Environment International 116 (2018) 239–247

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Outdoor air pollution and mosaic loss of chromosome Y in older men from the Cardiovascular Health Study

Jason Y.Y. Wong[a,*], Helene G. Margolis[b], Mitchell Machiela[a], Weiyin Zhou[c], Michelle C. Odden[d], Bruce M. Psaty[e,f], John Robbins[b], Rena R. Jones[a], Jerome I. Rotter[g], Stephen J. Chanock[a], Nathaniel Rothman[a,1], Qing Lan[a,1], Jennifer S. Lee[h,i,1]

[a] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA
[b] Department of Internal Medicine, School of Medicine, University of California, Davis, CA, USA
[c] Cancer Genomics Research Laboratory, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Leidos Biomedical Research Inc., Bethesda, MD, USA
[d] School of Biological and Population Health Sciences, Oregon State University, Corvallis, OR, USA
[e] Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA, USA.
[f] Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA
[g] Institute for Translational Genomics and Population Sciences and Department of Pediatrics, Los Angeles BioMedical Research Institute, Harbor-UCLA Medical Center, Torrance, CA, USA
[h] Division of Endocrinology, Gerontology, and Metabolism, Department of Medicine, and Division of Epidemiology, Department of Health Research and Policy, School of Medicine, Stanford University, Stanford, CA, USA
[i] Medical Services, Veteran Affairs, Palo Alto, Health Care System, CA, USA

ARTICLE INFO

Keywords:
Loss of chromosome Y
Genetic mosaicism
Genomic instability
Air pollution
PM_{10}

ABSTRACT

Background: Mosaic loss of chromosome Y (mLOY) can occur in a fraction of cells as men age, which is potentially linked to increased mortality risk. Smoking is related to mLOY; however, the contribution of air pollution is unclear.

Objective: We investigated whether exposure to outdoor air pollution, age, and smoking were associated with mLOY.

Methods: We analyzed baseline (1989–1993) blood samples from 933 men ≥65 years of age from the prospective Cardiovascular Health Study. Particulate matter ≤10 μm (PM_{10}), carbon monoxide, nitrogen dioxide, sulfur dioxide, and ozone data were obtained from the U.S. EPA Aerometric Information Retrieval System for the year prior to baseline. Inverse-distance weighted air monitor data were used to estimate each participants' monthly residential exposure. mLOY was detected with standard methods using signal intensity (median log-R ratio (mLRR)) of the male-specific chromosome Y regions from Illumina array data. Linear regression models were used to evaluate relations between mean exposure in the prior year, age, smoking and continuous mLRR.

Results: Increased PM_{10} was associated with mLOY, namely decreased mLRR (p-trend = 0.03). Compared with the lowest tertile (≤28.5 μg/m^3), the middle (28.5–31.0 μg/m^3; $\beta = -0.0044$, $p = 0.09$) and highest (≥31 μg/m^3; $\beta = -0.0054$, $p = 0.04$) tertiles had decreased mLRR, adjusted for age, clinic, race/cohort, smoking status and pack-years. Additionally, increasing age ($\beta = -0.00035$, $p = 0.06$) and smoking pack-years ($\beta = -0.00011$, $p = 1.4E-3$) were associated with decreased mLRR, adjusted for each other and race/cohort. No significant associations were found for other pollutants.

Conclusions: PM_{10} may increase leukocyte mLOY, a marker of genomic instability. The sample size was modest and replication is warranted.

Abbreviations: ChrY, Chromosome Y; mLOY, mosaic loss of Chromosome Y; mLRR, median log R ratio; ChrX, Chromosome X; CHS, Cardiovascular Health Study; EFAS, CHS Environmental Factors Ancillary Study; CVD, cardiovascular disease; PM_{10}, particulate matter < 10 μm; O_3, ozone; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; MSR, male-specific region

* Corresponding author at: National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850, USA.
E-mail address: jason.wong@nih.gov (J.Y.Y. Wong).

[1] These authors co-supervised this study.

https://doi.org/10.1016/j.envint.2018.04.030
Received 4 December 2017; Received in revised form 9 March 2018; Accepted 17 April 2018
Available online 24 April 2018
0160-4120/

1. Introduction

Chromosome Y (ChrY) is a defining genetic characteristic for maleness, and it includes genes that regulate crucial biological pathways related to fertility, maturation and basic cellular processes (Quintana-Murci and Fellous, 2001). Across the lifecourse, altered dosage of these critical genes affects essential biological processes (Mank, 2009). ChrY is gradually lost in a fraction of cells as men progressively age (Dumanski et al., 2015; Forsberg et al., 2014; Zhou et al., 2016), resulting in mosaic loss of chromosome Y (mLOY). Genetic mosaicisms occur when a population of cells within a person does not share the same genetic signatures (Carr, 1963; Zhou et al., 2016). Somatic abnormalities of ChrY can originate at any post-zygotic stage of development and across the lifecourse (Freed et al., 2014). ChrY mosaicisms may be due to erroneous DNA replication and segregation, environmental exposures, or other contributing factors (Carr, 1962, 1963; Dumanski et al., 2015; Freed et al., 2014). The occurrence rate of mosaicisms in ChrY is substantially greater than those of the X-chromosome (ChrX) and autosomes (Machiela et al., 2016). Approximately 7–18% of men over age 70 years have detectable mLOY in leukocytes (Forsberg et al., 2014; Zhou et al., 2016), compared with approximately 0.25% for ChrX in women (Machiela et al., 2016). The resulting disruption of gene expression and function from mLOY may have biological consequences for men. Recent studies found that older men with higher frequency of leukocyte mLOY have elevated risks of Alzheimer's disease and possibly some cancers (Forsberg et al., 2014; Machiela et al., 2017; Noveski et al., 2016; Zhou et al., 2016). Additionally, a previous study reported that mLOY in leukocytes was potentially associated with elevated risks of all-cause and non-hematologic cancer mortality (Forsberg et al., 2014); median survival times among men with detectable mLOY were 5.5 years shorter on average compared with those without mLOY (Dumanski et al., 2015). However, these findings were not replicated in a substantially larger independent study (Zhou et al., 2016).

Cigarette smoking is associated with mLOY (Dumanski et al., 2015; Zhou et al., 2016). A large pooled study found that current smokers had increased occurrence of leukocyte mLOY compared to never and former smokers in the TwinGene, Uppsala Longitudinal Study of Adult Men (ULSAM), and Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohorts (Dumanski et al., 2015). These findings were corroborated in a subsequent investigation in the prospective cohorts, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO), and Cancer Prevention Study-II (CPS-II) (Zhou et al., 2016).

Since exposure to cigarette smoke could promote mLOY in leukocytes, we hypothesized that exposure to outdoor air pollutants may be similarly detrimental to the genome. Air pollutants including particulate matter (PM) $< 10\,\mu m$ (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) are significant public health burdens that have been shown to promote inflammation, oxidative stress, and genomic aberrations (Bekki et al., 2016; Ceretti et al., 2014; Duan et al., 2016; Gao et al., 2016; Gualtieri et al., 2011; Vattanasit et al., 2014; Yan et al., 2016). Furthermore, outdoor air pollution in the form of PM_{10} has been found to infiltrate homes and contribute to indoor levels (Xu et al., 2014). Outdoor PM shares common toxic components with cigarette smoke and is associated with similar health outcomes (Gilmour et al., 2006); in particular, increased risks of lung cancer and non-accidental mortality (Dockery et al., 1993; Hystad et al., 2013; Loomis et al., 2013; Villeneuve et al., 2015). The relationships between exposure to air pollutants and mLOY have yet to be investigated. Therefore, we evaluated cross-sectional associations between average outdoor air pollutant concentrations (i.e. PM_{10}, O_3, NO_2, SO_2, and carbon monoxide (CO)) at the place of residence in the year prior to leukocyte DNA collection and the frequency of mLOY in men aged 65 years and older from the United States. In particular, we focused attention on PM_{10} because of accumulating evidence of associations with cardiovascular outcomes (Shanley et al., 2016), as well as lung cancer risk (Raaschou-Nielsen et al., 2013) and mortality (Dockery et al., 1993). Additionally, we evaluated the associations between age, smoking, and mLOY to assess the consistency of our findings with those from previous studies (Dumanski et al., 2015; Forsberg et al., 2014; Haitjema et al., 2017; Machiela et al., 2017; Noveski et al., 2016; Zhou et al., 2016).

2. Methods

2.1. Study population

The Cardiovascular Health Study (CHS) is a longitudinal, prospective cohort study of men and women aged ≥ 65 years, with the primary aim of investigating the development and progression of cardiovascular disease (CVD) (Eckel et al., 2012; Fried et al., 1991). A total of 5201 participants were recruited in 1989–1990 (Cohort 1) from four U.S. counties (i.e. Forsyth County, NC; Sacramento County, CA; Washington County, MD; Pittsburgh, PA) via age- and sex-stratified random sampling from Medicare eligibility lists. Eligibility criteria included being able to self-respond and give informed consent; not be institutionalized; not be wheelchair-bound; not be receiving treatment for cancer; and not likely to move away in the next three years. An additional 687 African-Americans were recruited in 1992–1993 (Cohort 2), bringing the total study population to 5888 participants. Demographic, anthropometric, lifestyle, and medical information were collected from participants during baseline and annual clinical examinations. Additionally, whole blood was collected from the participants at baseline (1989–1993).

2.2. Outdoor air pollution exposure estimation

The CHS Environmental Factors Ancillary Study (EFAS) was initiated in 1999 and included evaluation of the influence of long-term air pollution exposures on cardiovascular and pulmonary physical measures and outcomes. Reliable air monitoring data were available for three of the four CHS counties during the period of interest (1988–2000); therefore, EFAS was restricted to CHS participants in Forsyth County North Carolina, Sacramento County California, and Allegheny County Pennsylvania. Air pollution data for PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, and O_3 were obtained from the Environmental Protection Agency's Aerometric Information Retrieval System (EPA AIRS) and the California Air Resources Board (CARB). These data are subjected to quality checks by their respective data stewards, while limited additional quality checks were conducted by EFAS. All available data for $PM_{2.5}$ were retrieved; however, the National Ambient Air Quality Standard (NAAQS) (e.g., regulatory limit) for $PM_{2.5}$ was established by the EPA in 1997, and measurements before and around this time were too sparse to produce an exposure estimation comparable for other pollutants during our study period. Given the deficits in spatial and temporal coverage of the $PM_{2.5}$ data, monthly exposure could not be estimated for the entire study period. Therefore, $PM_{2.5}$ was excluded from the analyses. Sacramento County had O_3 data year-round; however, during the non-ozone season (November–March), Pittsburgh had limited O_3 data and Forsyth County had no O_3 data. Therefore, analyses for O_3 were restricted to months with data.

For each CHS participant in EFAS counties, a residential history (baseline through the last point of follow-up) was constructed from CHS records and each address was geocoded. An indicator for the quality of match data for each set of geocodes was provided as part of the geocoding service. A code of 1 indicated the best match, with the quality and accuracy degrading as the code number increased up to 4. Observations with codes of 3 and 4 were removed from our analyses.

Subject-specific monthly average daily ambient pollutant exposure for PM_{10}, NO_2, SO_2, CO, and O_3 were estimated using a previously published validated method (Eckel et al., 2016; Eckel et al., 2012; Rivera-Gonzalez et al., 2015; Wong et al., 2004). Briefly, inverse-