

County-Level Associations Between Airborne Toxicant Emissions and Ewing Sarcoma Diagnosis in the United States

Kole Preston Joachim, Adrian Lin, Brandon Stephen Gettleman, Christopher D Hamad, Amanda Perrotta, Sumin Jeong, Michael Fice, Nicholas M Bernthal, Alexander Christ

INTRODUCTION: Ewing sarcoma, a rare pediatric bone cancer with unclear origins, has been hypothesized to link with environmental factors like airborne toxins, though population evidence remains scarce. This study investigates associations between industrial airborne chemical emissions and Ewing sarcoma incidence across U.S. counties.

METHODS:

A cross-sectional ecological analysis using data from the 2023 EPA TRI program was conducted to determine the association between airborne toxicant emissions and cumulative Ewing Sarcoma diagnosis incidence across counties in the United States. County-level Ewing sarcoma case counts were obtained from the SEER database, a population-based individual-level data collection. Patients from the November 2023 SEER Research Plus dataset submission were queried using SEER*Stat 8.4.4. The November 2023 submission consists of patients from 22 registries diagnosed with cancer between 2000 and 2021 and covers approximately 26.5% of the US population. Cumulative county case counts were linked using Federal Information Processing Standards (FIPS) codes. Counties with reported data, including those with zero cases, were included in the analysis. The 2020 U.S. Decennial Census was used to determine county-level population estimates. ZIP Code Tabulation Area (ZCTA)-level populations were aggregated to the county level using a ZIP-to-county crosswalk provided by the U.S. Department of Housing and Urban Development, enabling accurate per capita rate calculations (per 1,000,000 population) for counties with varying population densities.

County-level industrial chemical emissions were extracted from the EPA TRI program and recorded for 24 pre-specified airborne toxicants relevant to cancer biology or musculoskeletal health. Total airborne toxicant exposure was determined by combining county-level stack (point source) and fugitive (non-point source) emission levels for each toxicant recorded in the EPA TRI program. County-level approximations of airborne emissions were extracted from the EPA TRI program at the ZIP code level and converted to county-level estimates using FIPS codes that assign unique identifiers to each US county. In this manner, ZIP codes were assigned to a county based on population distributions, with each ZIP code assigned to the county where most of its residents reside through ZIP-to-FIPS crosswalks. Counties were further sub-stratified as low versus high exposure by airborne chemicals corresponding to emitters' upper and lower 50th percentiles. Airborne chemicals in less than 10 counties in either low or high exposure groups were excluded from the analysis. The median difference in rates between groups was compared using the Mann-Whitney U test with significance set at $p < 0.05$. P-values were transformed using $-\log_{10}(p)$ for visualization.

RESULTS: Of 3,229 total U.S. counties, 1,090 had Ewing sarcoma data, and 656 had complete data on case counts, population, and chemical exposure. Cumulative Ewing sarcoma diagnosis incidence in high versus low exposure counties for each of the 17 airborne chemicals was analysed by comparing the median cumulative incidence rates per group. Xylene (12.95 vs 7.63, $p=0.001$), ethylbenzene (13.56 vs 9.33, $p=0.007$), toluene (12.88 vs 7.35, $p=0.01$), naphthalene (13.56 vs 10.65, $p=0.016$), nickel compounds (11.75 vs 9.41, $p=0.019$), and benzo[g,h,i]perylene (13.13 vs 10.84, $p=0.005$) were determined to be statistically significant in counties with high exposure levels. For the six significant airborne toxicants, median annual emissions in high-exposure counties were substantially higher than in low-exposure counties: xylene (41.00 vs. 13.00 lbs), ethylbenzene (51.00 vs. 9.00 lbs), toluene (44.00 vs. 10.00 lbs), naphthalene (40.00 vs. 10.00 lbs), nickel compounds (21.91 vs. 4.32 lbs), and benzo[g,h,i]perylene (26.00 vs. 9.70 lbs). A representative volcano plot was constructed to highlight the magnitude of median rate differences amongst the 17 airborne toxicants (**Figure 1**).

DISCUSSION AND CONCLUSION: This national ecological analysis identified significant associations between specific airborne toxicants (xylene, ethylbenzene, toluene, naphthalene, nickel compounds, and benzo[g,h,i]perylene) and increased Ewing sarcoma diagnosis rates at the county level. The observed correlations with polycyclic aromatic hydrocarbons (PAHs) and nickel compounds are mechanistically plausible given their established genotoxic properties and ability to induce DNA double-strand breaks, potentially contributing to the chromosomal translocations characteristic of Ewing sarcoma pathogenesis. By examining individual chemical pollutants rather than aggregate measures like PM_{2.5}, this study advances precision in environmental oncologic risk assessment and suggests that specific toxicants may drive cancer risk even when bulk particulate matter shows no association. While causality cannot be established from this ecological design, these findings highlight the importance of chemical-specific environmental monitoring and support prioritization of both mechanistic studies investigating toxicant-induced chromosomal instability and targeted environmental mitigation efforts in high-emission regions to potentially reduce Ewing sarcoma incidence.

Volcano Plot: Ewing Rate per 1M (High vs Low Exposure)

