University of Cincinnati

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I, Pai-Yue Lu, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Identifying a Link Between Uranium Exposure and Systemic Lupus Erythematosus in a Community Living near a Uranium Plant

Student's name: Pai-Yue Lu

This work and its defense approved by:

Committee chair: Erin Nicole Haynes, Dr.P.H.
Committee member: John Harley, M.D. Ph.D.
Committee member: Susan Pinney, Ph.D.
Committee member: Changchun Xie, PHD
Identifying a link between uranium exposure and systemic lupus erythematosus in a community living near a uranium plant

A thesis submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of

Master of Science in Clinical and Translational Research in the Department of Environmental Health of the College of Medicine

by

Pai-Yue Lu

M.D. New York Medical College

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Committee Chair: Erin Haynes, Dr.P.H.
ABSTRACT

Objective: Effects of environmental exposures on the development of systemic lupus erythematosus (SLE) are relatively unexplored in SLE pathogenesis. Our objective was to explore the hypothesis that SLE patients will be found more frequently in community members exposed to high prior uranium exposure in the Fernald Community Cohort (FCC).

Methods: A nested case control study was performed using data from the Fernald Community Cohort (FCC). The FCC is a volunteer population that lived within 5 miles of a uranium ore processing plant in Fernald, OH during plant operation (1951-1989) and followed from 1990-2008 in a medical monitoring program. Uranium plant workers were excluded. Potential SLE cases were identified with searches for lupus-associated ICD-9 codes and medication code for hydroxychloroquine. Cases were confirmed using American College of Rheumatology classification criteria and medical records. Each case was matched to four age-, race-, and sex-matched controls. Sera from potential cases and controls were screened for autoantibodies. Cumulative uranium particulate exposure was calculated using a dosimetry model developed by the US Centers for Disease Control and Prevention. Logistic regression with covariates (smoking, alcohol, and family history of SLE) was used to calculate odds ratios (OR) with 95% confidence intervals (CI).

Results: The FCC includes 4,187 individuals with background uranium exposure, 1,273 with moderate exposure, and 2,756 with higher exposure. SLE was confirmed in 23 of 26 individuals with a lupus ICD9 code, and in 2 of 43 other individuals prescribed hydroxychloroquine. The female:male ratio was 5.25:1. Of the 25 SLE cases, 12 were in the higher exposure group. SLE was associated with higher exposure (OR 3.92, 95% CI 1.13-13.58, p = 0.031).

Conclusion: High uranium exposure is associated with SLE relative to matched controls in this sample of uranium exposed individuals. Potential explanations for this relationship include
potential autoimmune or estrogen effects of uranium, somatic mutation, epigenetic effects, or effects of some other unidentified accompanying exposure.
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**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ANA</td>
<td>Anti-nuclear antibody</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>DOE</td>
<td>Department of Energy</td>
</tr>
<tr>
<td>FCC</td>
<td>Fernald Community Cohort</td>
</tr>
<tr>
<td>FMPC</td>
<td>Feed Materials Production Center</td>
</tr>
<tr>
<td>ICD-9</td>
<td>International Classifications of Diseases, 9th revision</td>
</tr>
<tr>
<td>IIF</td>
<td>Indirect immunofluorescence</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>
**Introduction**

Systemic lupus erythematosus (SLE) is a chronic, heterogeneous autoimmune disease. The estimated prevalence of SLE in the general population is between 20 and 70 per 100,000 individuals [1]. Women of child-bearing age are affected nine times more often than men. The development of SLE involves both an individual’s genetically determined immune system and environmental factors. The genetic contribution is illustrated by an SLE heritability of 66% [2, 3]. Many environmental factors have been investigated, and compelling evidence has associated silica quartz dust and Epstein Barr virus with increased SLE risk [4-9]. More recently, meta-analyses have shown an association with smoking [10, 11]. Other studies have assessed the role of solvents, insecticides, and lipstick, though their outcomes have not yielded reliable associations [11-16]. Identification of previously unassociated exposures often requires cohort or community studies. Such studies investigating an increase of SLE cases have previously been published [17-19].

**The Fernald Community Cohort**

Fernald, OH was the location of a United States Department of Energy (DOE) Feed Materials Production Center (FMPC) until 1988. The FMPC’s primary function was to convert uranium ore concentrates and materials received from other stages of nuclear weapons production to uranium metal. The FMPC processed approximately $3.62 \times 10^8$ kg of uranium, along with smaller amounts of thorium [20]. During plant operation between 1951 and 1988, approximately 310,000 kg of uranium were released into the air, and 99,000 kg were released into the water [20]. The community living around the plant filed a class action lawsuit when they learned of the contamination [21]. The settlement resulted in one of the largest medical monitoring programs of its kind in the country: The Fernald Community Cohort (FCC), as has been previously described [20, 21]. Community residents living near the plant were recruited through local media to voluntarily enroll in the study. Ultimately, 9,782 individuals were enrolled, which represents
approximately a quarter of the eligible population with high, medium, and minimal exposure to uranium. Medical monitoring of individuals included physical exams, questionnaires, and lab tests at regular intervals.

Upon an initial International Classifications of Diseases, 9th revision (ICD-9) code search of the FCC for systemic lupus erythematosus (ICD-9 code 710.0), 26 individuals were identified. This more than 3-fold excess of reported SLE cases in a carefully followed community provided an opportunity to evaluate the relationship between environmental uranium exposure and SLE.

Our objective was to explore the hypothesis that SLE patients will be found more frequently in community members exposed to high prior uranium exposure in the Fernald Community Cohort (FCC).

Methods

A nested case control study was performed with data from the FCC.

Population

The FCC is comprised of voluntarily enrolled individuals who lived within 5 miles of an active uranium ore processing facility in Fernald, OH for at least two consecutive years between January 1, 1952 and December 18, 1984 [21]. These individuals were recruited through television, radio, and newspaper announcements between 1990 and 1991, and they were followed until 2008. No uranium plant workers were included in this study.

Case Identification

Potential FCC SLE cases were identified with searches of the FCC electronic database for ICD-9 codes associated with lupus (710.0 and 695.4) and a medication code search for
hydroxychloroquine. FCC records and medical charts were retrieved on potential cases and reviewed by a physician (PL).

Cases were confirmed using an operational definition that included American College of Rheumatology (ACR) classification criteria, presence of auto-antibodies, and medical record documentation. Cases were considered either “definite,” “possible”, or not SLE. The operational case definition criteria are described in Table 1. For definite and possible SLE cases, the date of diagnosis was extracted or estimated from Fernald records and outside medical records.

Control Selection

A pool of potential controls was isolated from adults in the cohort. This pool excluded individuals who had been considered as potential cases. Additional exclusion criteria included non-white race, total white count less than \(4 \times 10^3/\text{mm}^3\), absolute lymphocyte count less than \(1.5 \times 10^3/\text{mm}^3\), or platelet count less than \(100 \times 10^3/\text{mm}^3\). From this pool, a maximum of four age-, race-, and sex-matched controls were selected for every case.

For comparison, analysis with rheumatoid arthritis (RA), another connective tissues disease with female predominance, was also performed. These cases were identified in the FCC through a search for the ICD-9 code 714.0 for RA.

Serum Analysis

Serum of potential controls was screened for the presence of auto-antibodies. Attempts were made to select serum closest to the date of diagnosis. Serum analysis for auto-antibody testing was performed by the Oklahoma Medical Research Foundation Clinical Lab. Over the past five years, the Bioplex™ 2200 multiplex immunoassay has become a new method for auto-antibody screening. Using Luminex xMap® technology, it works by identifying fluorescent antigen-coated microbeads that bind 13 different antibodies [22]. For confirmation, anti-nuclear antibodies were
detected with indirect immunofluorescence (IIF) of HEp-2 cells and anti-double-stranded DNA antibodies were detected with indirect immunofluorescence of *Crithidia* cells. Enzyme-linked immunosorbent assays were used to detect anti-cardiolipin antibodies. Methods for these tests have been described previously [23-25].

For comparison, control sera were screened for auto-antibodies using the Bioplex™ 2200 multiplex immunoassay and IIF of HEp-2 cells. The date of control serum specimens were matched as closely as possible to the date of the corresponding case serum sample.

*Uranium Exposure Calculation*

A cumulative uranium exposure estimate was used as the primary exposure measure. This estimate was developed by FCC investigators and was derived from an exposure algorithm developed by the CDC as part of the Fernald Dose-Reconstruction Project as previously described [26]. Cumulative airborne uranium exposure in μg/m³ was calculated for each individual with a uranium dosimetry model. Uranium exposure was then translated into cumulative exposure to ionizing radation. These exposure estimates were categorized into three levels, minimal (participants with minimal exposure, i.e., an estimated lifetime cumulative exposure with an equivalent of <0.25 Sievert [Sv]); moderate (0.25 to 0.50 Sv); or high (>0.50 Sv). The annual average dose for the United States population is approximately 0.003 Sv. Both the discrete exposure estimate values and the categorical exposure assignments were used in the statistical analysis.

*Statistical Analysis*

Median uranium exposure indices were calculated for each exposure group among SLE cases, controls, and RA cases. An association between covariates and uranium exposure category (minimal, moderate, high) was evaluated using the chi-square test. When the overall chi-square
test was significant, additional chi-square tests were performed to determine which exposure groups differed. The association between uranium exposure (minimal, moderate, high) and the incidence of lupus was evaluated using conditional logistic regression. Age at menopause was categorized into “< 50 years old”, “≥ 50 years old”, and “not yet”. Potential confounding variables (family history of lupus, alcohol use, history of smoking, age at menopause) were obtained via FCC questionnaires or medical exams. Measures of association for conditional logistic regression analyses were calculated as odds ratios (OR) with 95% percent confidence intervals (CI). All analyses were repeated in gender-specific strata to evaluate potential gender differences in the relationship between uranium exposure and the study outcomes. Regression analysis using the log transformed continuous exposure calculation was also performed. Association between uranium exposure and the incidence of rheumatoid arthritis was evaluated with a Fisher’s exact test. Analyses were performed using SAS version 9.2 (SAS Institute: Cary, NC).

Results

The FCC includes 4,187 individuals with low uranium exposure, 1,273 with moderate exposure, and 2,756 with high exposure. SLE was confirmed in 21 of 26 cases with an ICD-9 code of 710.0, in 2 of 5 cases with an ICD9 code of 695.4, and in 2 of 43 other cases prescribed hydroxychloroquine (Table 2). In other words, of the 74 individuals who were considered potential cases, 22 were considered “definite” cases and 3 were considered “possible” cases. The female to male ratio among the 25 cases was 5.25 to 1. Of the SLE cases, 5 were in the low exposure group, 8 in the moderate exposure group, and 12 in the high exposure group.

Case and control characteristics are summarized in Table 3. Figure 1 illustrates median exposure index scores in the cases and controls. Among the 25 cases included in the analysis, the median exposure index score was 0.47 (mean 1.18, range 0.01-4.31). Among the 99
controls, the median exposure index score was 0.29 (mean 0.75, range 0-6.99). Frequency of positive ANAs was increased in the cases compared to the controls, as summarized in Table 4.

Following conditional logistic regression modeling, SLE was found to be associated with high exposure (OR 3.92, 95% CI 1.13-13.59, p = 0.031). When the three “possible” cases were excluded from the analysis, an association with high exposure persisted (OR 3.62, 95% CI 1.05-12.56, p = 0.042). The OR for moderate uranium exposure and SLE was elevated, but not statistically significant. Outcomes of logistic regression are summarized in Table 5. Smoking, alcohol intake, and family history of SLE were not significantly associated with risk of SLE in this study. The analysis of female cases and controls showed an increased OR in women with high exposure compared to those with minimal exposure (OR 7.15, 95% CI 1.52-33.73, p = 0.01). Logistic regression using the log-transformed continuous exposure variable also yielded the statistically significant result of increased risk of SLE with increased exposure (OR 1.38, 95% CI 1.03-1.86, p = 0.03).

A summary of exposure group stratification by SLE cases, RA cases, and controls is shown in Figure 2. The distribution of exposure groups in the controls and RA cases are similar, whereas distribution of exposure groups in the SLE cases is weighted more heavily in the high exposure group. In the FCC overall, RA occurs at the predicted United States (U.S.) prevalence, while SLE is increased by 3.7-fold over the expected U.S. prevalence (Table 6) [1, 27-29].

**Discussion**

The Fernald Community Cohort provides an optimal setting to evaluate the effects of environmental exposures on disease. Our investigation of the relationship between environmental uranium exposure and lupus revealed a nearly four-fold increase in odds of lupus in individuals with high prior uranium exposure compared to subjects with minimal exposure. Other exposures, such as smoking and alcohol, had no significant effect.
The results of previous studies support an increased incidence of autoimmune disease and auto-antibodies in uranium miners exposed to silica dust [4, 5, 8, 9, 12, 13, 30, 31]. While specific effects of uranium on the development of autoimmunity have not been well studied, there has been some evidence regarding cadmium, a closely related heavy metal. In vivo, cadmium exposure has been related to immune-mediated glomerulonephritis and development of anti-nuclear antibodies in mice [32-34]. Furthermore, there could be several potential explanations for the relationship between uranium exposure and SLE based upon the molecular effects of uranium.

All uranium isotopes are radioactive and emit alpha particles, which are capable of inducing DNA damage [35-38]. Early investigations of somatic cell gene mutation in the FCC did not reveal a relationship between mutations and proximity to the FMPC [39]. However, quantitative estimates of exposure were not used in the analysis. Previous literature has shown that uranium can not only induce DNA damage through ionizing radiation, but it can also act directly through inherent properties [40-42]. In fact, uranium itself and ionizing radiation may independently lead to epigenetic changes [43-45]. Furthermore, radon, a radioactive decay product of uranium, has also been associated with abnormal DNA methylation [43, 46]. Interestingly, cadmium has also been shown to exert effects on the epigenome [47-50].

An interesting finding in our study was a lower than expected female to male ratio of 5.25:1. The adult female to male ratio in SLE cases of European ancestry is generally around 9:1. This dilution of female predominance raises several questions, such as the impact of estrogens and gene dose effects related to the X chromosome [51]. Uranium has been shown to affect estrogen receptor activity, similar to other heavy metals, such as cadmium [52, 53]. Furthermore, ionizing radiation itself can affect estrogen receptor activity [54]. Uranium miners have also been shown to have reduced levels of circulating testosterone [38]. X-chromosome dose effects have been identified by investigators as well [55-57].
The Fernald Dosimetry Reconstruction Project was focused primarily on uranium exposure and exposure to its associated decay products (thorium, radium, and radon). Solvents, however, were also suspected to have been released into the environment [58]. The association of solvents with SLE development has been debated, but enough question has been raised that warrants further studies [5, 31, 59, 60]. Unfortunately, we were unable to analyze potential effects of environmental solvent exposure on SLE. Another potential explanation for our findings is that there may be other unidentified and unexplored factors related to living near industrial processing.

**Limitations**

This study has highlighted a relationship between environmental uranium exposure and the frequency of lupus in this cohort, but some limitations require consideration. This cohort was built to allow for the future study of different conditions and parameters. Special emphasis was placed on the confirmation of reported malignancies, given known effects of uranium and ionizing radiation exposure. It is important to note that questionnaires and exams were not built to assess formal criteria for SLE. Case identification and exposure variables were all retrospectively gathered. Stringent criteria were used, however, allowing us to rule out 49 potential SLE cases.

Though factors could potentially lead us to overestimate our results, others could have led us to underestimate our results. Potential cases could have been missed with our screening methods. Also, we were unable to acquire medical records from several potential cases, which could have impaired our ability to confirm cases.

With respect to the cohort itself, issues with reporting bias and selection bias are possible. FCC cohort members may have been more likely to report symptoms and diagnoses. Alternatively, given the morbidity related to SLE and other chronic conditions, individuals with disease may
also have been too ill to participate. This would alternatively foster a healthy volunteer effect [21].

Conclusion

High levels of environmental uranium exposure are associated with a four-fold increase in lupus in the Fernald Community Cohort. Many explanations are possible. This association highlights the need to better understand 1) the impact of environmental uranium exposure on other diseases, and 2) the interaction between environmental exposures and SLE.
References


### Appendix

#### Table 1. Operational definition items for SLE case definition

<table>
<thead>
<tr>
<th>Self-report</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Physician documentation of diagnosis of SLE</td>
</tr>
<tr>
<td>Death certificate includes diagnosis of SLE</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Presence of at least 2 ACR criteria</td>
</tr>
<tr>
<td>Serologic confirmation of the presence of auto-antibodies</td>
</tr>
<tr>
<td>On anti-malarial</td>
</tr>
</tbody>
</table>

**Case Ascertainment**

- **No** = self-report only and/or diagnosis retracted
- **Possible** = self-report + 1 minor criteria
- **Definite** = self-report + at least 1 major and at least 1 minor criteria OR self-report + at least 2 minor criteria OR 3 minor criteria
Table 2. SLE case determination outcomes

<table>
<thead>
<tr>
<th>SLE Case Determination</th>
<th>Total considered</th>
<th>“Definite”</th>
<th>“Possible”</th>
<th>“No”*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD9 code 710.0</td>
<td>26</td>
<td>18</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>ICD9 code 695.4</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>HCQ medication code</td>
<td>43</td>
<td>2</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>74</strong></td>
<td><strong>22</strong></td>
<td><strong>3</strong></td>
<td><strong>49</strong></td>
</tr>
</tbody>
</table>

* "No": Exclusion based on failure to meet operational definition criteria. These persons were ineligible to be controls.
Table 3. Characteristics of cases and controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 25</td>
<td>n = 99</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>50 (29-78)</td>
<td>50 (29-79)</td>
</tr>
<tr>
<td>Females, number (%)</td>
<td>21 (84)</td>
<td>83 (83.8)</td>
</tr>
<tr>
<td>Smoking, cumulative pack-years, median (range)</td>
<td>0.25 (0-56.44)</td>
<td>10 (0-138)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none, n (%)</td>
<td>15 (60)</td>
<td>70 (70.7)</td>
</tr>
<tr>
<td>1-2 drinks/week, n (%)</td>
<td>5 (20)</td>
<td>14 (14.1)</td>
</tr>
<tr>
<td>≥ 3 drinks/week, n (%)</td>
<td>5 (20)</td>
<td>15 (15.2)</td>
</tr>
</tbody>
</table>
Table 4. Presence of anti-nuclear antibodies (ANA)* in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA tested, n (%)</td>
<td>25 (100)</td>
<td>85 (85.9)</td>
</tr>
<tr>
<td>Negative, n (%)</td>
<td>3 (12)</td>
<td>59 (69.4)</td>
</tr>
<tr>
<td>≥ 1:40, n (%)</td>
<td>22 (88)</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td>≥ 1:120, n (%)</td>
<td>17 (68)</td>
<td>17 (20)</td>
</tr>
<tr>
<td>≥ 1:360, n (%)</td>
<td>11 (44)</td>
<td>5 (5.9)</td>
</tr>
<tr>
<td>≥ 1:1080, n (%)</td>
<td>6 (24)</td>
<td>4 (4.7)</td>
</tr>
</tbody>
</table>

* ANA results based on Hep2 ANA indirect immunofluorescence
Table 5. Outcomes of logistic regression analysis

A. Exposure Group Comparison with All Cases and Controls (n = 124)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate vs Minimal exposure</td>
<td>2.65</td>
<td>(0.71, 9.84)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>High vs Minimal exposure</strong></td>
<td><strong>3.92</strong></td>
<td><strong>(1.13, 13.59)</strong></td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Alcohol 1-2 drinks/wk vs none</td>
<td>1.74</td>
<td>(0.47, 6.38)</td>
<td>0.41</td>
</tr>
<tr>
<td>Alcohol ≥ 3 drinks/wk vs none</td>
<td>2.11</td>
<td>(0.56, 8.00)</td>
<td>0.27</td>
</tr>
<tr>
<td>Smoking (cumulative pack-yrs)</td>
<td>0.98</td>
<td>(0.96, 1.01)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

B. Exposure Group Comparison with Definite Cases and Controls (n = 109)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate vs Minimal exposure</td>
<td>2.15</td>
<td>(0.54, 8.50)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>High vs Minimal exposure</strong></td>
<td><strong>3.62</strong></td>
<td><strong>(1.05, 12.56)</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Alcohol 1-2 drinks/wk vs none</td>
<td>2.15</td>
<td>(0.54, 8.62)</td>
<td>0.25</td>
</tr>
<tr>
<td>Alcohol ≥ 3 drinks/wk vs none</td>
<td>1.53</td>
<td>(0.40, 6.48)</td>
<td>0.50</td>
</tr>
<tr>
<td>Smoking (cumulative pack-yrs)</td>
<td>0.98</td>
<td>(0.96, 1.01)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Variables highlighted in bold indicate statistically significant results with a p-value < 0.05
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FCC SLE cases</th>
<th>SLE in the U.S.</th>
<th>FCC RA cases</th>
<th>RA in the U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>0.256 %</td>
<td>0.04-0.15 %</td>
<td>1.53%</td>
<td>0.9-1.1%</td>
</tr>
<tr>
<td>Female:Male ratio</td>
<td>5.25:1</td>
<td>9:1</td>
<td>3.17:1</td>
<td>2:1-3:1</td>
</tr>
</tbody>
</table>
Figure 1. Uranium exposure index scores

- Mean
Figure 2. Comparison of exposure groups among controls, RA cases, and SLE cases in the FCC.