

Scleroderma and Solvent Exposure Among Women

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Background

- Systemic Sclerosis (SSc)
 - Autoimmune connective tissue disease
 - Thickening & tightening skin
 - Analogous internal organ changes
- Major pathogenic events
 - Aberrant vascular reactivity
 - Distorted endothelial cytoarchitecture
 - Immune dysfunction
 - Increased collagen synthesis

Etiology

- Unknown cause
- Extremely complex pathogenesis
 - No single, unifying hypothesis
- Key cell types involved
 - Fibroblasts
 - Endothelial cells
 - Immune cells

Epidemiology

- Annual U.S. incidence rate
 - 20 per 1,000,000
- U.S. prevalence
 - 240 per 1,000,000
- Representative studies difficult
 - Case definition and rarity
 - Case reports and hospital-based series
 - Few rigorous epidemiologic studies

University of Michigan Study

- Case-control study in Michigan and Ohio
- Objective:
 - Systematically investigate potential associations between SSc and environmental, medical, and other factors in population-based epidemiologic study
- Cases
 - Women 18 years or older at diagnosis
 - Diagnosed Jan. 1, 1980 – Dec. 31, 1991
 - Jan. 1, 1980 – Dec. 31, 1992 in Ohio

Case Identification

- Four potentially overlapping sources
 - University of Michigan hospitals and Wayne State University-affiliated hospitals
 - National hospital discharge code database
 - HCIA, Ann Arbor, MI
 - Mailings to MI and OH rheumatologists
 - Other relevant specialists, e.g., dermatology
 - Mailings to Southeast Michigan Chapter of Scleroderma Foundation
- Estimated 75%-80% eligible women

Case Definition

- Medical record review
 - 1980 ACR classification criteria
 - Major criterion: Proximal scleroderma
 - Minor criteria (2 or more)
 - Sclerodactyly, digital pitting scars, bibasilar pulm. fibros.
 - Signs and symptoms characteristic of SSc
 - Sclerodactyly or CREST
 - Calcinosis, *Raynaud's* Phenomenon, *Esophageal* dysmotility, Sclerodactyly, *Telangiectasias*
- Estimated 80% of all incident cases in MI

Control Selection

- RDD telephone sampling
 - Frequency-matched on age, race, and region
 - 80% response in MI
 - 74% response in OH
 - 3:1 control:case ratio

Telephone Interviews

- UM Institute for Social Research
 - August, 1992 through February, 1996
- 30-minute telephone interview
 - Demographics, family history, occupations and hobbies, reproductive history, cigarette and alcohol use, personal medical history, medical devices

Exposure Ascertainment

- Occupations and hobbies that have high probability of exposure to solvents
 - At least once a week for 3 months or more
 - Ever work with solvents in those occupations and hobbies
- Ever work with individual solvents
 - At least once a week for 3 months or more

Occupations and Hobbies

Ever work at least once per week for 3 months or more in any of 16 jobs or hobbies

- Dry cleaning
- Chemical or dye mfg.
- Petroleum refining
- Vinyl chloride mfg.
- Plastics industry
- Rubber product mfg.
- Painting or paint mfg.
- Furniture refinishing
- Hair dressing
- Medical or diagnostic or pathology laboratory
- Prof. cleaning or maint.
- Film devel. or publish.
- Perf., cosm., drug mfg.
- Fiberglass industry
- Leather tanning or shoe mfg.
- Arts and crafts

Occupations and Hobbies (2)

- If yes, open-ended questions
 - Years in which participant first & last worked
 - Job title
 - Specific tasks involved
 - Name of place at which participant worked
 - Type of industry or business
- Ever work with 9 solvents or categories
 - Years in which participant first & last used
 - Directly or near; wore protective clothing

Occupations and Hobbies (3)

- Trichloroethylene (TCE)
- Perchloroethylene (Perc)
- Trichloroethane (TCA)
- Paint thinners / removers
- Mineral spirits, naphtha, or white spirits
- Gasoline
- Toluene
- Xylene
- Benzene
- Detailed use during occupations and hobbies
 - “Other solvents”
- For all women, ever use individual solvents
 - Details
 - “Other solvents”

Expert Review

- Solvent exposures reviewed by expert in exposure assessment (DHG)
 - Reviewed blinded to case or control status
 - Reference materials
 - Typical processes and materials used in these activities
 - Types of solvents used in these tasks
 - Exposure levels associated with specific tasks
 - Historical periods in which specific solvents were used for specific tasks

Expert Review (2)

- Confirmed exposures:
 - Solvent was commercially or industrially available during the period of reported use
 - Documentation existed that the solvent was used (or was a suitable substitute for solvents typically used)
 - Exposure was of nontrivial frequency, intensity, and duration
- Not confirmed exposures:
 - Implausible or trivial frequency, intensity, or duration

Statistical Analysis

- Adjusted for year of birth and attained age
 - Compared each case to all controls who were born in the same year
 - Solvent exposures only considered if they occurred before the case's age at diagnosis
 - Many cases born in the same year, so controls used in multiple strata
 - Conditional logistic regression for ORs & CIs
 - Estimates relative risk (RR) of SSc as a function of exposure to TCE or other solvents

Study Population

	Cases	Controls
Number	660	2,227
Age at interview	56.3	51.4
Age at diagnosis	49.5	n/a
White	86.8 %	89.5 %
Current smoker	14.9 %	23.5 %
High school graduate	84.2 %	85.2 %

TCE Exposure

	<u>Cases</u>		<u>Controls</u>	
	No.	Total	No.	Total
Any TCE reported	8	606	15	2,138
OR (95% CI)		2.0 (0.8 – 4.8)		
Conf. by expert review	4	606	8	2,137
OR (95% CI)		1.9 (0.6 – 6.6)		

TCA Exposure

	<u>Cases</u>		<u>Controls</u>	
	No.	Total	No.	Total
Any TCA reported	9	612	25	2,131
OR (95% CI)		1.5 (0.7 – 3.2)		
Conf. by expert review	4	611	17	2,131
OR (95% CI)		0.9 (0.3 – 2.8)		

Perc Exposure

	<u>Cases</u>		<u>Controls</u>	
	No.	Total	No.	Total
Any Perc reported	7	616	21	2,146
OR (95% CI)		1.4 (0.6 – 3.4)		
Conf. by expert review	5	616	17	2,146
OR (95% CI)		1.1 (0.4 – 2.9)		

Jobs & Hobbies with Potential TCE Exposure

	<u>Cases</u>	<u>Ctrls</u>	<u>OR</u>	<u>95% CI</u>
Professional cleaning or maintenance	42	116	1.8	1.3 – 2.7
Plastics industry	17	52	1.3	0.7 – 2.3
Rubber product manufacturing	3	14	0.9	0.3 – 3.3

Results Summary

- TCE exposure was positively but not statistically significantly associated with SSc
 - Low frequency of exposure in both cases and controls
 - One-half of reported exposures not confirmed
 - But increased risk remained
 - Over-reporting did not appear to be the only reason for the potential increased risk

TCE & Anti-Scl-70 Antibodies

- Anti-Scl-70 Ab (Anti-topoisomerase I)
 - Highly specific for SSc
 - Prevalence: 26% SSc and 34% Diffuse SSc
 - Nietert et al. case-control study: positive association between TCE & SSc in men only who tested positive for anti-Scl-70 Ab
 - Solvents bind topoisomerase & trigger autoimmune response?
- Anti-Scl-70 Ab known for 255 of 660 SSc
 - 0 of 8 SSc cases exposed to TCE had (+) Abs

Undifferentiated Connective Tissue Disease (UCTD)

- CTD signs & symptoms overlap
 - Specific diagnosis not immediately apparent
 - 15%-25% patients present with non-specific or overlapping rheumatic symptoms
- UCTD case group
 - Did not meet ACR criteria for any CTD but had at least 2 documented signs, symptoms, or laboratory abnormalities

TCE & UCTD

	<u>Cases</u>		<u>Controls</u>	
	No.	Total	No.	Total
Any TCE reported	1	189	15	2,015
OR (95% CI)		0.8 (0.1 – 7.0)		
Conf. by expert review	1	189	8	2,014
OR (95% CI)		1.7 (0.2 – 14.9)		

Study Strengths

- Large study population from representative area
- High levels of participation
- Extensive data collection
- Expert review of specific solvents

Study Limitations

- Low frequency of reported exposures
- Expert review only for reported exposures
 - No information on other unreported exposures
- Potential selection and information biases
 - Over 80% of eligible SSc patients & controls
 - Standardized interview
- Study included only women

Conclusions

- Suggestive evidence of an association between TCE exposure and risk of SSc
 - No conclusive evidence to date
- Exposure assessment is critical
 - Identifying & verifying specific exposures in populations are major challenges
 - Future studies should also consider bystander exposures

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