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Socio-Environmental Conditions Associated with Geospatial Clusters of Urothelial Carcinoma: A Multi-Institutional Analysis

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Study Need and Importance: The impact of social and environmental risk factors on the development of malignancy, including urothelial carcinoma, is poorly characterized. Understanding this relationship may offer insight into the identification of previously unrecognized at-risk patient populations.

What We Found: We identified geospatial clusters of patients with urothelial carcinoma (see figure) and determined that these patients were less likely to have a history of tobacco abuse, but more likely to live in proximity to sources of industrial carcinogen discharge. Additionally, they were more likely to be nonwhite and reside in lower income areas.

Limitations: This study is primarily limited by its retrospective approach. Additionally, the patient sample does not capture all possible urothelial carcinoma diagnoses within these geographic boundaries. Furthermore, proximity to sources of environmental carcinogen discharge is used as a proxy for exposure in these patients and may not be indicative of actual exposure.

Interpretation for Patient Care: It is common to consider factors such as tobacco or occupational exposure when assessing the risk of urothelial malignancy in a given patient. Although less often considered, the environment in which a patient resides may be relevant in select populations. While the association between environmental risk factors and urothelial carcinoma requires further validation and exploration, patients residing in proximity to sources of industrial discharge may benefit from more targeted screening. Additionally, clinicians may consider inquiring regarding proximity to such sites when evaluating hematuria or newly diagnosed urothelial carcinoma patients.

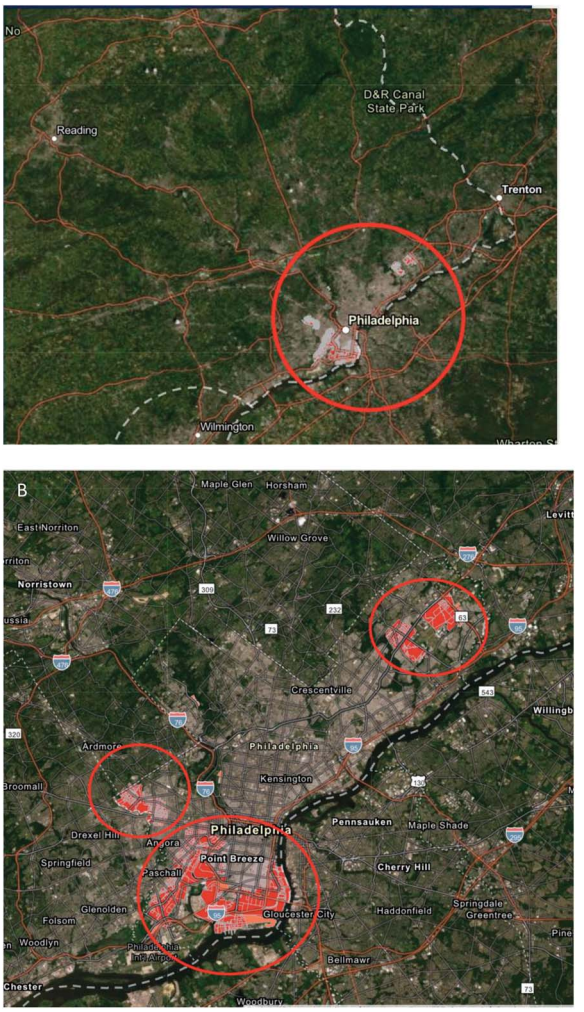

Figure. Urothelial carcinoma hotspots in Southeastern Pennsylvania. *A*, distant view. *B*, magnified view.

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Socio-Environmental Conditions Associated with Geospatial Clusters of Urothelial Carcinoma: A Multi-Institutional Analysis

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Purpose: The interaction between sources of industrial byproducts and environmental pollutants (IBP/EP) and the prevalence of urothelial carcinoma (UC) in surrounding communities has been infrequently explored. The purpose of this research is to identify microregional UC hotspots and associated industrial and environmental risk factors.

Materials and Methods: We retrospectively queried a multi-institutional database for UC patients diagnosed between 2008 and 2018. Addresses were geocoded and used to perform hotspot analysis on the census block level. Demographic and clinicopathological characteristics, census data and proximity to sources of IBP/EP were compared between patients who did vs did not reside in a hotspot. Associations were tested using multilevel logistic regression models using 95% confidence intervals.

Results: A total of 5,080 patients met inclusion criteria and 148 (2.9%) were identified as living in 1 of 3 UC hotspots. In univariate analyses, race, tobacco and alcohol use, household income, IBP/EP exposure and proximity to traffic, industrial discharge and airports were significantly associated with UC hotspots. Multivariable analysis demonstrated that polycyclic aromatic hydrocarbon exposure (OR: 48.09, $p \leq 0.001$) and proximity to high-density traffic (OR: >999, $p \leq 0.001$) increased the odds of living in a hotspot. Patients living in a hotspot were significantly less likely to be white (OR: 0.06, $p \leq 0.001$) or tobacco users (OR: 0.39, $p = 0.031$) on multivariate analysis.

Conclusions: Spatially related clusters of UC may be associated with locoregional environmental exposures rather than tobacco exposure and may also be correlated with socioeconomic disparities. Geospatial analysis can help to identify at-risk populations, offering the opportunity to better focus preventive and diagnostic interventions.

Key Words: healthcare disparities; urologic neoplasms; carcinogens, environmental

Abbreviations and Acronyms

AE = alcohol exposure
AIC = Akaike information criterion
EP = environmental pollutants
IBP = industrial byproducts
ICD = International Classification of Diseases
PAH = polycyclic aromatic hydrocarbons
TD = traffic density
TE = tobacco exposure
UC = urothelial carcinoma

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Tobacco exposure (TE) is the most well-documented risk factor for urothelial carcinoma (UC) and is associated with up to 65% of all urothelial cancers.[1] Occupational exposures to industrial byproducts and environmental pollutants (IBP/EP), such as polycyclic aromatic hydrocarbons (PAH), aromatic amines and heavy metals, are also associated with the

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development of UC in up to 7% of cases.[2,3] However, the relationship between UC and environmental exposures to IBP/EP has not been clearly defined, partially due to difficulties in quantifying exposures, long latency periods and the inadequate granularity of available data to draw appropriately specific geospatial conclusions.

Geospatial analytic techniques allow for the discovery of regional patterns of disease, classification of associated risk factors and identification of uniquely at-risk populations.[4–6] However, utilization of these techniques to evaluate patterns of UC remains sparse. For example, Khan et al performed hotspot analysis of bladder UC cases in western New York, noting potential relationships between industrial sites and water quality indicators in the region, but did not comment on patient-specific factors associated with UC in this population.[7] Similarly, Avruskin et al employed geospatial analysis to explore relationships between arsenic exposure and bladder cancer in Michigan, although no conclusions were ultimately drawn.[8] Ultimately, further investigation is necessary to effectively identify potential relationships between environmental risk factors and the development of UC.

The primary objectives of this study are to identify spatially related UC hotspots, to characterize patients residing in these hotspots based on clinicopathological and demographic factors, and to estimate the effects of locoregional environmental exposures on disease prevalence.

METHODS

This study was reviewed by an independent institutional review board, Western Copernicus Group IRB, and classified as exempt due to its retrospective nature. In order to facilitate efficient data collection, Western Copernicus Group IRB also granted a waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization.

A retrospective review of a geographically restricted multi-institutional database was performed to identify patients over 40 years old diagnosed with UC of the renal pelvis, ureters, bladder or urethra between January 1, 2008 and December 31, 2018. The diagnosis was queried using International Classification of Diseases (ICD) 9th and 10th coding schemes as follows: ICD9 (188.1−188.9; 189.1,189.2) and ICD10 (C65.1, C65.2, C65.9; C66.1, C66.2, C66.9; C67.1−C67.9). Exclusion criteria consisted of repeat entries, diagnosis prior to 2008, incomplete or insufficient address (ie P.O. box, prisons, nursing homes), address outside of the 5 metropolitan Southeastern Pennsylvania counties including and surrounding the city of Philadelphia (Philadelphia, Montgomery, Chester, Bucks and Delaware counties) and nonurothelial histology. The stage ($\leq$cT1 or $\geq$T2) and grade (high or low) of disease at initial presentation were indexed. Age at diagnosis, ethnicity, comorbid medical conditions, prior malignancy, TE and alcohol exposure (AE) and known industrial/occupational exposures were catalogued. TE and AE were measured as a binary (yes/no). Industrial occupational exposure was measured as a binary from a list of known occupational risk factors, but individual occupational exposures were not quantified. Patient addresses at time of diagnosis were recorded, geocoded via ArcMap® and tracked via ArcGIS® software.

UC hotspot analysis was performed using the Getis-Ord Gi* statistic (ArcGIS) and analyzed by census block using age-restricted population density. A hotspot is a statistically significant cluster of point events (in our case, patients) determined using the Getis-Ord-GI* statistic. The likelihood of a patient residing in a particular location is compared to the likelihood of all patients residing in all locations. When there is a significantly higher probability of a cluster of patients existing in a particular area compared to the expected probability of said cluster, a statistically significant score results.

Legacy data in ArcGIS servers were used to extract demographic data associated with patients based on census block or block group, including age-restricted population density, median yearly household income (dollars) and percentage of population with a 12th grade educational attainment (high school graduation or GED equivalent). Pennsylvania Department of Environmental Protection and United States Environmental Protection Agency legacy data registries were queried to identify sources of IBPs/EPs associated with known discharge of urothelial carcinogens into soil, air or waterways, and these were also geo-located. Additionally, traffic density (TD) was determined similarly using publicly available Pennsylvania Department of Transportation data. TD was calculated by creating a fishnet polygon mesh to overlap a map indicating traffic counts and then by using the Getis-Ord-GI* statistic to identify disproportionately high traffic counts within the polygon mesh, thereby identifying traffic hotspots. Local regional and international airports with greater than 1,000 enplanements per year were also geo-located. Three binary variables were created to flag whether patients lived within 1,000 yards of an industrial site, airport or area of increased TD.

Statistical analysis was performed using Stata®/MP 15.1. Significance was set at the 5% level and all statistical tests were 2-sided. Continuous and categorical variables were summarized as mean (SD) and frequency (percentage), respectively. Categorical and continuous patient-level variables and census block group-level variables were compared between patients who lived in a UC hotspot vs those who did not using chi-square tests of independence and 2-sample t-tests, respectively.

Multilevel logistic regression models (MLMs) were built to evaluate whether patient-level variables (level 1 variables) and census block group levels (level 2 variables) were associated with residing in a UC hotspot (table 1). Age at diagnosis (level 1 variable) was centered around the block group. Yearly household income and percentage of population with a 12th grade education (level 2 variables) were centered around their grand means. Examples of these techniques are referenced in table 1. Block group centering for continuous level 1 variables and grand mean centering for continuous level 2 variables are recommended if interactions between level 1 and level 2 variables are of interest, allowing for a more natural interpretation of the model's intercept.[9]

A null MLM model was built with block group as a random effect and confirmed that the variation in the proportion of patients residing in a UC hotspot varied by block group ($\chi^2 = 704.0$, 1 degree of freedom, $p \leq 0.001$). MLMs were fit using maximum likelihood estimation and built in a stepwise manner with a random intercept MLM for each level 1 predictor. Models were compared to the corresponding random slope and intercept model using a likelihood-ratio test; however, results indicated that the random intercept models were sufficient. All level 1 variables with a p value <0.10 were candidates for the multivariable MLM. Since TE, AE, PAH exposure and living within 1,000 yards of an industrial site, area of increased TD and airport were collinear, several multivariable models were considered. The models were reduced using backward elimination until all predictors had a p value <0.05, and their Akaike information criterion (AIC) values were compared. All 7 backward reduced candidate models and AICs are displayed in the supplementary table (https://www.jurology.com). The multivariable model with the lowest AIC was considered the final level 1 MLM. Level 2 variables were added to final level 1 MLM and assessed for significance. Level 1 interactions were tested, but parameter estimates were unstable due to the low event rate, and none of the level 2 variables were significant in the multivariable model. Odds ratios or adjusted OR and 95% confidence intervals are presented from each MLM.

RESULTS

Based on age and diagnosis criteria, 9,009 patients were identified for initial review. Individual charts were reviewed according to inclusion and exclusion criteria, resulting in 5,080 patients available for analysis (figs. 1–3). Given that census data approximate the population of the 5 counties of interest at 4 million persons and the estimated yearly

Table 1. *Distribution of patient demographics and census block data*

	UC HotSpot						
	No		Yes		p Value	Overall	
No. pts	4,932		148			5,080	
Demographic/history:							
Level 1 variables:							
Mean yrs age at diagnosis (SD)*	72.8	(11.4)	73.1	(12.2)	0.806	72.8	(11.4)
No. male (%)	3,703	(75.1)	99	(66.9)	**0.024**	3,802	(74.8)
No. ethnicity (%):					**< 0.001**		
White	4,391	(89.0)	92	(62.2)		4,483	(88.3)
Black/African American	384	(7.8)	48	(32.3)		432	(8.5)
Hispanic	40	(0.8)	0	(0.0)		40	(0.8)
Asian	62	(1.3)	4	(2.7)		66	(1.3)
Other	55	(1.1)	4	(2.7)		59	(1.2)
No. heart disease (%)	1,310	(26.6)	35	(23.7)	0.429	1,345	(26.5)
No. type 2 diabetes (%)	1,065	(21.6)	29	(19.6)	0.560	1,094	(21.5)
No. chronic kidney disease (%)	214	(4.3)	6	(4.1)	0.867	220	(4.3)
No. hypertension (%)	3,226	(65.4)	99	(66.9)	0.709	3,325	(65.5)
No. hyperlipidemia (%)	2,406	(48.8)	68	(46.0)	0.496	2,474	(48.7)
No. chronic obstructive pulmonary disease (%)	430	(8.7)	8	(5.4)	0.157	438	(8.6)
No. other malignancies (%)	1,187	(24.1)	30	(20.3)	0.286	1,217	(24.0)
No. tobacco use (%)	3,215	(65.2)	77	(52.0)	**0.001**	3,292	(64.8)
No. alcohol use (%)	3,266	(66.2)	76	(51.4)	**< 0.001**	3,342	(65.8)
No. industrial/occupational exposure (%)	67	(1.4)	2	(1.4)	0.994	69	(1.4)
No. any exposure (%)	204	(4.1)	18	(12.2)	**< 0.001**	222	(4.4)
No. type of exposure (%):					**< 0.001**		
No known	4,728	(95.9)	130	(87.8)		4,858	(95.6)
Nitrate	71	(1.4)	1	(0.7)		72	(1.4)
PAH	53	(1.1)	16	(10.8)		69	(1.4)
Chlorocarbon	46	(0.9)	1	(0.7)		47	(0.9)
Heavy metal	17	(0.3)	0	(0.0)		17	(0.3)
Di-n-butyl phthalate	16	(0.3)	0	(0.0)		16	(0.3)
Cadmium	1	(0.0)	0	(0.0)		1	(0.0)
Live within 1,000 yds of traffic hotspot (%)	65	(1.3)	70	(47.3)	**< 0.001**	135	(2.7)
Live within 1,000 yds of airport (%)	178	(3.6)	61	(41.2)	**< 0.001**	239	(4.7)
Live within 1,000 yds of industrial site (%)	203	(4.1)	18	(12.2)	**< 0.001**	221	(4.4)
Level 2 variables:							
Mean $ yearly household income (SD)†	90,389	(38,817)	59,668	(28,799)	**< 0.001**	89,500	(38,904)
Mean % population with 12th grade education (SD)†	74.3	(13.0)	69.4	(13.6)	**< 0.001**	74.2	(13.1)

Results in bold are statistically significant.

* Average age at diagnosis was computed for each block group, and then individual patient age at diagnosis was subtracted from block group's average age at diagnosis. For example, if a patient was 50 years old at time of diagnosis, and average age of diagnosis for their block group was 55 years, then their centered age at diagnosis was 50−55 = 5.

† Yearly household income and percentage of population with 12th grade education (level 2 variables) were centered around their grand means. That is, average household income ($89,450) and average percentage of population with 12th grade education (74.2%) was estimated across all patients, regardless of block group. For example, if a patient lived in a block group with a yearly household income of $90,000 and 80% had a 12th grade education, then their grand mean centered values were $90,000−$89,450 = 550, and 80%−74.2% = 5.8, respectively.

incidence of UC is approximately 25 per 100,000 persons, our cohort represents an estimated 50.8% of the total incidence of UC in this geographic region throughout the time period in question.[10]

Hotspot analysis ultimately revealed 3 statistically significant hotspots of UC patients (fig. 4). Among these UC hotspots, the 148 identified patients represented 2.9% of the total patient sample.

In total, 175 unique industrial discharge sites were identified as potential sources of UC carcinogens (fig. 5). Of the 175 sites, 7 were geospatially associated with the identified UC hotspots. TD across the region is displayed in fig. 6 and areas with increased TD were included as a risk factor. Two airports within the 5 counties (Philadelphia International Airport and Northeast Philadelphia Regional Airport) met inclusion criteria and were included in the subsequent analyses (fig. 7).

Hotspot patients were significantly more likely to be female (33.1% vs 24.9%, p=0.024), be Black/African American (32.3% vs 7.8%, p $\leq$0.001) and live within 1,000 yards of an airport (41.2% vs 3.6%, p $\leq$0.001), site of industrial discharge (12.2% vs 4.1%, p $\leq$0.001) or increased TD (47.3% vs 1.3%, p $\leq$0.001). TE (52% vs 65.2%, p=0.001) and AE (51.4% vs 66.2%, p $\leq$0.001) were significantly lower among hotspot patients. Hotspot patients were significantly more likely to have an exposure to any IBP/EP and specifically PAH (10.8% vs 1.1%, p $\leq$0.001). Notably, all PAH exposures occurred in hotspot patients. On average, hotspot patients also lived in census block groups that had significantly lower household incomes ($59,668 [SD: $28,799] vs $90,389 [SD: $38,817)], p $\leq$0.001) and education levels (69.4% [SD: 13.6%] vs 74.3% [SD: 13.0%] with a 12th grade education, p $\leq$0.001; table 1).

There were no significant differences in pathological characteristics between those residing and not residing in hotspots (table 2). Most patients had pure UC (93.2% vs 95.6%, p=0.729), with the bladder as the most common site of diagnosis (96.0% vs 95.3%, p=0.446). The majority of cancers were staged cTa (62.2% vs 61.7%, p=0.524), and approximately 33% of patients in both groups had invasive disease (>cT1; 34.5% vs 33.2%; p=0.751).

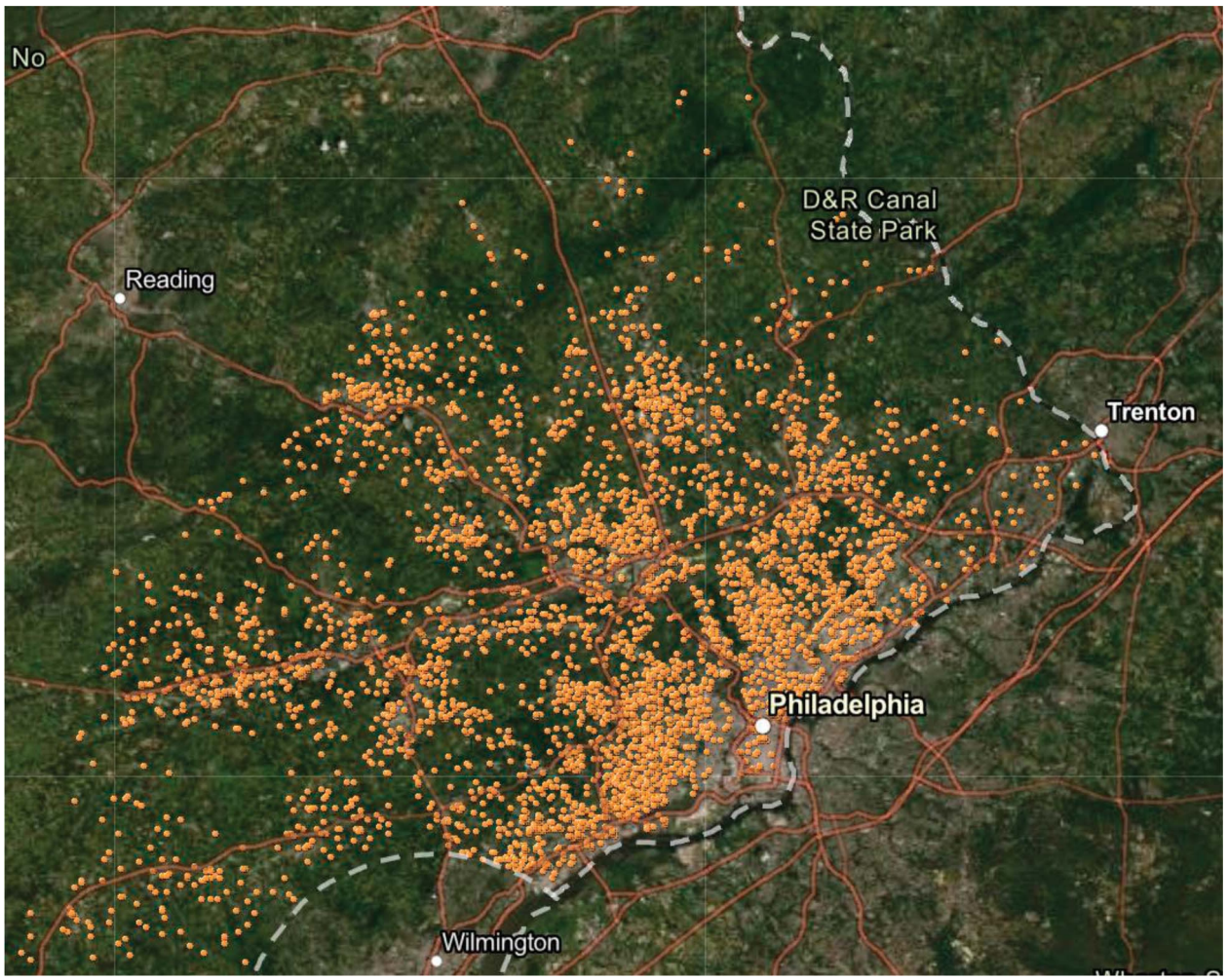

Figure 1. Patient point-locations distributed across Southeastern Pennsylvania.

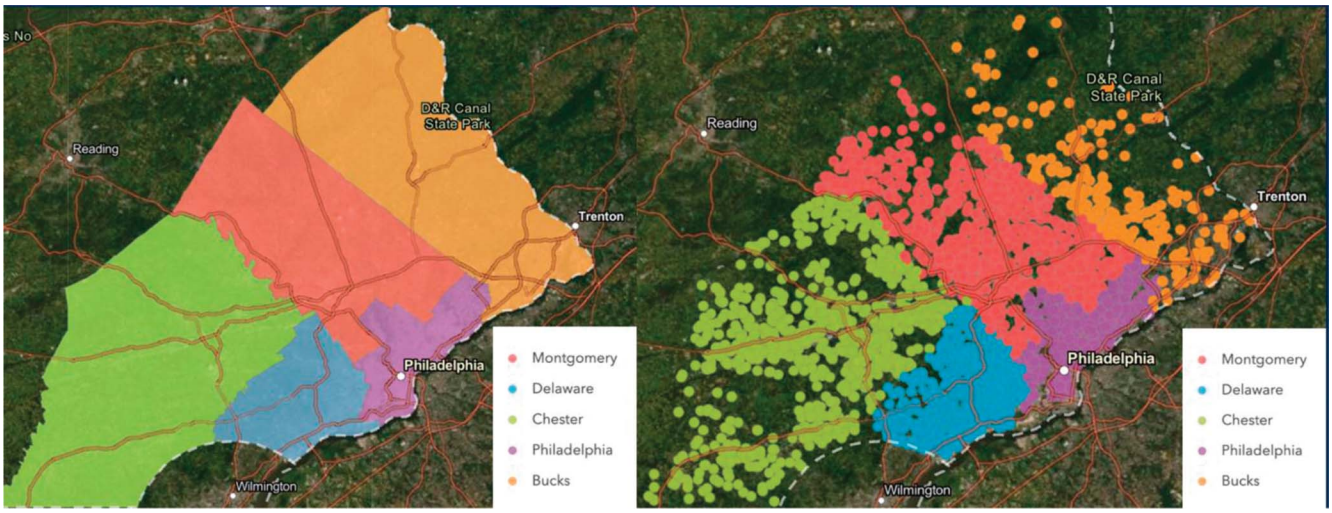

Figure 2. Patient distribution by county.

The univariable MLMs agreed with the results in table 1. Race, TE, AE, household income, living within 1,000 yards of increased TD, an airport, an industrial site and PAH exposure were significantly associated with living in a UC hotspot (table 3). All significant variables were candidates for the multivariable model.

In the backward reduced multivariable MLM, race, TE, PAH exposure and living within 1,000 yards of increased TD remained significantly associated with living in a UC hotspot (table 4). White patients were 94% less likely to reside in a UC hotspot than nonwhite patients (adjusted OR: 0.06, 95% CI: 0.02–0.15, $p \leq 0.001$). Additionally, the likelihood of living in a UC hotspot was 61% lower for patients with TE (adjusted OR: 0.39, 95% CI: 0.16–0.91; $p = 0.031$). Lastly, patients who had PAH exposure (adjusted OR: 48.09, 95% CI: 9.29–248.9) or lived within 1,000 yards of increased TD (adjusted OR: >999, 95% CI: not applicable) were significantly more likely to live in a UC hotspot (both $p < 0.001$).

DISCUSSION

Environmental carcinogens may exist in the atmosphere, be deposited in urban soils or exist within industrial runoff.[11,12] Consequently, they may transmit from source to patient via inhalation, ingestion or dermal contact.[13] The impact on health depends on length and route of exposure, concentration and relative toxicity of the carcinogen.[14] Research has suggested strong relationships between not only the amount of measurable pollution and the incidence of UC, but also relationships between pollution and UC mortality.[15,16]

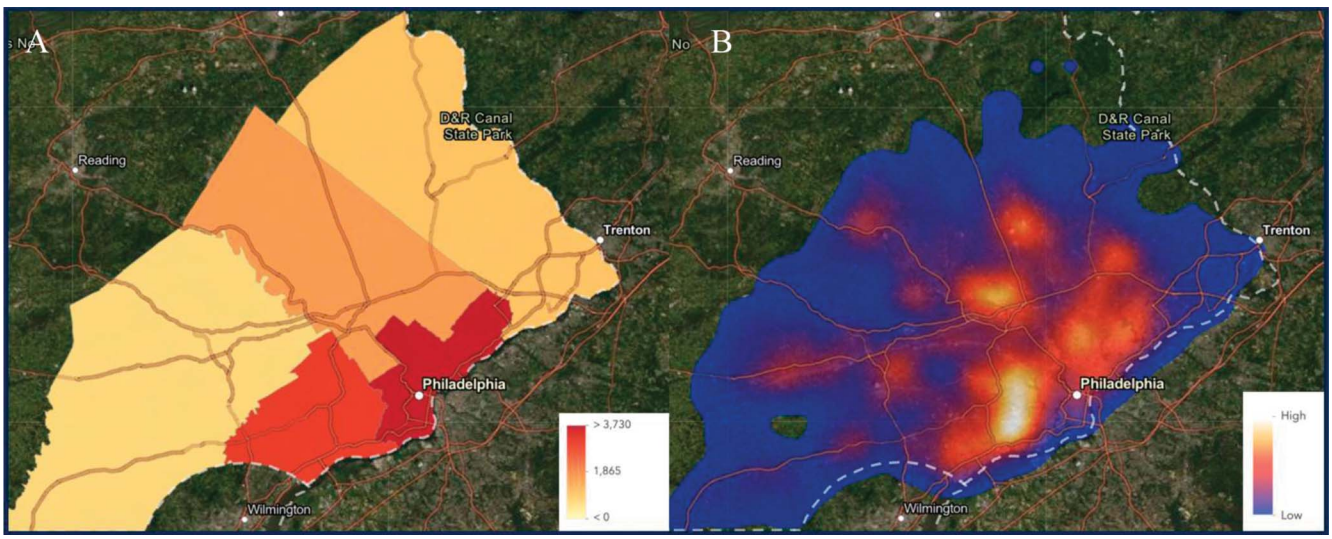

Figure 3. Density distribution of county-level population (*A*) and patient sample (*B*).

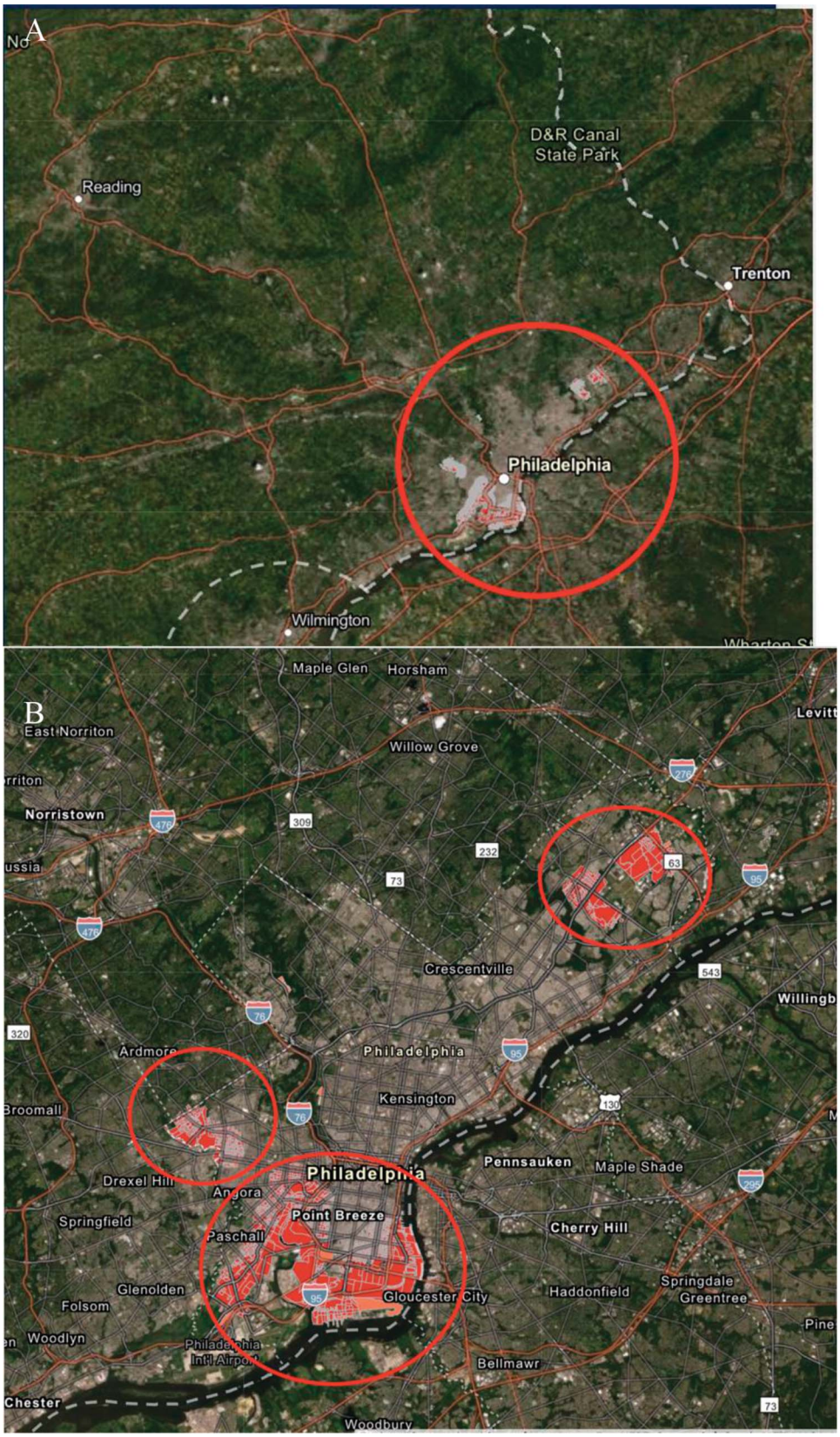

Figure 4. Urothelial carcinoma hotspots in Southeastern Pennsylvania. *A,* distant view. *B,* magnified view.

There are many industrial and environmental sources of urothelial carcinogens, but for this study we limited our search to facilities reporting discharge of PAH, aromatic amines, heavy metals,

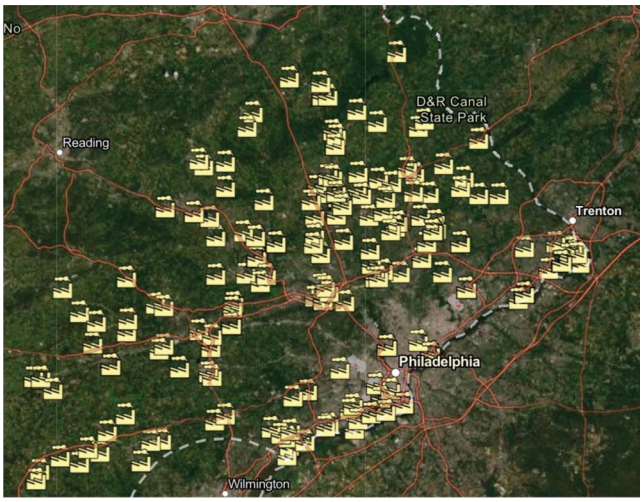

Figure 5. Source of industrial discharge containing known urothelial carcinogens in Southeastern Pennsylvania.

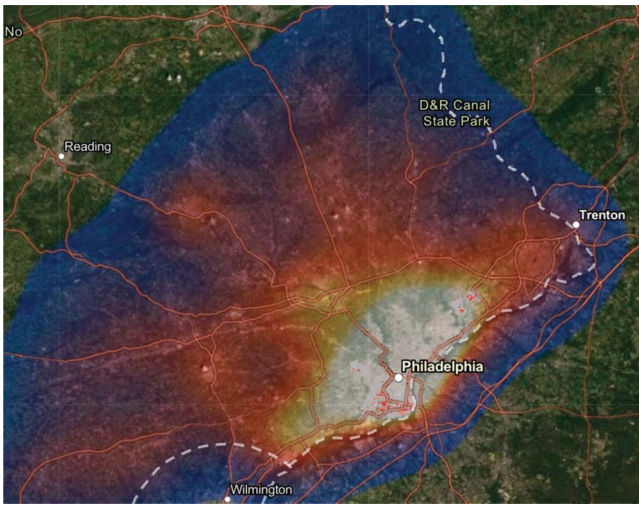

Figure 6. Traffic density across region based on census block population.

nitrite preservatives and disinfection byproducts in order to represent compounds with strong associations with the development of UC.[11] Seven industrial sites known to discharge these carcinogens were identified to be in proximity to UC hotspots, including 2 petroleum refineries, 2 shipbuilding and manufacturing sites, 1 sewage treatment plant, 1 cola bottling plant and 1 airport.

Interestingly, hotspot patients were not more likely to have worse pathological features than patients not living in hotspots. Also, worse pathological features were not associated with environmental exposures. These findings suggest other patient-specific factors like genetics and health care access may have a greater effect on pathological features than environmental exposures. Additionally, we found that patients residing in geospatial hotspots were less likely to have TE, which further suggests a significant environmental factor for the development of UC in these patients.

We also identified a significant relationship between UC hotspots and increased TD. Combustion of motor fuels is a major source of vehicular organic compounds such as benzene, vinyl chloride and pyrogenic PAHs, and it has been demonstrated that traffic volume is the main factor that influences the PAH content in urban dust.[17–19] Additionally, recent studies have reported positive associations between exposure to high concentrations of exhaust and development of bladder cancer.[17,20] The concentration of vehicular organic compounds is significantly enhanced in urban settings in particular due to reduced wind dispersion and trapping of pollutants by high buildings and narrow streets.[21]

While our results suggested that close proximity to airports was more likely in hotspot patients, this association did not remain significant on multivariate analysis. Airport pollution contributors include not only engine exhaust emissions, but also associated maintenance traffic, heating facilities and refueling operations.[22] Studies have demonstrated that airport-related pollutants can affect air quality near surroundings areas of the airport.[23,24] Concerningly, a study regarding O'Hare International Airport in Chicago estimated that cancer risks associated with the airport exceeded 10^6 for a 1,000 square mile area surrounding the airport, with a maximum individual risk of 10^4 based on extrapolated exposure of these compounds.[25]

Finally, our study demonstrated that patients within hotspots were more likely to be nonwhite, lower income and less educated, indicating a potential relationship between socioeconomic disparities and likelihood of residing in UC hotspots. Prior studies have demonstrated similar findings, including that

Figure 7. Regional and international airports meeting inclusion criteria.

Table 2. *Distribution of patient-level cancer characteristics by hotspot indication*

	UC Hotspot						
	No		Yes		Total		p Value
No. pts	4,932		148		5,080		
No. Ca characteristics (%):							
Histology							0.729
Pure urothelial	4,716	(95.6)	138	(93.2)	4,854	(95.6)	
Urothelial (squamous)	95	(1.9)	4	(2.7)	99	(2.0)	
Urothelial (sarcomatoid)	20	(0.4)	2	(1.4)	22	(0.4)	
Urothelial (micropapillary)	20	(0.4)	0	(0.0)	20	(0.4)	
Urothelial (neuroendocrine/small cell)	7	(0.1)	0	(0.0)	7	(0.1)	
Urothelial (nested)	6	(0.1)	0	(0.0)	6	(0.1)	
Urothelial (glandular)	30	(0.6)	2	(1.4)	32	(0.6)	
Urothelial (lymphoepithelioma)	1	(0.0)	0	(0.0)	1	(0.0)	
Urothelial (clear cell)	12	(0.2)	1	(0.7)	13	(0.3)	
Urothelial (microcystic)	1	(0.0)	0	(0.0)	1	(0.0)	
Urothelial (other)	24	(0.5)	1	(0.7)	25	(0.5)	
No. histology collapsed (%):							0.167
Pure urothelial	4,716	(95.6)	138	(93.2)	4,854	(95.6)	
Variant	216	(4.4)	10	(6.8)	226	(4.5)	
No. stage (%):							0.524
Ta	3,045	(61.7)	92	(62.2)	3,137	(61.8)	
Tis	249	(5.1)	5	(3.4)	254	(5.0)	
T1	998	(20.2)	27	(18.2)	1,025	(20.2)	
≥T2	640	(13.0)	24	(16.2)	664	(13.1)	
No. invasive, ≥T1 (%):							0.751
No	3,294	(66.8)	97	(65.5)	3,391	(66.8)	
Yes	1,638	(33.2)	51	(34.5)	1,689	(33.3)	
No. muscle invasive (%):							0.249
No	4,292	(87.0)	124	(83.8)	4,416	(86.9)	
Yes	640	(13.0)	24	(16.2)	664	(13.1)	
No. grade for diagnosis (%):							0.687
Low	2,582	(52.4)	75	(50.7)	2,657	(52.3)	
High	2,350	(47.7)	73	(49.3)	2,423	(47.7)	
No. site for diagnosis (%):							0.446
Bladder	4,698	(95.3)	142	(96)	4,840	(95.3)	
Kidney	121	(2.5)	4	(2.7)	125	(2.5)	
Ureter	102	(2.1)	1	(0.7)	103	(2)	
Urethra	11	(0.2)	1	(0.7)	12	(0.2)	

low-income families are 3 times more likely to live within high TD areas than those with high income, and that African Americans are threefold more likely to have high air toxin exposure in their communities due to proximity to vehicular traffic.[26,27]

There were several imitations. It was not possible to account for all instances of disease incidence or varied referral patterns in the area. Additionally, patient data were retrospectively catalogued and may be vulnerable to clerical errors and reporting biases. Data that were not available in the medical record were approximated based on census data, specifically income and educational attainment, and may not be representative of a given specific patient. Exposure data were limited in that the industrial and environmental sources of carcinogens were gleaned from government databases and may not be inclusive of the entirety of all sources of IBPs/EPs across all times within the region. Traffic data were estimated based on a specific year in question and may not be representative of traffic pattern exposures across a patient's lifetime. Addresses were catalogued at time of diagnosis, and it is assumed that the patient resided in said or similar address for a period of time necessary to receive significant environmental exposure. Additionally, proximity to source of exposure was used as a surrogate for actual exposure and may not be representative.

CONCLUSIONS

Spatially related clusters of UC may be associated with locoregional environmental exposures and may be the result of socioeconomic determinants. Further research that investigates the interplay between socioeconomic status, race and environmental risk factors has the potential to better identify at-risk populations and inform preventive and diagnostic policies.

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Table 3. *Univariate multilevel logistic regression models (random intercept models) for association with residing in UC hotspot*

	95% CI for OR			
	OR	Lower Confidence Limit	Upper Confidence Limit	p Value
Level 1 predictors:				
Age at diagnosis (yrs)*	0.97	0.94	1.02	0.226
Male	0.44	0.16	1.22	0.115
White (reference group = Black, Asian, Hispanic, other)	**0.10**	**0.05**	**0.19**	**< 0.001**
Heart disease	0.72	0.24	2.23	0.574
Type 2 diabetes	0.28	0.06	1.39	0.119
Chronic kidney disease	0.94	0.37	2.40	0.897
Hypertension	0.66	0.25	1.74	0.398
Hyperlipidemia	0.42	0.15	1.14	0.089
Chronic obstructive pulmonary disease	0.58	0.26	1.27	0.170
Other malignancies	0.39	0.12	1.26	0.116
Tobacco use	**0.24**	**0.09**	**0.63**	**0.004**
Alcohol use	**0.35**	**0.14**	**0.85**	**0.021**
Industrial/occupational exposure	3.51	0.22	56.30	0.376
Any exposure	**8.24**	**2.37**	**28.70**	**0.001**
Polycyclic aromatic hydrocarbon exposure	**> 999***	**> 999***	**> 999***	**< 0.001**
Live within 1,000 yds of traffic hotspot	**> 999***	**> 999***	**> 999***	**< 0.001**
Live within 1,000 yds of airport	**> 999***	**> 999***	**> 999***	**< 0.001**
Live within 1,000 yds of industrial site	**8.78**	**2.44**	**31.66**	**0.001**
Histology:				
Variant	Reference	—	—	—
Pure urothelial	0.64	0.10	4.06	0.639
Stage:				0.452
Ta	Reference	—	—	—
Tis	3.63	0.73	18.08	0.115
T1	1.04	0.30	3.56	0.953
T2	0.98	0.22	4.26	0.973
Invasive	1.09	0.71	1.68	0.695
Muscle invasive	0.88	0.22	3.49	0.856
Grade:				
Low	Reference	—	—	—
High	1.38	0.55	3.52	0.494
Site:				
Bladder	Reference	—	—	—
Other	0.03	0.00	6.20	0.201
Level 2 predictors:				
Median yearly household income (in $10,000 increments)†	**0.73**	**0.58**	**0.91**	**0.005**
% Population with 12th grade education (in 10% increments)†	0.72	0.48	1.09	0.123

Results in bold are statistically significant.
* OR is very large due to sparse data.
† Grand mean centered.

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Table 4. *Multivariable multilevel logistic regression model (random intercept models) for association with residing in UC hotspot*

	95% CI for Covariate Adjusted OR			
	Covariate Adjusted OR	Lower Confidence Limit	Upper Confidence Limit	p Value
	Fixed effects			
White (reference group = Black, Asian, Hispanic, other)	0.06	0.02	0.15	**< 0.001**
Tobacco use	0.39	0.16	0.91	0.031
Polycyclic aromatic hydrocarbon exposure	48.09	9.29	248.9	**< 0.001**
Live within 1,000 yds of traffic hotspot	>999*	>999*	>999*	**< 0.001**
	Random effect			
$\sigma 2_{u0}$†	47.5 (estimate)	31.7	70.9	**< 0.001**

Results in bold are statistically significant.
* OR is very large due to sparse data.
† Between-block group intercept variance.

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EDITORIAL COMMENTS

In this large, multi-institutional, retrospective, population-based study of over 5,000 patients diagnosed with UC in Southeastern Pennsylvania between 2008 and 2018 (representing 50% of the estimated incidence in the area of interest over the 10-year study period), Yankelevich et al identified hotspots of UC associated with proximity to areas of high traffic density, airports or sites of industrial discharge (ie PAH exposure), which were independent risk factors when accounting for tobacco use. These patients were more likely to be female, be nonwhite, be less educated and have a lower income, highlighting the continued socioeconomic disparities that are seen across our health care system across multiple disease states.

Although tobacco use is a well-known risk factor in the development of UC, exposure to industrial byproducts and environmental pollutants continues to be an important yet underreported occupational hazard. This study further emphasizes this relationship as these patients were also less likely to

have tobacco exposure. Locally here in Texas, there is increasing evidence that proximity to oil refineries puts populations at greater risk for UC. Williams et al reported that proximity to an oil refinery was also associated with a statistically significantly increased risk of incident cancer diagnosis across all cancer types.[1] Patients diagnosed with bladder cancer living within 0–10 versus 21–30 miles of an oil refinery were also at increased risk for distant disease (relative risk = 1.3) after adjusting for various demographic and socioeconomic variables.[1]

These data could be used in the future to identify at-risk populations for improved screening and early diagnosis of UC to improve patient outcomes. They could also be utilized in city/urban planning to minimize environmental hazard from industrial waste and vehicular exhaust as well as raise awareness about the socioeconomic disparities in exposure to these pollutants.

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1. Williams SB, Shan Y, Jazzar U et al: Proximity to oil refineries and risk of cancer: a population-based analysis. JNCI Cancer Spectr 2020; **4:** pkaa088.

The impact of social determinants of health was brought front and center with the COVID-19 pandemic.[1] However, structural inequality is neither new nor limited to pandemics. For example, within urology, increasing data show that Black men with prostate cancer have the same or better outcomes as other races when there is equal access to health care.[2] Neighborhood and physical environment are key parts of social determinants of health.[3] From a risk standpoint, urothelial cancer is strongly associated with carcinogen exposure. While tobacco and occupational exposures are best defined, the impact of environmental exposure has been more difficult to quantify. In this study, Yankelevich et al utilize geospatial analytics in metropolitan Philadelphia to evaluate environmental exposure and urothelial carcinoma, with notable findings.

First, they found 5 hotspots in the greater Philadelphia area where the incidence of UC exceeded the expected probability. Residents within these hotspots lived within 1,000 yards of chemical plants that released carcinogenic compounds (specifically polyaromatic hydrocarbons) and were exposed to greater traffic pollution than those outside of hotspots. Importantly, the authors controlled for both occupation and tobacco exposure. This finding is notable for showing an association of environmental exposure and risk of developing urothelial carcinoma.

In addition, the authors demonstrate that residents of hotspots were more likely to be nonwhite and of lower socioeconomic status (and less likely to have tobacco exposure) than patients who developed urothelial cancer outside of hotspots. Interestingly, patients in hotspots did not have worse pathological features than those outside, although oncologic outcomes were beyond the scope of the paper. While there may be residual confounding, if this method for identification of urothelial carcinoma hotspots is validated in other regions, it may provide opportunities for targeted screening and intervention.

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REPLY BY AUTHORS

We appreciate the insightful commentary by our colleagues Drs. Westerman and Sharma. Tobacco exposure is indicated as the proximate cause of urothelial carcinoma in the majority of cases, while a much smaller portion is linked to occupational exposures. However, isolated environmental exposures

are infrequently implicated, and parsing the relationship between environmental exposures and the development of urothelial carcinoma becomes difficult within the context of multifactorial and interrelated risk elements such as tobacco exposure and socioeconomic status. Furthermore, identifying relevant numbers of affected persons requires large volumes of data, but the registry or claims-based databases often employed for this purpose rarely possess the geographic granularity necessary to associate individual patients with specific exposures, and instead typically correlate residence within a particular boundary (ie ZIP code) with proximity to risk factors. The major strengths of our study involved the utilization of individual patient addresses and census block data to create highly specific zones of interest, while also using environmental registry data to identify uniquely relevant sources of industrial discharge and other environmental risk factors. We agree with Dr. Westerman and strongly encourage our peers across the nation to use these analytic techniques to examine local patient populations in the context of locoregional environmental risk factors. If similar findings appear to be repeatedly validated, research such as this can indeed be valuable, as Dr. Sharma suggests, not only with regard to improved screening, diagnosis and treatment, but also to improve urban planning and avoid structural injustices for marginalized populations (reference 27 in article).