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Authors
Moreau, Jacqueline F
Buchanich, Jeanine M
Geskin, Jacob Z
et al.

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Non-random geographic distribution of patients with cutaneous T-cell lymphoma in the Greater Pittsburgh Area

Jacqueline F. Moreau MS[1], Jeanine M. Buchanich PhD[2], Jacob Z. Geskin[3], Oleg E. Akilov MD PhD[4], Larisa J. Geskin MD[4]

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[1]University of Pittsburgh School of Medicine, Pittsburgh, PA

[2]University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

[3]University of California, Berkeley, Berkeley, CA

[4]Department of Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Correspondence:

Larisa J. Geskin, MD
200 Lothrop Street, Suite 3880
Pittsburgh, PA 15213
Phone: (412) 864-3679
Fax: (412) 864-3740
Email: geskinlj@gmail.com

Abstract

Background: Environmental hazards may play a role in the etiology of cutaneous T-cell lymphoma (CTCL). Some studies have found an increased incidence of CTCL among workers in chemical science, transportation, and manufacturing industries, but other studies have not. This discrepancy may be attributable to population migration, complicating accurate assessment of lifetime exposures. The Pittsburgh population has very low migration rates and most CTCL patients seen at the University of Pittsburgh Medical Center (UPMC) Cutaneous Lymphoma Center are life-long local residents. The Greater Pittsburgh Area used to be an industrial hub. There are residential communities positioned within close proximity to inactive industrial sites that continue to contain pollutants.

Objective*:* To determine whether CTCL patients' residences cluster within specific Pittsburgh regions, in particular, those with high levels of environmental pollutants.

Methods*:* Our study included patients diagnosed with CTCL at the UPMC Cutaneous Lymphoma Center between 2000 and 2012. We mapped the longitudinal and latitudinal coordinates of patients' residences at diagnosis, superfund sites, toxic release inventory sites, particular matter levels, and dermatologists' offices using ArcMap 10.1. We then performed a SaTScan analysis using zip codes to assess for geographic clustering of patients' residences in the Pittsburgh metropolitan statistical area. We assessed for a correlation between case distribution and both environmental hazards sites and dermatologist density in the area.

Results*:* We identified 274 patients with CTCL in the Greater Pittsburgh area. We identified a statistically significant geographic cluster ($p<.001$) in zip code 15213, which is the most densely populated neighborhood in Pittsburgh and the site of the region's only CTCL clinic. We observed no relationship between the locations of superfund sites, toxic release inventory sites, or particular matter levels and CTCL case distribution.

Conclusion*:* Our findings do not support an association between exposure to environmental toxins and CTCL. CTCL cases clustered in areas with the highest population density, which also happen to include a regional CTCL center. To evaluate a possibility of urban pollutants playing a role in etiology of CTCL, dermatologist density and access to care need to be addressed as potential confounders in the future studies.

Keywords: Cutaneous T cell lymphoma; Skin neoplasms; United States; epidemiology, cluster analysis, environmental risk

Abbreviations: CTCL: cutaneous T-cell lymphoma; MSA: Metropolitan Statistical Area; NPL: National Priorities List; TRI: Toxic Release Inventory; PM: particulate matter

Introduction

Cutaneous T-cell lymphoma (CTCL) is an epidermotropic form of non-Hodgkin's lymphoma caused by mutation of T cells; the most common forms are Mycosis Fungoides and Sezary Syndrome. The incidence of CTCL increased from 2.8 per million in 1973-1977 to 9.6 per million in 1998-2002; the incidence has since remained steady [1,2]. As the etiology of CTCL is unknown, the reasons behind this dramatic rise are unknown, but may include improved detection or an increase in exposure to underlying etiologic agents. A new CTCL classification scheme was introduced in 2005, though this should not have affected overall CTCL incidence [3]. Instead, the recent leveling off in incidence may relate to a plateauing of former improvements in physician detection or a stabilization of exposure to etiologic agents. Several European studies have identified associations between CTCL incidence and environmental exposures [4,5]. US-based studies have reported conflicting results regarding the association between CTCL incidence and both environmental exposures [6-8] and geographic residence [1,9]. Discrepancies may be attributable to occupational mobility and geographic migration, complicating history of lifetime exposures.

The University of Pittsburgh Medical Center (UPMC) Cutaneous Lymphoma Center is one of the largest in the country. It cares for over 300 patients, the majority of whom are life-long local residents. Pittsburgh has very low migration rates; only 8% of Pittsburgh Metropolitan Statistical Area (MSA) residents in 2000 were not living in the region in 1995, which represents the lowest rate among any major MSA [10]. Pittsburgh used to be an industrial hub and there are residential communities positioned in close proximity to inactive industrial sites that continue to contain pollutants. These characteristics make Pittsburgh well suited for an epidemiologic study aiming to determine whether CTCL patients' residences at diagnosis cluster in areas with high levels of environmental pollutants.

Methods

We conducted a cross-sectional study using patients seen at the University of Pittsburgh Medical Center from 2000-2012 with a pathologically confirmed diagnosis of CTCL (biopsy dates ranging from 1979-2012) and residing in the Pittsburgh MSA at diagnosis. The MSA includes the city proper as well as Allegheny, Armstrong, Beaver, Butler, Fayette, Washington, and Westmoreland counties; it includes 322 zip codes. We used ArcMap 10.1 to map the longitudinal/latitudinal coordinates of patient addresses at diagnosis, National Priorities List (NPL) Superfund sites, facilities on the Toxic Release Inventory (TRI), year 2005 fine particulate matter (PM2.5) levels, and dermatologists' offices. Superfund is the federal government's program to locate, investigate, and clean up the worst uncontrolled and abandoned toxic waste sites nationwide and it is administered by the Environmental Protection Agency. TRI-covered industries include mining, utilities (electric, water, and sewage), manufacturing (food, beverages, tobacco, textiles, apparel, leather products, wood products, paper, printing/publishing, petroleum and coal products, chemicals, plastics and rubber products, nonmetallic mineral products, metal products, machinery, computer and electronic products, electrical equipment, transportation equipment, furniture), merchant wholesalers (non-durable goods and chemical, petroleum-based, and electronic products), publishing, and hazardous waste. We used the American Academy of Dermatology's online directory (http://www.aad.org/find-a-derm) to identify dermatologists' addresses and determined dermatologist density by dividing the number of dermatologists per zip code by the 2000 Census population per zip code. We used the zip codes of case addresses at diagnosis to perform SaTScan (Version 7.0.3) analyses for evidence of geographic clustering in the Pittsburgh MSA. SaTScan uses a Poisson-based model, in which the number of events in a geographical area is Poisson-distributed according to the age and sex distribution of the underlying population at risk.

Between 2000-2007, we asked patients to complete a questionnaire including open-ended questions about lifetime residential history and known occupational and residential exposures to toxins or pollutants. We calculated the median migration distance among individuals who were both residents of the Pittsburgh MSA at time of diagnosis and provided complete lifetime residential histories in the analysis. The University of Pittsburgh IRB approved this study.

Results

We identified 274 patients diagnosed with CTCL from 1979-2012 in the Greater Pittsburgh Area. We identified a statistically significant geographic cluster ($p<.001$) with a radius of 5.26 km centered in zip code 15213 (Figure 1), which is the most densely populated neighborhood in Pittsburgh [11]. Thirty-four cases resided in this area at the time of diagnosis, whereas 11.1 were expected (observed/expected ratio 3.1). The only regional CTCL specialty clinic is located within the cluster. We observed no relationship between the locations of superfund sites, TRI sites, or $PM_{2.5}$ levels and CTCL case distribution. The majority of patients lived in zip codes with no superfund and TRI sites (Figure 1), and <10% of patients lived in zip codes with high $PM_{2.5}$ levels (data not shown). Fifty percent of patients lived within 2 km of a dermatologist's office (Figure 2).

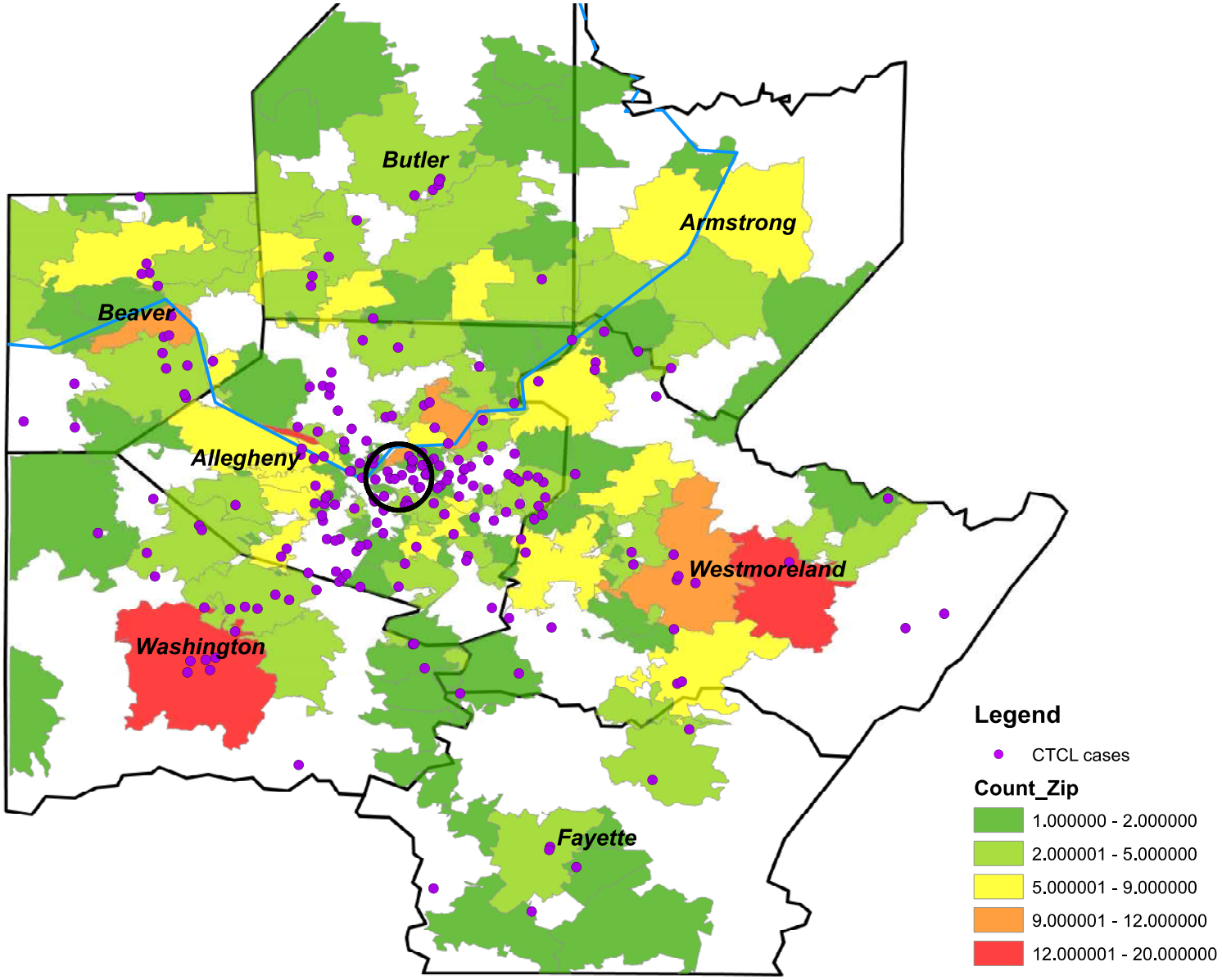

Figure 1. Relationship between the locations of CTCL cases and clusters compared to Superfund and Toxic Release Inventory facilities

Cases include patients treated at the UPMC CTCL clinic between 2000 and 2012.

TRI sites per zip code:

1-2: darkest green

2-5: lighter green

5-9: yellow

9-12: orange

12-20: red

Purple dots denote CTCL cases

The black circle denotes a cluster

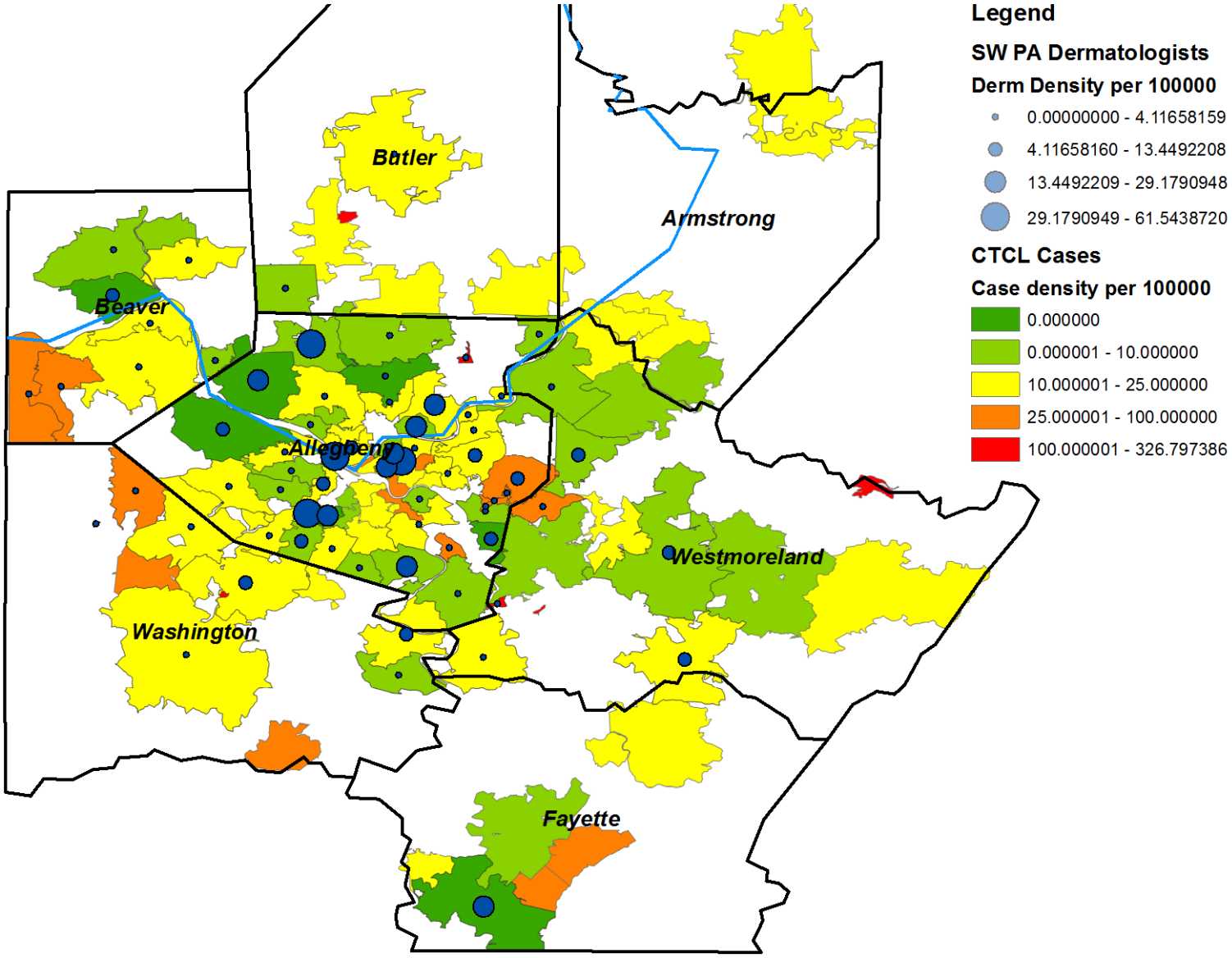

Figure 2. CTCL case density per 100,000 compared to dermatologist density per 100,000

Cases include patients treated at the UPMC CTCL clinic between 2000 and 2012.

<u>Dermatologist density per 100,000:</u>

No dot: no dermatologists

Smallest blue dot: 0.01-4.12

Small blue: 4.12-13.45

Medium blue: 13.45-29.18

Large blue: 29.18-61.54

CTCL Case density per 100,000:

Dark green: 0.00

Light green: 0.01-10.00

Yellow: 10.01-25.00

Orange: 25.01-100.00

Red: 100.01-326.80

Sixty-six of 194 patients returned the consent form and questionnaire (34% response rate); 53 of 66 (80.3%) were included in analysis because they resided in the Greater Pittsburgh area at the time of diagnosis and provided a complete residential history; 8 were excluded because they were not residents of the Pittsburgh MSA at time of diagnosis; 5 were excluded because they failed to provide a complete residential history. The median distance moved between birth and diagnosis was 6.20 km (50% of patients had a net lifetime move of $\leq$ 6.20 km); eight (15%) patients resided in the same location all their life or moved only an insignificant distance (<0.5 km); forty-three (81%) patients moved less than 30 km. Forty-nine (92.5%) patients included were born in Pennsylvania.

Discussion

Our study included a population with relatively long-term daily exposure and minimal exposure variability, thus addressing population migration as a potential confounder regarding the association between exposure to environmental toxins and CTCL. In agreement with two other US studies, including one of the largest case control studies conducted on this topic [7, 8], our results do not support an association between exposure to residential environmental toxins and CTCL. However, we found that CTCL cases clustered in areas with high population density, which were also areas with high dermatologist density in Pittsburgh.

CTCL is commonly misdiagnosed as benign dermatoses such as eczema and psoriasis; some patients may never be diagnosed correctly if not evaluated and biopsied by a specialist with a high index of suspicion. This is consistent with previous research using SEER data that found a significant correlation between CTCL incidence and physician density and an even stronger correlation between CTCL incidence and medical specialist density [1]. Thus, dermatologist density may be a confounder. Dermatologists' practices tend to cluster in urban areas, so is unclear whether an unidentified urban-related environmental factor or sociodemographic factor accounts for this association or if it reflects increased diagnosis. Increased incidence of CTCL was previously noted in areas with high population density [1]. This may reflect common exposure to an infectious agent or unidentified hazard.

On the other hand, Pittsburgh may not have adequate representation of environmental toxins associated with CTCL. Previously, two European studies and one US study found increased odds of CTCL among individuals working in industries focused on non-metallic mineral products (particularly glass, pottery, and ceramic), paper products, wholesale trade, and publishing/printing [5, 12]. These have not historically been dominant trades in the Pittsburgh area. It is also possible that the amount of exposure through employment may exceed that obtained by living in an area with a high number of TRI sites and high $PM_{2.5}$ levels, as we were not able to analyze the quantity of each CTCL patient's exposure.

This study demonstrated a lack of association between residential environmental toxins in one's area of residence and CTCL incidence. Its greatest strength is that it was conducted in a location with low migration rates. The study also has limitations. Although the vast majority of CTCL cases in the Pittsburgh MSA are seen at the UPMC Cutaneous Lymphoma Center, cases diagnosed and treated elsewhere were not included in our analysis. CTCL also appears to have been underdiagnosed in areas with fewer dermatologists and we lacked a control population. Because the Pittsburgh MSA represents a favorable setting owing to low migration rates, a follow-up study may be considered to better articulate the quantity of residential and occupational exposures among CTCL cases and controls.

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