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Associations between ambient air pollutants and clonal hematopoiesis of indeterminate potential (CHIP)

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Abstract

Background—Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related somatic mutation associated with incident hematologic cancer. Environmental stressors which, like air pollution, generate oxidative stress at the cellular level, may induce somatic mutations and some mutations may provide a selection advantage for persistence and expansion of specific clones.

Materials and Methods—We used data from the Multi-Ethnic Study of Atherosclerosis (MESA) N=4,379 and the Women's Health Initiative (WHI) N=7,701 to estimate cross-sectional associations between annual average air pollution concentrations at participant address the year before blood draw using validated spatiotemporal models. We used covariate-adjusted logistic

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Authorship Contributions

CLL, JDK, EW, and AR contributed to the development of the project concept and statistical plan. CLL gathered and analyzed the data. CLL drafted the manuscript. All authors commented on and approved the finalized manuscript. This study was approved by the University of Washington Institutional Review board under IRB numbers STUDY00001950 and STUDY00000384.

Conflicts of Interest

The authors report nothing to disclose.

regression to estimate risk of CHIP per interquartile range increases in $PM_{2.5}$ (4 ug/m^3) and NO_2 (10 ppb) as odds ratios (95% confidence intervals).

Results—Prevalence of CHIP at blood draw (variant allele fraction > 2%) was 4.4% and 8.7% in MESA and WHI, respectively. The most common CHIP driver mutation was in *DNMT3A*. Neither pollutant was associated with CHIP: $OR_{MESA\ PM2.5}$=1.00 (0.68–1.45), $OR_{MESA\ NO2}$=1.05 (0.69–1.61), $OR_{WHI\ PM2.5}$=0.97 (0.86–1.09), $OR_{WHI\ NO2}$=0.98 (0.88–1.10); or with *DNMT3A*-driven CHIP.

Conclusions—We did not find evidence that air pollution contributes to CHIP prevalence in two large observational cohorts.

Impact—This is the first study to estimate associations between air pollution and CHIP.

Keywords

Air pollution; CHIP; PM2.5; NO2; clonal hematopoiesis

Introduction

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related acquisition of somatic mutations representing a pre-malignant state marked by expansion of hematopoietic clones in peripheral blood samples [1–3]. Approximately 10% of individuals over age 70 have detectable CHIP[1]. CHIP is commonly associated with loss-of-function mutations in *DNMT3A*, *TET2*, and *ASXL1*, with approximately 90% of CHIP carriers having a single mutation[1–3]. Inherited causes of CHIP are known[3], but information on environmental risk factors including air pollution is limited. Given previous evidence that exposure to air pollution is associated with systemic inflammation and that inflammation is a risk factor for CHIP [4,5], we explored exposure to ambient air pollution as a potential risk factor for CHIP. We estimated associations between long-term air pollution exposure and CHIP prevalence in two epidemiological cohorts, the Multi-Ethnic Study of Atherosclerosis (MESA) and the Women's Health Initiative (WHI).

Materials and Methods

MESA and WHI participants selected to the US National Heart Lung and Blood Institute's Trans-Omics for Precision Medicine (TOPMed) program represent our sample. Designs of both cohorts are described[6,7]. MESA is a longitudinal study of 6,814 adults aged 45–84 years recruited from six US cities. MESA subjects are self-reported 38% White, 28% African American, 22% Hispanic, and 12% Asian. WHI includes 161,808 women aged 50–79 years enrolled at 40 clinical centers across the US between 1993–1998. WHI participants are self-reported 82% White, 9% Black or African American, 4% Hispanic, 3% Asian or Pacific Islander, 0.4% American Indian or Alaskan Native, and 1% Other race/ethnicity. Participants in WHI were all dbGaP-eligible stroke or venous thromboembolism cases 1:1 matched to an age-, race-, and hormone therapy-stratified, random sample of controls. CHIP mutations were identified in TOPMed. Information on CHIP mutation identification is available[3]. We applied the GATK MuTECT2 somatic variant caller to whole genome sequencing of blood-derived DNA and identified CHIP based on a list of pre-specified

leukemogenic driver mutations. CHIP was defined as variant allele fraction (VAF) > 2%. Individuals with history of hematologic malignancy or prior use of antineoplastic medication were excluded. Universal kriging models predicted individual-level concentrations for fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) weighted by time in residential address[8]. Primary exposures were average annual $PM_{2.5}$ and NO_2 concentrations one year prior blood sampling (MESA 2000–2006, WHI 1994–2003). Sample selection is available (Supplementary Figure 1). Our sample included N_{MESA} = 4445 and N_{WHI} = 7701. Cross-sectional associations between air pollutant concentrations and CHIP prevalence at blood draw were estimated by logistic regression, separately for MESA and WHI and per interquartile range (IQR). MESA models adjusted for age, education, income, smoking, sex, race/ethnicity, site, neighborhood income, and year. WHI models adjusted for age, education, income, smoking, race/ethnicity, and year. We explored models restricted to *DNMT3A*-specific mutations and restricted to smokers (Supplementary Table 2). Sensitivity analysis in WHI involved weighting models for the inverse probability of sampling (Supplementary Table 1).

Data Availability

The data generated in this study are not publicly available as information collected could compromise patient privacy and consent, but are available upon reasonable request from the corresponding author.

Results

Table 1 shows descriptive statistics. CHIP was identified in 196(4.4%) MESA participants and 668 (8.7%) WHI participants. Most commonly mutated genes were *DNMT3A, TET2*, and *ASXL1*. Participants with CHIP were on average older than participants without CHIP (66.9 years vs 61.0 years in MESA; 71.6 years vs 69.2 years in WHI). Participants with CHIP were more likely to have history of smoking. Air pollution exposure was similar between participants with and without CHIP ($PM_{2.5\ –\ CHIP}$ = 16.9 μg/m^3 vs $PM_{2.5\ –\ NO\ CHIP}$ = 16.8 μg/m^3; $NO_{2\ –\ CHIP}$ = 22.6 ppb vs $NO_{2\ –\ NO\ CHIP}$ = 22.0 ppb in MESA) ($PM_{2.5\ –\ CHIP}$ = 13.4 μg/m^3 vs $PM_{2.5\ –\ NO\ CHIP}$ = 13.5 μg/m^3; $NO_{2\ –\ CHIP}$ = 14.1 ppb vs $NO_{2\ –\ NO\ CHIP}$ = 14.1 ppb in WHI). Table 2 shows the results of logistic regression. IQR increases in $PM_{2.5}$ were not associated with odds of CHIP in MESA (OR_{MESA} = 1.00; 95% CI 0.68 – 1.45) or WHI (OR_{WHI} = 0.97; 95% CI 0.86 – 1.09). IQR increases in NO_2 were not associated with odds of CHIP in MESA (OR_{MESA} = 1.05; 95% CI 0.69 – 1.61) or WHI (OR_{WHI} = 0.98; 95% CI 0.88 – 1.10). We did not find evidence of associations between air pollutants and *DNMT3A*- specific mutations.

Conclusions

To our knowledge, this is the first study to estimate associations between air pollution and CHIP; we did not find associations. Limitations include this study's cross-sectional nature. Some selection bias is probable due to selection of participants into TOPMed, however WHI results were robust to weighting for inverse probability of sampling (Supplementary Table 1). Consistent with other studies of CHIP, age was the strongest predictor of

CHIP and individuals with CHIP were more likely to have a history of smoking[2,4]. Strengths of this study include our air pollution assessment, geographic variation of the population, and extensive covariate information. Given biologic plausibility and otherwise unknown environmental risk factors for CHIP, future studies exploring associations of other environmental exposures and CHIP should be conducted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:
Descriptive Statistics Participants at Baseline Examination

Multi-Ethnic Study of Atherosclerosis				Women's Health Initiative			
Characteristic	**CHIP Mutation**	**No CHIP Mutation**	**Total**	**Characteristic**	**CHIP Mutation**	**No CHIP Mutation**	**Total**
No. participants	196 (4.4)	4249 (95.6)	4445 (100)	No. participants	668 (8.7)	7033 (91.3)	7701 (100)
Age (years)	66.9 (45–84)	60.9 (44–84)	61.2 (44–84)	Age (years)	71.6 (52–86)	69.2 (50–87)	69.4 (50–87)
Sex				Sex			
Male	90 (45.9)	2071 (48.7)	2161 (48.6)	Male	0 (0.0)	0 (0.0)	0 (0.0)
Female	106 (54.1)	2178 (51.3)	2284 (51.4)	Female	668 (8.7)	7033 (91.3)	7701 (100)
Smoking Status				Smoking Status			
Never	90 (45.9)	2156 (50.7)	2246 (50.5)	Never	320 (47.9)	3577 (50.9)	3897 (50.6)
Former	86 (43.9)	1561 (36.7)	1647 (37.1)	Former	300 (44.9)	2880 (41.0)	3180 (41.3)
Current	19 (9.7)	524 (12.3)	543 (12.2)	Current	44 (6.6)	488 (6.9)	532 (6.9)
Missing	1 (0.5)	8 (0.2)	9 (0.2)	Missing	4 (0.6)	88 (1.3)	92 (1.2)
Race/Ethnicity				Race/Ethnicity			
White	88 (44.9)	1708 (40.2)	1796 (40.4)	White, Non-Hispanic	573 (85.8)	5774 (82.1)	6347 (82.4)
Chinese American	18 (9.2)	545 (12.8)	563 (12.7)	Asian or Pacific Islander	10 (1.5)	96 (2.0)	106 (1.4)
Black/African American	51 (26.0)	1071 (25.2)	1122 (25.2)	Black/African American	65 (9.7)	875 (12.4)	940 (12.2)
Hispanic	39 (19.9)	925 (21.8)	964 (21.7)	Hispanic/Latino	11 (1.7)	217 (3.1)	228 (3.0)
AI/AN	0 (0.0)	0 (0.0)	0 (0.0)	AI/AN	3 (0.5)	31 (0.4)	34 (0.4)
Other	0 (0.0)	0 (0.0)	0 (0.0)	Other	6 (0.9)	40 (0.6)	46 (0.6)
Total Gross Family Income				Total Gross Family Income			
<$19999	49 (25.0)	835 (19.7)	884 (19.9)	<$20000	119 (17.8)	1367 (19.4)	1486 (19.3)
$20000–39999	51 (26.0)	1080 (25.4)	1131 (25.4)	$20000–49999	336 (50.3)	3245 (46.1)	3581 (46.5)
$40000–99999	63 (32.1)	1590 (37.4)	1653 (37.2)	$50000–99999	139 (20.8)	1602 (22.8)	1741 (22.6)
$100000+	24 (12.2)	632 (14.9)	656 (14.8)	$100000+	31 (4.6)	382 (5.4)	413 (5.4)
Missing	9 (4.6)	112 (2.6)	121 (2.7)	Missing	43 (6.4)	437 (5.4)	480 (6.2)
Education				Education			
Less than High School	28 (14.3)	640 (15.1)	659 (15.1)	Less than High School	26 (3.90)	376 (5.4)	402 (5.2)
High School Degree	70 (35.7)	1433 (33.7)	1481 (33.8)	High School Degree	103 (15.4)	1277 (18.2)	1380 (17.9)

Multi-Ethnic Study of Atherosclerosis				Women's Health Initiative			
Characteristic	**CHIP Mutation**	**No CHIP Mutation**	**Total**	**Characteristic**	**CHIP Mutation**	**No CHIP Mutation**	**Total**
College or Technical Degree	53 (27.0)	1340 (31.5)	1372 (31.3)	Some College	277 (41.5)	2765 (39.3)	3042 (39.5)
Graduate or Professional Degree	44 (22.5)	828 (19.5)	858 (19.6)	College Degree or Higher	259 (38.8)	2568 (36.5)	2827 (36.7)
Missing	1 (0.5)	8 (0.2)	9 (0.2)	Missing	3 (0.5)	47 (0.7)	50 (0.7)
Year of Blood Draw				Year of Blood Draw (masked)			
				1994			
				1995			
				1996			
				1997			
				1998			
				1999			
2000	32 (16.3)	644 (15.2)	676 (15.2)	2000			
2001	91 (46.4)	2251 (53.0)	2342 (52.7)	2001			
2002	71 (36.2)	1295 (30.5)	1366 (30.7)	2002			
2003	0 (0.0)	0 (0.0)	0 (0.0)	2003			
2004	1 (0.5)	23 (0.5)	24 (0.5)				
2005	1 (0.5)	36 (0.9)	37 (0.8)				
Annual average $PM_{2.5}$	16.9 (9.4–30.1)	16.8 (8.5–31.6)	16.8 (8.5–31.6)	Annual average $PM_{2.5}$	13.4 (3.5–22.5)	13.5 (2.5–23.2)	13.5 (2.5–23.2)
Annual average NO_2	22.6 (6.2–51.5)	22.0 (4.0–60.1)	22.02 (4.03–60.07)	Annual average NO_2	14.1 (1.5–41.9)	14.1 (1.3–77.9)	14.1 (1.3–77.9)

* $PM_{2.5}$ = Particulate matter >2.5 μm ($\mu g/m^3$)

* NO_2 = Nitrogen dioxide (ppb)

Rows are N(%) or Mean (range)

AI/AN = American Indian/Alaskan Native

Table 2:

The Association between Air Pollutants and CHIP Mutation Prevalence: Results of Logistic Regression

	Multi-Ethnic Study of Atherosclerosis (N=4,379)	**Women's Health Initiative (N=7,701)**
Pollutant	CHIP Odds Ratio (95% Confidence Interval)	
$PM_{2.5}$	1.00 (0.68, 1.45)	0.97 (0.86,1.09)
NO_2	1.05 (0.69, 1.61)	0.98 (0.88, 1.10)
	DNMT3A-specific CHIP Odds Ratio (95% Confidence Interval)	
$PM_{2.5}$	1.06 (0.68, 1.68)	1.09 (0.95, 1.26)
NO_2	1.25 (0.75, 2.06)	0.99 (0.88, 1.12)

$PM_{2.5}$ exposure per 4 $\mu g/m^3$ increase

NO_2 exposure per 10 ppb increase

All parameters refer to the participant's characteristic at time of blood draw

MESA results adjusted for age, sex, education, smoking status, self-reported race/ethnicity, individual socioeconomic status (household income), neighborhood socioeconomic status (median household income), clinical site, year of blood draw

WHI results adjusted for age, education, smoking status, self-reported race/ethnicity, individual socioeconomic status (household income), year of blood draw