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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Dry-Cleaning Chemicals and a Cluster of Parkinson's Disease and Cancer: A Retrospective Investigation

E. Ray Dorsey, MD,[1,2*] Dan Kinel, JD,[1,2] Meghan E. Pawlik, BA,[2] Maryam Zafar, BS,[2,3] Samantha E. Lettenberger, BS,[2] Madeleine Coffey, BA,[4] Peggy Auinger, MS,[1,2] Kevin L. Hylton, MS,[5] Carol W. Shaw, NP,[6] Jamie L. Adams, MD,[1,2] Richard Barbano, MD,[1] Melanie K. Braun, MD,[1] Heidi B. Schwarz, MD,[1] B. Paige Lawrence, PhD,[7] Karl Kieburtz, MD, MPH,[1,2] Caroline M. Tanner, MD, PhD,[8] Briana R. de Miranda, PhD,[9] and Samuel M. Goldman, MD, MPH[10]

[1]*Department of Neurology, University of Rochester Medical Center, Rochester, New York, USA* [2]*Center for Health & Technology, University of Rochester Medical Center, Rochester, New York, USA* [3]*Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA* [4]*Donald and Barbara Zucker School of Medicine, Uniondale, New York, USA* [5]*Kevin Hylton Environmental Services, Inc., Rochester, New York, USA* [6]*Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, New York, USA* [7]*Department of Environmental Medicine, University of Rochester Medical Center, Rochester, New York, USA* [8]*Department of Neurology, UCSF Health, San Francisco, California, USA* [9]*Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama, USA* [10]*Division of Occupational, Environmental, and Climate Medicine, University of California San Francisco, San Francisco, California, USA*

ABSTRACT: Background: Environmental exposure to trichloroethylene (TCE), a carcinogenic dry-cleaning chemical, may be linked to Parkinson's disease (PD).

Objective: The objective of this study was to determine whether PD and cancer were elevated among attorneys who worked near a contaminated site.

Methods: We surveyed and evaluated attorneys with possible exposure and assessed a comparison group.

*__Correspondence to:__ Dr. E. Ray Dorsey, Department of Neurology, University of Rochester Medical Center, 265 Crittenden Blvd, CU 420694, Rochester, NY 14642, USA; E-mail: ray.dorsey@chet.rochester.edu

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Results: Seventy-nine of 82 attorneys (96.3%; mean [SD] age: 69.5 [11.4] years; 89.9% men) completed at least one phase of the study. For comparison, 75 lawyers (64.9 [10.2] years; 65.3% men) underwent clinical evaluations. Four (5.1%) of them who worked near the polluted site reported PD, more than expected based on age and sex (1.7%; $P = 0.01$) but not significantly higher than the comparison group (n = 1 [1.3%]; $P = 0.37$). Fifteen (19.0%), compared to four in the comparison group (5.3%; $P = 0.049$), had a TCE-related cancer.
Conclusions: In a retrospective study, diagnoses of PD and TCE-related cancers appeared to be elevated among attorneys who worked next to a contaminated dry-cleaning site. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; trichloroethylene; tetrachloroethylene (perchloroethylene); environment; disease hotspot

Trichloroethylene (TCE) and perchloroethylene (PCE) are six-atom molecules with many uses, including decaffeinating, degreasing, and dry cleaning.[1,2] Both readily distribute in the brain, likely mediate their toxicity through a common metabolite,[3] and appear to inhibit mitochondrial complex I activity at high doses. Like *LRRK2* mutations, TCE induces LRRK2 kinase activity and causes the loss of dopaminergic neurons.[4-9]

Case reports have linked TCE use to Parkinson's disease (PD) since 1969,[10] and hobby or occupational exposure 10 to 40 years earlier is associated with a 500% increased risk of PD.[3] Environmental exposure can also occur, for example, at the US Marine Base Camp Lejeune where service members have a 70% increased risk of developing PD.[11] These solvents pollute soil and groundwater,[1,12] travel from their source, and, like radon,[13] evaporate and enter homes, schools, and workplaces (Supplementary Fig. S1).[14,15]

Exposure to TCE and PCE is associated with other adverse health outcomes.[1] TCE is a known carcinogen, and PCE is a likely one.[16-18] A meta-analysis found, "[Occupational] exposure to TCE was associated with excess incidences of liver cancer, kidney cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma."[19]

A few small PD clusters have been reported,[20-23] but systematic investigations are lacking. Here we evaluate attorneys who worked near a contaminated site to determine if the prevalence of PD and cancer was elevated.

Methods

Site

A large dry cleaner operated in Rochester, New York, from 1950 to 1994. In 1992, an environmental assessment found that the surrounding soil was contaminated with TCE, PCE, and other chemicals (Supplementary Fig. S2; see Supplementary Data for details).[24] Three hundred feet across the street is an 18-floor retail and office tower with a three-level underground parking garage toward which the groundwater flows.[25]

Study Design

The University of Rochester's institutional review board reviewed and approved the two-phase study, and participants provided informed consent. Phase I surveyed partners who worked at a law firm in the tower ("tower cohort") for at least 1 year between 1968 and 2001 (Supplementary Fig. S3). Because the firm retained detailed information only on its partners, other attorneys or staff were excluded from the cohort. The tower cohort, their next of kin, or other family members completed the survey.

In phase II, the tower cohort was evaluated clinically for PD, cancer, and related conditions.[26] The visits were conducted either in person or remotely via video depending on the participant's location and preference. For deceased or incapacitated participants, we obtained authorizations from their legal representatives and reviewed obituaries, the National Death Index, and other public records.

Study Group

In addition to the partners, we recruited a comparison group of attorneys for phase II of the study via the local bar association's newsletter, flyers, and word of mouth. These lawyers were at least 45 years old and had worked for at least 1 year between 1968 and 2001.

Assessments

In phase I, we collected demographics, a brief work history, and diagnoses of PD, cancer, or related diseases. Respondents also completed a survey of common PD symptoms.[27]

In phase II, we collected detailed demographics; a work, medical, and family history; and a medication list. Participants underwent standard assessments of PD and related disorders (see Supplementary Data), including the Gelb Criteria for the Diagnosis of Parkinson's Disease.[28]

The Gelb criteria classify individuals based on the following: (1) four characteristic features of PD; (2) unusual, early features; (3) response to levodopa or a dopamine agonist; and (4) histopathological diagnosis. "Possible" PD requires two characteristic features, the absence of unusual features, and a favorable medication response if tried. The criteria were applied to those who had not been diagnosed with PD. To the extent feasible, investigators were masked to whether the attorney was part of the tower cohort or the comparison group.

Analysis

The study's primary objective was to determine whether the tower cohort had an increased prevalence of PD or cancer. To do so, we compared the proportion of individuals with PD in the tower cohort to that expected in the general population based on sex[29] and age (in 10-year age groups) at either the time of the assessment (for the living) or the time of death (for the deceased) using a binomial test. We also evaluated the prevalence in relation to that in the comparison group using a Fisher's exact test. Finally, we compared the mean values in clinical assessments (eg, Movement Disorders Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS]) and the prevalence of TCE-related cancers[19] to determine if there was additional evidence of exposure. We used general linear models for age-adjusted analyses due to small differences in age between the two groups.

Data Sharing

Study data are not available for sharing.

Results

Phase I

Of the 81 attorneys invited, 65 (80.2%) participated (Supplementary Fig. S4). Proxies completed responses for 14 disabled or deceased individuals. Four (6.2%) reported PD and one (1.5%) multiple system atrophy (MSA). Two individuals with PD and one with MSA had died. Twelve (18.5%) additional respondents endorsed at least one parkinsonian symptom.

Phase II and Aggregate Results

After phase I, one additional individual who was erroneously omitted was added to the cohort. As shown in Supplementary Figure S4, 64 (78.0%) of the 82 completed at least some portion of phase II between August 2021 and March 2023. In all, 79 (96.3%) completed at least one phase of the study, but we could not locate any medical records for one deceased person. For the comparison group, 119 attorneys indicated interest, of whom 75 (63.0%) were eligible and participated. The baseline characteristics (Table 1) of the two groups were generally similar except that the tower cohort was older (69.5 vs. 64.9 years) and had more men (89.9% vs. 65.3%).

Eighteen (22.0%) attorneys in the tower cohort died before phase II. Their average age was 75.1 (8.6) years. We obtained health information for 15, 2 of whom died with PD, 1 with MSA and prostate cancer, and 8 others with a TCE-related cancer (n = 6 prostate cancer; n = 1 multiple myeloma; n = 1 kidney cancer). In all, 11 (73.3%) of the 15 deceased had at least one TCE-associated condition.

Four (5.1%) of the participants in the tower cohort had PD based on reports from a proxy and review of medical records (n = 2), report from a proxy and the National Death Index (n = 1), and self-report and clinical evaluation (n = 1). The proportion with PD was more than expected based on age and sex (1.7%; $P = 0.01$).[29] The number was also numerically but not significantly greater than in the comparison group (n = 1 [1.3%]; $P = 0.21$).

Of the 64 participants in the tower cohort, 48 (75.0%) underwent clinical evaluations. Death (n = 12) and disability (n = 4) precluded full participation. The proportion with possible PD did not differ (19.1%) from the comparison group (18.9%; $P = 0.65$; Table 2).

As shown in Table 2, 15 (19.0%) of the 79 individuals in the tower cohort had a TCE-related cancer compared to 4 (5.3%; $P = 0.049$) in the comparison group. Among men only, TCE-related cancers still tended to be more frequent (21.1% vs. 8.2%; $P = 0.09$). In contrast, the proportion of individuals who had any type of cancer was similar (Table 2).

Discussion

The prevalence of PD and TCE-associated cancers appeared to be elevated among attorneys who worked near a site contaminated with dry-cleaning chemicals. These findings are consistent with the chemical's known carcinogenicity and supportive of the emerging preclinical[6-9] and epidemiological[30] evidence that ties TCE exposure to PD. This study, which evaluated over 90% of the cohort, is the largest such cohort to be assessed clinically and the first to include a comparison group. This and the recent Camp Lejeune study[11] are also the first to tie possible *environmental* exposure to PD.

Because the study was retrospective, its biggest limitation is the uncertainty of exposure. The time lag between exposure and diagnosis makes environmental studies challenging. In this case, the extent to which vapors entered the tower or garage over 20 years ago is unknown as no testing (to our knowledge) was performed. However, the extent of contamination, the likely flow of chemicals, and an underground tunnel all suggest that vapor intrusion was possible.[31] In New York, PCE levels in buildings with or near a dry cleaner have ranged up to 55,000 $\mu g/m^3$,[32] 1000 times above the level in the current safety guidelines.[33] Larger, prospective studies that evaluate the effects of toxicants on a cohort would be better positioned to assess the dose and duration of exposure and its consequences and help determine whether a dose–response relationship is present.

Alternative explanations could elucidate our findings. Genetic mutations are found in ~15% of the population and were not assessed.[34,35] However, the majority with these mutations do not develop PD,[36]

TABLE 1 *Baseline characteristics of participants from phase I and/or phase II of the study**

Characteristic	Tower cohort (n = 79)	Comparison group (n = 75)
Age (y), mean (SD)	69.5 (11.4)*	64.9 (10.2)
Male, n (%)	71 (89.9)	49 (65.3)
Race, n (%) (tower cohort = 75)		
Asian	0 (0.0)	1 (1.3)
Black/African-American	0 (0.0)	0 (0.0)
White	73 (97.3)	71 (94.7)
Prefer not to answer	2 (2.7)	3 (4.0)
Ethnicity, n (%) (tower cohort = 74)		
Hispanic/Latino	2 (2.7)	1 (1.3)
Not Hispanic/Latino	70 (94.6)	72 (96.0)
Prefer not to answer	2 (2.7)	2 (2.7)
Veteran, n (%) (tower cohort = 48)	10 (20.8)	5 (6.7)
Education, n (%) (tower cohort = 75)		
Doctorate	3 (4.0)	2 (2.7)
Professional degree	72 (96.0)	72 (96.0)
Master's degree	0 (0.0)	1 (1.3)
Employment status, n (%) (tower cohort = 48)		
Employed, full-time	20 (41.7)	47 (62.7)
Employed, part-time	4 (8.3)	12 (16.0)
Retired	24 (50.0)	15 (20.0)
Disabled (unable to work)	0 (0.0)	1 (1.3)
Household income, n (%) (tower cohort = 48)		
Less than $100,000	1 (2.1)	11 (14.7)
More than $100,000	43 (89.6)	56 (74.7)
Prefer not to answer	4 (8.3)	8 (10.7)
Marital status, n (%) (tower cohort = 48)		
Single, never married	3 (6.3)	4 (5.3)
Married or domestic partnership	42 (87.5)	63 (74.0)
Widowed, divorced, or separated	3 (6.3)	7 (9.3)
Prefer not to answer	0 (0.0)	1 (1.3)
Living situation, n (%) (tower cohort = 48)		
Independent living facility	2 (4.2)	1 (1.3)
Reside in the community (eg, private home or apartment)	46 (95.8)	74 (98.7)
Household members, n (%) (tower cohort = 48)		
Spouse, partner, or significant other	43 (89.6)	63 (84.0)
Adult child/children	6 (12.5)	15 (20.0)
Minor child/children	8 (16.7)	13 (17.3)

(Continues)

TABLE 1 *Continued*

Characteristic	Tower cohort (n = 79)	Comparison group (n = 75)
Another related individual	1 (2.1)	1 (1.3)
No one	3 (6.3)	5 (6.7)
Family history of Parkinson's disease, n (%) (tower cohort = 48)	8 (16.7)	12 (16.0)
Risk factor questionnaire (tower cohort = 46)		
Smoked 100 or more cigarettes (five packs) in lifetime, n (%)	17 (37.0)	28 (37.3)
Used smokeless tobacco at least once a day for ≥6 months, n (%)	1 (2.2)	2 (2.7)
Drank caffeinated coffee at least once a week for ≥6 months, n (%)	39 (84.8)	63 (84.0)
Drank caffeinated black tea at least once a week for ≥6 months, n (%)	10 (21.7)	31 (41.3)
Drank caffeinated green tea at least once a week for ≥6 months, n (%)	5 (10.9)	8 (10.7)
Ever had a job with exposure to any pesticide, n (%)	5 (10.9)	6 (8.0)
Ever had exposure to any pesticide in a nonwork setting, n (%)	35 (76.1)	57 (76.0)
Ever used solvents or degreasers ≥ 100 days at work or home, n (%)	3 (6.5)	7 (9.3)

Note: Demographic data collected in phase I of the study were more limited than those in phase II.
Abbreviation: SD, standard deviation.
*Mean age includes age at the time of the study (63 participants) or age of death (16 participants).

TABLE 2 *Results of phase II clinical assessments and aggregate diagnoses from either phase*

Phase II assessments	Tower cohort n = 48	Comparison group n = 75	*P*-value†
Diagnostic criteria			
Gelb criteria for the diagnosis of PD, n (%) (tower cohort = 47, comparison = 74)			0.65
Unlikely	38 (80.9)	60 (81.1)	
Possible	9 (19.1)	14 (18.9)	
Current consensus criteria for the diagnosis of MSA "unlikely," n (%)	48 (100.0)	75 (100.0)	
Revised criteria for the clinical diagnosis of probable and possible DLB, n (%)			0.95
Unlikely	48 (100.0)	74 (98.7)	
Possible	0 (0.0)	1 (1.3)	
NINDS-SPSP criteria for the diagnosis of PSP (revised) "criteria cannot be applied," n (%)	48 (100.0)	75 (100.0)	
Clinical assessments			
MDS-UPDRS			
Part I, mean (SD)	5.7 (4.0)	5.6 (4.9)	0.80
Part II, mean (SD)	1.3 (3.0)	1.3 (2.7)	0.84
Part III, mean (SD)			
In-person	9.0 (8.0)	7.7 (7.6)	0.54
Remote	4.9 (6.3)	3.2 (3.2)	0.81
Modified Schwab and England Scale, n (%) scoring 100	42 (87.5)	72 (96.0)	0.21
Montreal cognitive assessment, mean (SD)	27.6 (2.9)	27.6 (2.1)	0.48

(Continues)

TABLE 2 *Continued*

Phase II assessments	Tower cohort n = 48	Comparison group n = 75	*P*-value†
Number of finger taps on the smartphone research application, mean (SD)			
Right hand (tower cohort = 31, comparison = 63)	159 (68)	182 (75)	0.20
Left hand (tower cohort = 32, comparison = 63)	146 (69)	170 (75)	0.20
Timed up and go (s), mean (SD) (tower cohort = 33, comparison = 64)	9.7 (2.3)	9.7 (2.1)	0.78
10-Meter Walk Test (tower cohort = 33, comparison = 64)			
Self-selected velocity average time (s), mean (SD)	4.9 (1.1)	4.6 (0.8)	0.23
Average self-selected velocity (m/s), mean (SD)	1.3 (0.2)	1.3 (0.2)	0.23
University of Pennsylvania smell identification test score below age-sex cutoff, n (%) (tower cohort = 43, comparison = 73)	6 (14.0)	16 (21.9)	0.47
Questionnaires			
Brief Motor Screen, mean (SD)	0.6 (1.4)	0.4 (0.9)	0.44
Number (%) Scoring >0	15 (31.3)	19 (25.3)	0.66
Epworth Sleepiness Scale, mean (SD) (comparison = 74)	4.5 (2.6)	5.0 (3.4)	0.36
REM sleep behavior disorder screening questionnaire, mean (SD)	3.5 (2.3)	3.5 (2.1)	0.91
Geriatric Depression Scale-15, mean (SD)	1.4 (1.9)	1.7 (2.3)	0.62
Parkinson Anxiety Scale, mean (SD)	5.9 (5.2)	6.5 (5.6)	0.85
Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms, mean (SD)	8.5 (5.3)	10.0 (6.2)	0.06
Aggregate diagnoses of Parkinson's disease, MSA, and cancer	**n = 79**	**n = 75**	***P*-value†**
Identified Parkinson's disease, n (%)	4 (5.1)	1 (1.3)	0.21
Identified MSA, n (%)	1 (1.2)	0 (0.0)	0.32
Identified any cancer, n (%)	26 (32.9)	26 (34.7)	0.47
Total cases of cancer, n	34	28	
Any TCE-related cancer (unique individuals)	15 (19.0)	4 (5.3)	0.049
Prostate (men in the tower cohort = 71, men in the comparison group = 49)	11 (15.5)	4 (8.2)	0.33
Multiple myeloma	2 (2.5)	1 (1.3)	0.76
Kidney	1 (1.3)	0 (0.0)	0.30
Non-Hodgkin's lymphoma	1 (1.3)	0 (0.0)	0.47
Liver	0 (0.0)	0 (0.0)	
Other cancers			
Melanoma	4 (5.1)	4 (5.3)	0.90
Skin (non-melanoma)	10 (12.7)	7 (9.3)	0.60
Breast (women in the tower cohort = 8, women in the comparison group = 26)	1 (12.5)	4 (11.5)*	0.73
Glioblastoma	3 (3.9)	0 (0.0)	0.12
Bladder	0 (0.0)	1 (1.3)	0.23
Colon	0 (0.0)	1 (1.3)	0.25
Lung	0 (0.0)	1 (1.3)	0.21
Ovarian (women in the tower cohort = 8, women in the comparison group = 26)	0 (0.0)	1 (3.8)	0.46
Thyroid	0 (0.0)	1 (1.3)	0.33

(Continues)

TABLE 2 *Continued*

Aggregate diagnoses of Parkinson's disease, MSA, and cancer	n = 79	n = 75	*P*-value†
Uterine (women in the tower cohort = 8, women in the comparison group = 26)	0 (0.0)	1 (3.8)	0.63
Other	1 (1.3)	2 (2.6)	0.36

Note: The tower group included 48 living participants at the time of the phase II assessment.
Abbreviations: PD, Parkinson's disease; MSA, multiple system atrophy; DLB, dementia with Lewy bodies; NINDS-SPSP, National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; SD, standard deviation; TCE, trichloroethylene.
*One man in the comparison group had breast cancer and was excluded from the calculation of the relative proportion of women with breast cancer and the ensuing comparison between the two groups.
†*P*-value based on comparisons adjusted for age at either time of assessment (for the living) or time of death (for the deceased).

less than 20% of the study population had a family history of PD, and the occurrence of any mutations would likely be nondifferential. As with Camp Lejeune,[11] other toxicants at the site or elsewhere could have contributed to the findings for PD, cancer, or both. Finally, the higher proportion of men in the tower cohort likely increased the numbers of prostate cancer. The link between TCE[37] and PCE[38] and prostate cancer, which accounted for the majority of the "TCE-related" cancers in this study, is also not as strong as it is for some other cancers (eg, kidney).

The next limitation applies to the comparison group, which was recruited from living individuals who may have been healthier (~80% were still employed at least part-time) than a random or contemporaneous cohort that was followed prospectively. As such, the prevalence of cancer, for example, may have been lower. By contrast, although we had complete assessments for the comparison group, we had only clinical measures for 48 (59%) of the tower cohort, which may have understated its true disease burden. In addition, the study's modest size limited the ability to detect differences between the two groups.

Finally, other factors limited the study. The investigators may have been biased toward identifying parkinsonian features, and full masking was sometimes difficult. Attorneys themselves may be at higher risk of developing PD[39] perhaps due to indoor air pollution or dry-cleaned clothes, which can release PCE.[40] Because the tower cohort was largely limited to white, male law partners, the results, though valid, may not be generalizable. Lastly, if TCE or PCE did pollute the air, thousands who worked, shopped, or visited the tower or parked in the garage could have been exposed but were not assessed in this study.

Historically, clusters have provided insights into the causes of infectious diseases[41] and cancer.[42] In this cohort of attorneys who worked near a site polluted with dry-cleaning chemicals, we found a high prevalence of PD and cancer. Although the evidence is circumstantial and not definitive, the findings are concerning for the role TCE and PCE may be playing. Given their widespread use, efforts to limit their spread and additional investigations into their contribution to the rise of PD[43] are long overdue. ■

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Data Availability Statement

Research data are not shared.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Buspirone and Zolmitriptan Combination for Dyskinesia: A Randomized, Controlled, Crossover Study

Peter A. LeWitt, MD,[1*] Glenn T. Stebbins, PhD,[2] Kenneth Vielsted Christensen, PhD,[3] Riswanto Tan, MSc,[4] Anél Pretorius, MD,[5] and Mikael Thomsen, PhD[3]

***Correspondence to:** Peter A. LeWitt, Sastry Family Endowed Chair in Neurology, Department of Neurology, Wayne State University School of Medicine, 4201 St. Antoine Street, 8D-UHC, Detroit, MI 48201 USA; E-mail: aa1142@wayne.edu

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