EXPOSURE TO LOW DOSES OF BENZENE AND ALTERATIONS IN MITOCHONDRIAL DNA COPY NUMBER: A MULTI-CENTER STUDY

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Background and Aims: Benzene is a widespread environmental chemical that has been associated with increased risk of leukemia. Though potential carcinogenic mechanisms are still unknown, recent evidences suggest that high benzene exposures might be associated with increased mitochondrial DNA copy number (mtDNAcn), possibly due to benzene-induced oxidative DNA damage. Whether benzene determines mtDNAcn alterations even at low doses remains uncertain.
Methods: The study enrolled 519 participants from three Italian cities (Genoa, Milan, Cagliari), including 341 individuals with low-level benzene exposures (bus drivers [BD], police officers [PO], gas-station attendants [GSA], petrochemical plant workers [PPW]), and 178 referents. Blood samples and lifestyle information were collected at enrollment. We measured individual exposure to benzene with personal passive samplers during the work shift, and blood relative mtDNAcn by real-time PCR. For the Milan participants, DNA methylation information were also available. We fitted linear regression models, adjusted for age, sex, smoking habit, and number of cigarettes/day, to investigate association between benzene and mtDNAcn.
Results: In each city, mtDNAcn was significantly higher in benzene-exposed subjects than in referents: 0.90 relative units in Genoa BD and 0.75 in referents (p=0.019); 0.90 in Milan GSA, 1.10 in PO, 0.75 in referents (p-trend=0.008); 1.63 in Cagliari PPW, 1.25 in referents close to the plant, 0.90 in farther referents (p-trend=0.046). In multivariate analyses an interquartile range (IQR) increase in personal airborne benzene exposure was associated with a mtDNAcn increase of 10.3% in all subjects combined (p<0.001), 10.5% in Genoa (p=0.014), 8.2% in Milan (p=0.008), 7.5% in Cagliari (p=0.223). In Milan, an IQR increase in mtDNAcn was associated with LINE-1 hypomethylation (-2.41%, p=0.007) and p15 hypermethylation (+15.95%, p=0.008).
Conclusions: Our study shows a mtDNAcn increase with low-level exposure to benzene and mtDNAcn-related variations in DNA methylation markers associated with leukemogenesis; it thus indicates potential toxicity of benzene even at low doses.