
<td>0.0276</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>0.0463</td>
<td>—</td>
<td>0.0463</td>
<td></td>
<td>—</td>
<td>0.0260</td>
</tr>
<tr>
<td>Age</td>
<td>0.0335</td>
<td>-0.0190</td>
<td>0.0145</td>
<td></td>
<td>0.1453</td>
<td>-0.0111</td>
</tr>
<tr>
<td>Log_Hydcre</td>
<td>0.3266</td>
<td>—</td>
<td>0.3266</td>
<td></td>
<td>0.1910</td>
<td>—</td>
</tr>
<tr>
<td>CYP1A1</td>
<td>-0.0309</td>
<td>0.0148</td>
<td>-0.0167</td>
<td></td>
<td>-0.1328</td>
<td>0.0086</td>
</tr>
<tr>
<td>GSTP1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>0.0345</td>
<td>—</td>
</tr>
<tr>
<td>XRCC1-exon 6</td>
<td>0.1061</td>
<td>—</td>
<td>0.1061</td>
<td></td>
<td>0.1136</td>
<td>—</td>
</tr>
<tr>
<td>XRCC1-exon 9</td>
<td>0.2012</td>
<td>—</td>
<td>0.2012</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ERCC2-exon 10</td>
<td>0.1195</td>
<td>—</td>
<td>0.1195</td>
<td></td>
<td>0.1213</td>
<td>—</td>
</tr>
</tbody>
</table>

**NOTE:** The total effect for each variable is decomposed to direct effect and indirect effect.

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**Figure 1.** The path diagram reflected the hypotheses of the causation between the dependents (Olive tail moment and frequencies of CBMN) and exogenous variables (coke-oven exposure, smoke, age, and several primary genotypes) or intermediary variable (urinary 1-OHP). Each arrow was accompanied with a path coefficient, and the dashed lines, negative causal relation.
still desired. Perera et al. (12) had detected the association between PAH environmental exposure and aromatic adducts, and the aromatic adducts were then found to correlate with chromosomal aberrations. In such a case, aromatic adducts could be thought of as a molecular link between environmental exposure and a genetic alteration relevant to cancer risk. As the progression of lung cancer must go through several stages, from PAH exposure to the clinical end point, it is critical to identify such links that could integrate various stages as a whole. Due to the lack of sufficient and related data, we were unable to map a coherent picture for the development of lung cancer in these coke workers at the present time.

However, the path analysis used in this study has several limitations. First, the path analysis cannot neither prove causality nor establish the direction of causality. It is meant to be exploratory rather than confirmatory because it is possible that some potential confounding variables were not taken into account (24, 26, 62), as indicated by the large residuals for the Olive tail moment and CBMN frequencies. Nevertheless, this does not prohibit us from further exploring factors that have more influence on the Olive tail moment and CBMN frequencies. Secondly, the path analysis cannot be applied when feedback loops are included in the hypotheses. Thirdly, there were strong correlations between duration of smoking and age at onset of smoking and age at interview (not presented in the results). To avoid multicollinearity, focus was placed on the most important variable, cigarettes smoked per day compared with other smoking variables in which effects on genetic damage, in addition, might be masked by smoking status. In current smokers (63), Fourthly, in terms of the measurement of PAH exposure, this cross-section investigation neither measured personal PAH exposure nor collected dietary PAH exposure.

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Li Qiu, Shuguang Leng, Zhongxu Wang, et al.


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