

## **The Role of Metabolic Perturbations in Mediating the Effects of Ambient Air Pollution on Lung Cancer in the Cancer Prevention Studies\***

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**Background.** Exposure to ambient air pollution is an established risk factor for lung cancer. The underlying mechanisms of air pollution carcinogenicity remain unclear due to the complex composition of air pollution and a lack of sensitive biomarkers. To address these gaps, we applied high-resolution metabolomics to identify metabolic signatures of exogenous air pollution exposures and endogenous processes involved in lung carcinogenesis.

**Methods.** 1,366 matched lung cancer and control participants within the established Cancer Prevention Study-II (CPS-II) Nutrition and CPS-3 cohorts completed comprehensive questionnaires during enrollment and follow-up to assess changes in personal and lifestyle factors and medical conditions. From these participants, we profiled the serum metabolome from non-fasting blood samples (collected between 1998 and 2001 for CPS-II and 2006 to 2013 for CPS-3) using ultrahigh-performance liquid chromatography-tandem mass spectrometry. Assessment of exposure to six ambient air pollutants, including carbon monoxide (CO), nitrogen dioxide (NO<sub>2</sub>), particulate matter (PM<sub>10</sub>), fine particulate matter, sulfur dioxide, and ozone, was conducted using spatiotemporally-resolved models based on residential address at blood draw and calculated based on yearly average levels. We conducted metabolome-wide association studies with multivariate linear regression models to assess associations of ambient air pollution and lung cancer with a meet-in-the-middle approach.

Models controlled for potential confounders and covariates including age at blood draw, sex, race, body mass index, alcohol consumption, smoking status, passive smoke exposure, vegetable and fruit intake, and educational level. Significant metabolites (at FDR < 0.2) from the air pollution modeling were subsequently analyzed in the lung cancer model. High-dimensional mediation analysis was used as a secondary analysis to compare results from the meet-in-the-middle analysis.

**Results.** Among 1,204 metabolic features extracted from the blood samples, seven features were significantly associated with air pollution exposure and lung cancer incidence in the meet-in-the-middle analysis. Six features were significant from the results of the high-dimensional mediation analysis. All confirmed metabolites were enriched within peptide, lipid, and amino acid pathways. Gamma-glutamylglutamine and gamma-glutamylmethionine were statistically significantly associated with CO, NO<sub>2</sub>, and PM<sub>10</sub> exposure and lung cancer incidence in both analyses.

**Conclusion.** This is the largest prospective metabolomics study examining biological perturbations associated with air pollution exposure and lung cancer outcomes. The current results point to peptide metabolism playing an important role mediating the association between air pollution and lung cancer. Findings from this study will lay the foundation for future analyses on the biological mechanisms of air pollution-related carcinogenicity.

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