Petroleum Distillate Solvents as Risk Factors for Undifferentiated Connective Tissue Disease (UCTD)

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Occupational solvent exposure may increase the risk of connective tissue disease (CTD). The objective of this case-control study was to investigate the relation between undifferentiated connective tissue disease (UCTD) and solvent exposure in Michigan and Ohio. Women were considered to have UCTD if they did not meet the American College of Rheumatology classification criteria for any CTD but had at least two documented signs, symptoms, or laboratory abnormalities suggestive of a CTD. Detailed information on solvent exposure was ascertained from 205 cases, diagnosed between 1980 and 1992, and 2,095 population-based controls. Age-adjusted odds ratios (OR) and 95 percent confidence intervals (CI) were calculated for all exposures. Among 16 self-reported occupational activities with potential solvent exposure, furniture refinishing (OR = 9.73, 95 percent CI 1.48–63.90), perfume, cosmetic, or drug manufacturing (OR = 7.71, 95 percent CI 2.24–26.56), rubber product manufacturing (OR = 4.70, 95 percent CI 1.75–12.61), work in a medical diagnostic or pathology laboratory (OR = 4.52, 95 percent CI 2.27–8.97), and painting or paint manufacturing (OR = 2.87, 95 percent CI 1.06–7.76) were significantly associated with UCTD. After expert review of self-reported exposure to ten specific solvents, paint thinners or removers (OR = 2.73, 95 percent CI 1.80–4.16) and mineral spirits (OR = 1.81, 95 percent CI 1.09–3.02) were associated with UCTD. These results suggest that exposure to petroleum distillates increases the risk of developing UCTD.
like condition that includes Raynaud's phenomenon, sclerodactyly, arthritis, and pulmonary fibrosis (12). Other chlorinated solvents such as perchloroethylene (tetrachloroethylene, Perc), trichloroethylene (TCE), and 1,1,1-trichloroethane (TCA) are structurally similar to vinyl chloride and have been reported in association with SSc and SSc-like illness (10, 13–17). Symptoms suggestive of early SLE were reported in higher frequency among Arizona residents exposed to drinking water contaminated with TCE, TCA, and other chemicals than in nonexposed referent groups (18).

Numerous solvents have been linked to the development of autoimmune and connective tissue disease, but whether these environmental triggers represent true causal agents for classic SSc or whether they induce other forms of connective tissue disease, such as UCTD, has not been adequately investigated in controlled epidemiologic studies. The objective of this study was to investigate exposures to solvents as risk factors for UCTD.

MATERIALS AND METHODS

Study sample and case definition

All women with UCTD who were at least 18 years old and living in Michigan or Ohio when diagnosed were considered eligible. Cases of UCTD (defined below) who had been diagnosed between January 1, 1980 and December 31, 1991 in Michigan or between January 1, 1980 and December 31, 1992 in Ohio were recruited between 1992 and 1995 along with cases of SSc in a case-control study (19).

Women with UCTD were identified from several overlapping sources: 1) a national hospital discharge diagnosis database (Health Care Investment Analysts, Inc. [HCIA], Ann Arbor, Michigan), 2) databases from the University of Michigan Hospitals (Ann Arbor, Michigan) and Wayne State University Affiliated Hospitals (Detroit, Michigan), 3) a mailing list of all rheumatologists in Michigan and Ohio, and of other relevant specialists in Ohio (dermatology, gastroenterology, internal medicine, family practice, general practice, and obstetrics and gynecology), and 4) the mailing list of the Southeast Michigan chapter of the United Scleroderma Foundation (SE-USF), which is a support group for SSc patients and their families. HCIA made the initial contact of the hospitals and requested that consent forms be sent to all women discharged during the study period with an International Classification of Diseases (9th Revision) diagnostic code of either 710.9 ("unspecified diffuse connective tissue disease") or 710.1 ("systemic sclerosis").

SSc and UCTD cases were recruited simultaneously, and a final diagnosis was not determined until after medical record review. Because eligibility usually could not be determined prior to obtaining informed consent, exact response rates for UCTD could not be calculated. After adjusting for patients identified from multiple sources, ineligible subjects, and incorrect mailing addresses, the response rate to patient mailings was estimated to be between 75 and 80 percent. A total of 243 of 386 hospitals (representing 71–78 percent of inpatients) and 161 of 254 rheumatologists (63 percent) agreed to identify and contact potentially eligible patients. After being contacted by the study researchers, agreement to participate was obtained from 150 of 202 patients at the University of Michigan hospitals (74 percent), 255 of 330 patients at Wayne State University hospitals (77 percent), and 230 of 527 SE-USF patients (44 percent). Of those who returned forms, 93 percent of potentially eligible Michigan women and 87 percent of potentially eligible Ohio women agreed to participate. During recruitment, the aims of the study, i.e., investigation of solvents as risk factors for connective tissue disease, were not disclosed to the participating hospitals, rheumatologists, and potential patients.

Written informed consent and the names of physicians and medical care facilities who provided treatment were obtained from each potential case. Using a standardized coding form (19), study rheumatologists and trained study personnel reviewed and abstracted patients' medical records, and study rheumatologists (TJL, MDM) verified the diagnosis of UCTD in all eligible patients. Dates at onset (as recorded in the medical chart) for selected clinical signs and laboratory abnormalities were recorded.

UCTD was defined as at least two documented signs, symptoms, or laboratory abnormalities that suggested a rheumatic disease but did not meet ACR classification criteria for any defined connective tissue disease. Patients with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) or other limited forms of SSc were not considered to have UCTD. Patients who had been given a previous diagnosis of SSc but who, after medical record review, did not satisfy the ACR criteria for SSc were eligible to be classified as UCTD. The date of diagnosis was defined as the date that UCTD or SSc (for those who did not meet ACR criteria) was first mentioned by the primary physician in the medical record. If the medical record mentioned the diagnosis year but not the month, July was assigned as the month of diagnosis.

Selection of controls

The Institute for Social Research at the University of Michigan used random digit dialing telephone sam-
pling (20) to identify population-based adult female controls. Within each state, controls were frequency-matched at a 3:1 control:case ratio to women with SSc on age at interview (within 5-year intervals), race/ethnicity (White, Black, or Hispanic), and geographic region (via the stratified random digit dialing). Because fewer UCTD cases than SSc cases were identified, the final control:UCTD ratio for this analysis was 10:1.

Questionnaire administration and exposure classification

A 30-minute interview was administered to all consenting, eligible cases and controls by trained personnel using Computer Assisted Telephone Interview software (SurveyCraft Pty, Ltd., Montmorency, Victoria, Australia). Women were asked whether they had ever worked at least once a week for 3 months or more in any of the 16 jobs or hobbies that commonly involve solvents and that had been implicated in published case reports. Each woman who reported ever participating in these activities was then asked the years in which she first and last participated, her job title, the specific tasks involved, the name of the place where she worked, and the type of industry or business. Each woman who had participated in these activities was also asked whether she worked with any of ten specific solvents or categories of solvents, the years in which she first and last used those solvents, whether she had worked directly with or near the solvent, and whether she had worn protective equipment (gloves, masks, clothing, etc.) while working with the solvent. The analysis assumed that among women with the same solvating properties. This definition excluded all aqueous solvent mixtures, such as ammonia-based cleaning agents, window cleaners, and citrus oil-based cleaners.

For each reported exposure to a solvent, an expert (DHG) in retrospective exposure assessment reviewed the detailed descriptions to verify exposure. All exposures were reviewed blinded to case or control status. Reference materials describing typical processes and materials used in these activities (including activities that were common in Michigan or Ohio, such as automotive manufacturing or rubber tire manufacturing) were reviewed to determine the types of solvents that are used in these tasks, the exposure levels associated with specific tasks, and the historic period in which specific solvents were used for specific tasks. A self-reported exposure was confirmed when 1) the solvent was commercially or industrially available during the period of reported use, 2) documentation existed that the solvent was used (or was a suitable substitute for solvents typically used) for the stated activity or purpose, and 3) the reported exposure was of non-trivial frequency, intensity, and duration. A self-reported exposure was not confirmed when exposure was considered implausible or exposure was of trivial frequency, intensity, or duration.

Statistical analyses

The average age difference between cases at diagnosis (46.0 years) and controls at interview (51.0 years) was 5 years, which resulted in an extended period of potential exposure for the controls. To adjust for this potential bias, adjusted odds ratios were calculated by post-hoc matching on both age at diagnosis and year of birth. For each potential risk factor, conditional logistic regression calculations were performed. A stratum was created for each case based on the month and year of UCTD diagnosis. Included in the stratum was the case diagnosed in that month and all controls who were born in the same year as that case. Each case with the same year of birth had a unique month of diagnosis, but those cases with the same year of birth had the same set of matched controls, so the same controls were included in multiple strata. To adjust for this repeated use of controls, variance estimates were calculated using the method of Barlow (21). Exposure was evaluated in each stratum: cases were considered exposed if exposure occurred prior to their diagnosis, and controls were considered exposed only if their exposure date was prior to the date of diagnosis of the case in that stratum (22). For controls in multiple strata, the exposure was reevaluated in each stratum. The analysis assumed that among women with the same year of birth, cases were a random sample from all eligible UCTD cases, and controls were a random sample of subjects from the population in which the cases arose.

All responses of “don’t know” or “refused” were excluded from the analyses of that risk factor. For exposures to which no case was exposed, conditional logistic regression calculations could not be performed, so crude odds ratios (i.e., OR = 0.00) were calculated using standard methods for case-control studies (23), and exact confidence intervals were calculated using StatXact 3 for Windows (CYTEL Software Corporation, Cambridge, Massachusetts). All other analyses were completed using the SAS statistical package (24) on a Sun Ultra 1 170 workstation (Sun Microsystems, Palo Alto, California). After expert review, one case who reported two solvent exposures...
and 22 controls who reported 28 solvent exposures did not report a corresponding date of exposure. Assigning the median age at exposure of all cases and controls within each exposure category to the missing dates for these cases and controls did not appreciably change the results (data not shown), and therefore exclusion of these missing values was felt to be justified.

RESULTS

In Michigan, 102 women with UCTD diagnosed between 1980 and 1991 agreed to participate, and in Ohio, 110 women with UCTD diagnosed between 1980 and 1992 agreed to participate. Three cases from Michigan and one case from Ohio could not be interviewed, and one case from Michigan and two cases from Ohio were excluded because their self-reported date of diagnosis could not be confirmed. Of the 205 cases, 115 were identified through HCIA, 56 through physician referrals, 31 from the University of Michigan Hospitals, 12 from Wayne State University Affiliated Hospitals, and 17 through the United Scleroderma Foundation; 22 of the 205 cases were identified by 2 sources and 2 cases were identified by 3 sources. The maximum number of documented clinical or laboratory manifestations of connective tissue disease among the final group of 205 cases was 30, while the mean was 10. The most frequent manifestation was a positive ANA (87.2 percent). Polyarthralgia, Raynaud’s phenomenon, rash, and fatigue were present in approximately 50 percent of cases, while myalgia, sicca syndrome, puffy hands, and at least one observation of an erythrocyte sedimentation rate >40 mm/hr were present in approximately 33 percent.

A total of 2,258 controls from both states were interviewed. The interview response rate for cases who returned consent forms was 97.3 percent in Michigan and 99.1 percent in Ohio, while for controls it was 80.0 percent in Michigan and 73.6 percent in Ohio. The 31 controls who did not report their date of birth and the 132 controls who reported in their medical history that their physician had previously diagnosed a connective tissue disease (SSc, SLE, UCTD or mixed connective tissue disease, rheumatoid arthritis, seronegative spondyloarthropathy, myositis, Sjögren’s syndrome, polymyalgia rheumatica, polyarthritis nodosa, or temporal arteritis) were excluded. Ethnicity, annual household income, education, and marital status were similar among the 205 cases and 2,095 controls, as were the frequencies of ever smoking cigarettes and consuming alcohol (table 1).

Of the 16 job categories specifically investigated, five showed significantly increased risks: furniture refinishing (odds ratio (OR) = 9.73, 95 percent confidence interval (CI) 1.48–63.90), perfume, cosmetic, or drug manufacturing (OR = 7.71, 95 percent CI 2.24–26.56), rubber product manufacturing (OR = 4.70, 95 percent CI 1.75–12.61), medical diagnostic or pathology laboratory jobs (OR = 4.52, 95 percent CI 2.27–8.97), and painting or paint manufacturing (OR = 2.87, 95 percent CI 1.06–7.76) (table 2). A summary category for exposure to any of the jobs with potential exposure to solvents was associated with UCTD (OR = 1.67, 95 percent CI 1.21–2.31). Among the jobs or hobbies that were associated with UCTD, the prevalence of exposure was low among both cases and controls. Review of these job descriptions revealed that, although the jobs were reported correctly, the specific tasks reported by the women often did not plausibly involve solvent use or solvent exposure. For example, jobs in medical diagnostic and pathology laboratories were frequently phlebotomy, centrifugation, and cell counting in hematology laboratories; these activities typically do not involve solvents other than isopropanol or aqueous cleaning agents. Thus, although these job categories were associated with UCTD, the descriptions of the job tasks did not confirm the use of or exposure to solvents.

All exposures to specific solvents and categories of solvents were assessed both by self-report and by expert review (table 3) to address over-reporting of self-reported occupational solvent exposure (25, 26). Paint thinners or removers were associated with UCTD both by self-report (OR = 2.80, 95 percent CI 1.86–4.20) and after expert review (OR = 2.73, 95 percent CI 1.80–4.16). Self-reported exposure to mineral spirits was associated with an increased risk of UCTD (OR = 1.55, 95 percent CI 0.93–2.58), but after expert review of these exposures the association became stronger and achieved statistical significance (OR = 1.81, 95 percent CI 1.09–3.02). None of the self-reported or expert-reviewed chlorinated solvents (TCA, TCE, or Perc) was associated with UCTD. Gasoline, xylene, benzene, and toluene were not associated with UCTD by self-report or after expert review.

The category “other solvents” captured exposures to a specific solvent, a solvent product, or a solvent mixture that was not one of the nine specific solvents queried. This category included a wide range of chemicals (e.g., degreasers), including those for which the ingredients were not always specified, and thus it may not have reflected exposure to any specific chemical or family of chemicals. Exposure to “other solvents” was associated with UCTD by self-report (OR = 2.10, 95 percent CI 1.22–3.60) and after expert review (OR = 2.40, 95 percent CI 1.31–4.42).

Exposure to any of the solvents (including “other solvents”) was associated with UCTD by self-report (OR = 2.14, 95 percent CI 1.52–3.01) and after expert
review (OR = 2.32, 95 percent CI 1.61–3.34). The 52 cases exposed to any of the solvents reported a total of 87 individual exposures across the ten solvent categories, and 70 (80.5 percent) of these exposures were confirmed by expert review, while the 364 controls with any solvent exposure reported 649 individual exposures, of which 500 (77.0 percent) were confirmed. Addition of a variable for smoking status did not change the odds ratios for any of the solvent exposure categories (data not shown).

Paint thinners or removers and mineral spirits were the most common exposures reported by cases and controls, and expert review largely confirmed these self-reported exposures. The detailed job and hobby descriptions revealed that paint thinners or removers, mineral spirits, gasoline, and “other solvents” were all frequently used to clean paint brushes and paint supplies. Women with self-reported or expert-confirmed exposure to any of these four petroleum distillates were significantly more likely to report exposure to any of the other three. Aggregate exposure categories were created to assess the potential impact of these related exposures, and odds ratios, adjusted for age and year of birth, were generated for these exposure categories using conditional logistic regression models, where age at exposure was defined as the earliest age at exposure to any of the included solvents. Each adjusted odds ratio for these summary exposure categories was approximately 2.50 and each 95 percent confidence interval did not include 1.00 (data not shown).

In order to explore the possibility that concurrent exposure to multiple petroleum distillate solvents might explain some of the associations with UCTD, the authors constructed a series of hierarchical models that included each of these four solvents, then each combination of any two solvents, then each combination of any three solvents, and then a final model that included all four solvents. The likelihood ratio test was used to determine whether any of the complex models were better than the models with individual solvent categories at predicting UCTD. The “best” models (defined as the models with the highest chi-square statistics from the likelihood ratio tests) all included paint thinners and removers, and always yielded an adjusted odds ratio for paint thinners or removers >2.00 with a confidence
The risk of developing UCTD increased by 4 percent with each additional year of confirmed exposure to "other solvents" (OR = 1.05, 95 percent Cl 1.02-1.07). The hierarchical models indicated that paint thinners or removers was the exposure category that were consistently and significantly associated with UCTD. The adjusted odds ratio for "other solvents" identifies a particular chemical or product that may account for the increased risk. However, the association is not explained by the other risk factors investigated in this study, nor is it explained by concurrent exposure to the other solvents in this study. The term "paint thinner" is often used interchangeably with mineral spirits, white spirit, naphtha, Stoddard solvent, and Varso, all of which refer to petroleum distillation fractions that typically boil between 95°C and 210°C and which contain mixtures of paraffinic, olefinic, aromatic, and naphthenic hydrocarbons with 5 to 12 carbon atoms (27). Paint removers typically contain combinations of benzene, methanol, acetone, toluene, TCA, methylene chloride, mineral spirits, phenols, cresols, detergents, and concentrated alkali (28, 29). Subjects who reported these exposures may not have known the specific ingredients to which they were exposed, and the tendency for cases and controls to have reported concurrent exposure to these petroleum distillates makes it difficult to identify a particular chemical or product that may account for the increased risk. However, the association between UCTD and paint thinners or removers remained after all adjustments for multiple exposures and potential confounders, and all summary categories for exposure to any of the petroleum distillates were consistently and significantly associated with UCTD. The hierarchical models indicated that paint thinners or removers was the exposure category that most accounted for the significant associations with UCTD.

**DISCUSSION**

These results suggest that exposure to paint thinners or removers is associated with UCTD in women. This association is not explained by the other risk factors investigated in this study, nor is it explained by concurrent exposure to the other solvents in this study. The term "paint thinner" is often used interchangeably with mineral spirits, white spirit, naphtha, VM & P naphtha, Stoddard solvent, and Varso, all of which refer to petroleum distillation fractions that typically boil between 95°C and 210°C and which contain mixtures of paraffinic, olefinic, aromatic, and naphthenic hydrocarbons with 5 to 12 carbon atoms (27). Paint removers typically contain combinations of benzene, methanol, acetone, toluene, TCA, methylene chloride, mineral spirits, phenols, cresols, detergents, and concentrated alkali (28, 29). Subjects who reported these exposures may not have known the specific ingredients to which they were exposed, and the tendency for cases and controls to have reported concurrent exposure to these petroleum distillates makes it difficult to identify a particular chemical or product that may account for the increased risk. However, the association between UCTD and paint thinners or removers remained after all adjustments for multiple exposures and potential confounders, and all summary categories for exposure to any of the petroleum distillates were consistently and significantly associated with UCTD. The hierarchical models indicated that paint thinners or removers was the exposure category that most accounted for the significant associations with UCTD.

**TABLE 2.** Self-reported jobs and hobbies with potential exposure to solvents among 205 undifferentiated connective tissue disease (UCTD) cases, diagnosed between 1980 and 1992, and 2,095 controls in Michigan and Ohio

<table>
<thead>
<tr>
<th>Job or hobby</th>
<th>Cases exposed No. (total*)</th>
<th>Controls exposed No. (total*)</th>
<th>Odds ratio†</th>
<th>95% Cl‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furniture refinishing</td>
<td>2 (205)</td>
<td>4 (2,094)</td>
<td>9.73</td>
<td>1.48-63.9</td>
</tr>
<tr>
<td>Perfume, cosmetic, or drug manufacturing</td>
<td>4 (205)</td>
<td>5 (2,094)</td>
<td>7.71</td>
<td>2.24-26.56</td>
</tr>
<tr>
<td>Rubber product manufacturing</td>
<td>5 (205)</td>
<td>13 (2,094)</td>
<td>4.70</td>
<td>1.75-12.61</td>
</tr>
<tr>
<td>Medical diagnostic or pathology laboratory</td>
<td>13 (205)</td>
<td>38 (2,092)</td>
<td>4.52</td>
<td>2.27-8.97</td>
</tr>
<tr>
<td>Painting or paint manufacturing</td>
<td>5 (205)</td>
<td>22 (2,090)</td>
<td>2.87</td>
<td>1.06-7.76</td>
</tr>
<tr>
<td>Leather tanning or shoe manufacturing</td>
<td>1 (205)</td>
<td>6 (2,093)</td>
<td>1.83</td>
<td>0.20-16.3</td>
</tr>
<tr>
<td>Chemical or dye manufacturing</td>
<td>1 (204)</td>
<td>6 (2,093)</td>
<td>1.61</td>
<td>0.17-15.21</td>
</tr>
<tr>
<td>Plastics industry</td>
<td>6 (204)</td>
<td>46 (2,089)</td>
<td>1.60</td>
<td>0.67-3.78</td>
</tr>
<tr>
<td>Dry cleaning</td>
<td>9 (205)</td>
<td>79 (2,083)</td>
<td>1.38</td>
<td>0.68-2.78</td>
</tr>
<tr>
<td>Film developing or publishing</td>
<td>11 (204)</td>
<td>96 (2,088)</td>
<td>1.32</td>
<td>0.67-2.61</td>
</tr>
<tr>
<td>Professional cleaning or maintenance</td>
<td>10 (205)</td>
<td>108 (2,089)</td>
<td>1.28</td>
<td>0.67-2.47</td>
</tr>
<tr>
<td>Hairdressing</td>
<td>7 (205)</td>
<td>61 (2,094)</td>
<td>1.20</td>
<td>0.53-2.69</td>
</tr>
<tr>
<td>Arts and crafts using glues, paints, or solvents</td>
<td>2 (205)</td>
<td>38 (2,089)</td>
<td>0.67</td>
<td>0.16-2.87</td>
</tr>
<tr>
<td>Fiberglass industry</td>
<td>0 (205)</td>
<td>14 (2,093)</td>
<td>0.00</td>
<td>0.00-3.08§</td>
</tr>
<tr>
<td>Vinyl chloride manufacturing</td>
<td>0 (205)</td>
<td>1 (2,094)</td>
<td>0.00</td>
<td>0.00-398.00§</td>
</tr>
<tr>
<td>Petroleum refining</td>
<td>0 (205)</td>
<td>1 (2,094)</td>
<td>0.00</td>
<td>0.00-398.40§</td>
</tr>
<tr>
<td>Any of the above activities</td>
<td>56 (204)</td>
<td>438 (2,080)</td>
<td>1.67</td>
<td>1.21-2.31</td>
</tr>
</tbody>
</table>

* Excludes responses of "don't know" and "refused".
† Adjusted for age and year of birth.
‡ CI, confidence interval.
§ Crude odds ratio with exact 95% CI.

Interval that excluded the null value. After controlling for exposure to paint thinners or removers, mineral spirits and "other solvents" were not associated with UCTD. The adjusted odds ratio for "other solvents" was elevated and approached statistical significance in the models that included paint thinners or removers or gasoline, but not in the models that included both paint thinners or removers and mineral spirits.

The time interval between first exposure and UCTD diagnosis was used to investigate whether an increased duration of exposure to solvents was associated with increasing risk of UCTD. There were no associations between UCTD and the duration of confirmed exposure to gasoline, toluene, TCE, or TCA; a dose-response could not be evaluated for benzene, xylene, or Perc because zero cases had confirmed exposure. The risk of developing UCTD increased by 4 percent with each additional year of confirmed exposure to paint thinners or removers (OR = 1.04, 95 percent CI 1.02-1.06), by 3 percent with each additional year of confirmed exposure to mineral spirits (OR = 1.03, 95 percent CI 1.00-1.05), and by 5 percent with each additional year of confirmed exposure to "other solvents" (OR = 1.05, 95 percent CI 1.02-1.07).
TABLE 3. Self-reported and expert-reviewed exposure to solvents among 205 undifferentiated connective tissue disease (UCTD) cases, diagnosed between 1980 and 1992, and 2,095 controls in Michigan and Ohio

<table>
<thead>
<tr>
<th>Type of solvent</th>
<th>Cases exposed</th>
<th>Controls exposed</th>
<th>Odds ratio†</th>
<th>95% Cl†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (total*)</td>
<td>No. (total*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydrocarbons</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paint thinners or removers</td>
<td>36 (201)</td>
<td>185 (2,056)</td>
<td>2.80</td>
<td>1.86–4.20</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>32 (201)</td>
<td>167 (2,055)</td>
<td>2.73</td>
<td>1.80–4.16</td>
</tr>
<tr>
<td>Mineral spirits, naphtha or white spirits</td>
<td>18 (191)</td>
<td>164 (2,036)</td>
<td>1.55</td>
<td>0.93–2.58</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>18 (191)</td>
<td>142 (2,036)</td>
<td>1.81</td>
<td>1.09–3.02</td>
</tr>
<tr>
<td>Gasoline</td>
<td>7 (199)</td>
<td>52 (2,063)</td>
<td>1.89</td>
<td>0.86–4.16</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>3 (199)</td>
<td>40 (2,062)</td>
<td>1.07</td>
<td>0.32–3.55</td>
</tr>
<tr>
<td>Xylene</td>
<td>2 (188)</td>
<td>14 (2,033)</td>
<td>1.88</td>
<td>0.45–7.86</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>0 (188)</td>
<td>8 (2,032)</td>
<td>0.00</td>
<td>0.00–6.36§</td>
</tr>
<tr>
<td>Benzene</td>
<td>3 (187)</td>
<td>33 (2,034)</td>
<td>1.18</td>
<td>0.36–3.85</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>0 (186)</td>
<td>13 (2,034)</td>
<td>0.00</td>
<td>0.00–3.60§</td>
</tr>
<tr>
<td>Toluene</td>
<td>1 (169)</td>
<td>24 (2,029)</td>
<td>0.52</td>
<td>0.07–3.86</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>1 (169)</td>
<td>16 (2,029)</td>
<td>0.77</td>
<td>0.10–5.78</td>
</tr>
<tr>
<td><strong>Chlorinated solvents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichloroethylene (TCE)</td>
<td>1 (189)</td>
<td>15 (2,015)</td>
<td>0.88</td>
<td>0.11–6.95</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>1 (189)</td>
<td>8 (2,014)</td>
<td>1.67</td>
<td>0.19–14.90</td>
</tr>
<tr>
<td>Trichloroethane (TCA)</td>
<td>2 (189)</td>
<td>24 (2,007)</td>
<td>0.98</td>
<td>0.22–4.36</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>2 (189)</td>
<td>16 (2,007)</td>
<td>1.55</td>
<td>0.34–7.18</td>
</tr>
<tr>
<td>Perchloroethylene (Perc)</td>
<td>0 (191)</td>
<td>21 (2,022)</td>
<td>0.00</td>
<td>0.00–2.03§</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>0 (191)</td>
<td>17 (2,022)</td>
<td>0.00</td>
<td>0.00–2.57§</td>
</tr>
<tr>
<td>Other solvents</td>
<td>17 (197)</td>
<td>117 (2,048)</td>
<td>2.10</td>
<td>1.22–3.60</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>13 (197)</td>
<td>73 (2,048)</td>
<td>2.40</td>
<td>1.31–4.42</td>
</tr>
<tr>
<td>Any of the above solvents</td>
<td>52 (194)</td>
<td>364 (2,005)</td>
<td>2.14</td>
<td>1.52–3.01</td>
</tr>
<tr>
<td>Confirmed by expert review</td>
<td>44 (190)</td>
<td>292 (1,982)</td>
<td>2.32</td>
<td>1.61–3.34</td>
</tr>
</tbody>
</table>

* Excludes responses of "don't know" and "refused".
† Adjusted for age and year of birth.
‡ CI, confidence interval.
§ Crude odds ratio with exact 95% CI.

Neither self-reported nor expert-reviewed exposure to TCA, TCE, or Perc was associated with statistically significant increases in risk of UCTD. These chlorinated solvents were of particular interest in SSc and SSc-related conditions because of published case reports (15–17, 30–32). Most of the women who reported exposure worked in the dry cleaning industry. Dry cleaning operations have used TCA, TCE, Perc, and mineral spirits as cleaning solvents, but have also used non-chlorinated petroleum distillates for spot- and stain-removal (33). Exposure to this class of petroleum distillates, rather than to TCA, TCE, or Perc, may account for the reported association between SSc or other CTD and dry cleaning or other solvent-based industries. A recent case series noted a significantly higher frequency of exposure to solvents in cases with SSc compared with controls with other connective tissue disease, and although TCA and Perc were individually identified, stronger associations were seen for "petroleum solvent" and for any "organic solvent" (34). Many additional case reports of solvent exposure include a history of exposure to petroleum distillates (35–39). Previous studies that have focused on the chlorinated solvents may have overlooked the importance of exposure to these petroleum distillates, but paint thinners or removers, mineral spirits, and other petroleum distillates merit increased scrutiny in future investigations of occupational exposure in patients.
with CTD. The concurrence of significantly increased risks associated with painting or paint manufacturing and with paint thinners or removers further supports a role for the petroleum distillates in UCTD.

Exposures to the hydrocarbons benzene, xylene, and toluene were rare among the cases and controls. Benzene, xylene, and toluene have been reported to induce localized SSC-like diseases in the areas of direct contact, unlike the chlorinated solvents, which are hypothesized to generate a systemic response (40). These results do not support a role for these hydrocarbons in UCTD.

The 16 jobs or hobbies that were chosen for this investigation had been reported in previous case reports or were likely to involve the particular solvents that had been implicated in those case reports. This analysis used job and hobby descriptions to ascertain exposure to specific solvents. As such, the expert review to confirm self-reported solvent exposures did not attempt to confirm the accuracy of the job activity, i.e., whether all women who reported dry cleaning actually worked in that industry. For example, cashiers at dry cleaning stores may have had different opportunities for exposure to solvents than dry cleaning workers who handled the clothes throughout the cleaning process, and not all of the workers who handled clothes were exposed to the solvents of interest for this analysis. The analyses of jobs (table 2) did not distinguish between the cashier and the clothes handler (i.e., both would be considered exposed to “dry cleaning”), but the analyses of exposures confirmed by expert review (table 3) did reflect the likelihood of exposure to the specific solvents. Thus, the analyses by solvent are believed to be more precise than the analyses by job.

With the exception of work in a medical diagnostic or pathology laboratory, all of the jobs or hobbies with significantly increased associations were based on few exposed cases and controls, and the wide confidence intervals reflect this imprecision. A high proportion of the cases and controls who reported working in a medical diagnostic or pathology laboratory described their jobs as x-ray technicians or hematology laboratory technicians, who do typically use solvents. No other patterns emerged from the descriptions of perfume, cosmetic, or drug manufacturing, furniture refinishing, painting or paint manufacturing, or rubber product manufacturing to suggest that respondents systematically and incorrectly reported their exposure histories. Other factors or exposures besides solvents in those jobs may account for the increased but statistically nonsignificant odds ratios, and further investigation of these activities is warranted.

In this study, the authors used a combination of close-ended and open-ended questions to identify all potential occupational solvent exposures, then assessed each reported exposure against referenced standards to confirm solvent exposures of non-trivial frequency, intensity, and duration. The validity of self-report supplemented by expert review depends on the sensitivity and specificity of the data collection tool, the subjects' knowledge of their occupational exposures, and the use of an appropriate “gold standard” for the expert review. Fritschi et al. (26) examined the use of self-reported versus expert-assessed occupational exposure data in case-control studies and concluded that expert assessment substantially reduces the misclassification introduced by use of only self-reported data.

Although autoimmune and rheumatic diseases are more prevalent in women than in men, women are less likely than men to experience solvent exposures at work. The authors attempted to capture all potential solvent exposures by asking about specific solvent exposures in particular jobs and hobbies followed by open-ended exploration of the solvent use, and by asking open-ended questions about any other potential activities in which specific solvents were used. Additional studies of UCTD in both women and men may be required to fully describe the potential role of solvents in the development of UCTD.

Crucial to understanding UCTD, and to interpreting the relevance of potential etiologic factors, will be longitudinal data on the natural history of UCTD and its potential relation to the clinical and laboratory manifestations that are characteristic of SSC or other autoimmune entities (41–44). Our ascertainment of UCTD cases concurrently with SSC cases, and the reclassification of women considered to have SSC but who did not meet the ACR criteria, generated a UCTD group that may be more similar to SSC than to other rheumatic diseases or to other patients with undifferentiated connective tissue syndromes. In addition, the 12-year span over which incident cases were retrospectively collected may have selected for patients with slowly progressing disease. These concerns will remain until classification criteria for UCTD are adopted. However, the consistent manner in which we recruited cases, abstracted and reviewed medical records, randomly selected controls, and collected exposure information that was subjected to blinded expert review insures appropriate control of information bias.

Another concern about the validity and generalizability of investigations of UCTD is the diversity of patient populations selected in different studies. However, the most common clinical and laboratory features of these patients with UCTD—positive antinuclear antibodies (ANA), polyarthralgia, Raynaud’s
phenomenon, arthritis, rash, fatigue, myalgia, sicca syndrome, puffy hands, and an erythrocyte sedimentation rate >40 mm/hr—are those listed in other reports of undifferentiated connective tissue syndromes (41, 45). The women with UCTD in these analyses averaged 10 documented manifestations of connective tissue disease, suggesting that referring physicians and study rheumatologists recognized in these women a constellation of signs and symptoms that reflected a more definable condition than a syndrome of subjective complaints.

Recruitment of cases from multiple sources served to mitigate against selection bias. Although the authors were unable to estimate the exact proportion of all cases with UCTD that were captured, an examination of recruitment at the University of Michigan Hospitals and Wayne State University Affiliated Hospitals, where access to medical records facilitated the identification of potentially eligible cases, revealed that 86 percent of eligible SSc and UCTD cases participated, and that participation did not differ by age group or disease severity (46). This assessment of recruitment of eligible cases was limited to the patients referred to these two academic medical centers in Michigan, and is slightly higher than the overall participation rate of between 75 and 80 percent of all eligible cases in Michigan and Ohio.

In summary, the authors have identified cases of UCTD in women in whom signs and symptoms of connective tissue disease were present but not sufficient to meet the diagnostic criteria for any other systemic rheumatic disease. After expert review, blinded to case or control status, UCTD was associated with paint thinners or removers, mineral spirits, and "other solvents." These petroleum distillates appear to increase the risk of UCTD in women.

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REFERENCES


