Unique Geospatial Accumulations of Uveal Melanoma

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• PURPOSE: The main purpose of this paper was to describe the unique accumulation of cases of uveal melanoma (UM). All patients were white and did not have known occupational risk factors. From the authors' standpoint, there were no lifestyle factors in common in the reported cases. Results of more extensive analyses, including geospatial analysis, are currently being conducted and will be presented in a separate paper.

• DESIGN: Observational case series.

• METHODS: Descriptive data from medical records, patient interviews, and questionnaires were obtained from 5 patients from North Carolina, 6 patients from Alabama, and 14 patients from New York. Standard incidence ratio (SIR) calculations were provided by the respective states' cancer registries. UM is the most common primary malignant eye tumor in adults, although it is rare, with 2,500 cases diagnosed annually in the United States. Despite a growing understanding of the molecular characteristics, there remains uncertainty regarding epidemiologic trends and environmental risk factors. This study identified 3 geographic accumulations of UM: 1) Huntersville, NC; 2) Auburn, AL; and 3) Broome and Tioga Counties, New York. Investigation of these groups will guide ongoing efforts to discover potential risk factor and assist with future treatment and prevention.

• RESULTS: In North Carolina, 5 females who were identified as living in Huntersville, NC, were diagnosed with UM at ages 20, 22, 24, 30, and 31. The SIR calculations considering the observed and expected incidence ratios was 0.7 (95% confidence interval [CI], 0.5-0.9) in Mecklenburg County. In Alabama, 6 individuals who were identified as either attending Auburn University or employed there from 1989 to 1993 had diagnoses of UM. Initial SIR calculations for white females of all ages was 1.15 (95% CI, 0.989-1.328). In New York, SIR for Broome and Tioga counties were 0.93 and not significant. However, in Tioga county, for males and females and females alone, SIRs were 2.00 ($P = .04$) and 3.33 ($P = .006$).

• CONCLUSIONS: Although most of the conclusions that the SIR does not meet statistical criteria that defines these accumulations as true "cancer clusters," considering the incidence and demographics of UM, these accumulations of cases is unexpected and worth additional exploration. Further investigation into these cases with additional geospatial analyses and blood and tumor testing is ongoing. Information learned from the study of these unique populations may inform a better understanding of the pathogenesis of UM. (Am J Ophthalmol 2020;220:102–109. © 2020 Elsevier Inc. All rights reserved.)

UVEAL MELANOMA (UM), ALTHOUGH CONSIDERED a rare cancer, is the most common primary intraocular malignancy in adults. The incidence has reportedly remained stable, with an age-adjusted incidence of 5 per million people in the United States.[1] The median age at diagnosis of this disease is documented to be 55 to 62 years of age, affecting men slightly more than women.[1,2]

Various host risk factors have been identified, including the presence of light colored eyes, fair skin, an inability to tan, ocular melanocytosis, dysplastic nevus syndrome, and germline *BAP1* mutations.[3,4] The role of sun exposure as a risk factor for UM is controversial.[5,6] Meta-analysis suggests that chronic ultraviolet light exposure and geographic latitude are not associated with the disease; however, welding has been identified as a risk factor.[7] Importantly, tumor whole-exome sequencing has not demonstrated an ultraviolet radiation signature in UM.[8,9]

Because UM is rare, the identification of environmental risk factors using conventional epidemiologic approaches has been challenging. Unique geospatial accumulations of patients provide unique opportunities to explore causation. There were 2 suspected UM "clusters" documented in the medical literature in the early 1980s which were investigated for potential causes. One group of cases involved 3 individuals from a small rural community, with diagnoses over a 2.5-year period. The other group involved 5 employees of a chemical plant with diagnoses over a 25-year period.[10,11] In neither case could a likely causal agent be identified.

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This study identified 3 additional unique geospatial accumulations of patients with UM in North Carolina, Alabama, and New York. This paper summarizes the initial observations made regarding these cases.

SUBJECTS AND METHODS

INITIAL OBSERVATIONS REGARDING POTENTIAL GEOSPATIAL accumulations occurred while speaking to patients seen at Wills Eye Hospital and the Department of Medical Oncology at Thomas Jefferson University, Philadelphia, Pennsylvania. Additional assistance was subsequently provided by other treating physicians at Duke University Eye Center and Retinal Consultants of Alabama, Birmingham, AL. This study was approved by the institutional review board Thomas Jefferson University (IRB, 19D.144).

During each clinical visit, detailed medical, surgical, family, and social histories were recorded for each patient. During this process, patients were identified as potential cases within an accumulation based on certain criteria. The following general criteria for screening potential unusual accumulations of patients included: 1) unusual age at time of diagnosis (younger than 40 years old); 2) diagnosis of UM in close contacts; and 3) exposure to environmental toxins and/or uncommon infections.

When unusual accumulations of patients were identified, more detailed individual information was collected. In addition to gathering information regarding current addresses, lifetime residential histories were requested from suspected cases, as a number of the patients were not living in the concerning geographic areas at the exact time of diagnosis. Also, referring physicians were contacted to obtain more information on similar cases in the same geographical areas.

As recommended by cancer cluster investigation guidelines set forth by the Centers for Disease Control and Prevention (CDC), relevant state cancer registries were contacted to calculate the standard incidence ratios (SIR) of UM in the respective states or counties.[12] SIR is a calculation used to determine whether the suspected accumulation of cases truly represents a statistically significant increase in the observed-to-expected ratio of cases. The SIR is defined as

$$SIR = \frac{\sum_{k=1}^{M} D_k}{\sum_{k=1}^{M} t_k \lambda_k^*} = \frac{D}{E^*}$$

Where the total number of events observed in the cohort is $D = \sum_{k=1}^{M} D_k$, and the total number of expected events is $E^* = \sum_{k=1}^{M} E_k^* = \sum_{k=1}^{M} t_k \lambda_k^*$.[13]

RESULTS

THIS STUDY IDENTIFIED 3 UNIQUE GEOSPATIAL ACCUMULATIONS of patients in North Carolina, Alabama, and New York.

• **NORTH CAROLINA:** In Huntersville, North Carolina, 5 young women were initially identified, all of whom resided in Huntersville during a time period overlapping in 2005 and in whom UM was diagnosed in 2008, 2009, 2011, 2013, and 2014 (Table 1). The first 3 patients were young women whose diagnoses were found at the ages of 22, 24, and 20. All three attended the same high school, Hopewell High School in Huntersville, NC, over a 10-year period. Subsequently, 2 additional females with diagnoses of UM at the ages of 31 and 30 were identified. These last patients did not attend Hopewell High School but did reside in Huntersville around the same time.

A request for an investigation of a "cancer cluster" was subsequently submitted to the North Carolina Central Cancer Registry (CCR). In a formal report provided by North Carolina CCR in January 2015, SIR calculation considering expected and observed cases of UM was 0.7 (95% confidence interval [CI], 0.5-0.9) (Table 2, Supplemental Material). The report concludes that "the standard incidence ratios for both case definitions were less than one, indicating that the incidence of UM between 2000 and 2013 in Mecklenburg County (including Huntersville, North Carolina) was not higher than expected." Such a finding led to the initial conclusion that there was no concern for a UM cancer cluster based on this approach. However, it was also noted that "the incidence rates may be underestimated because the North Carolina Central Cancer Registry (CCR) does not have complete cases for 2012 and 2013." Furthermore, no data for cases diagnosed in 2014 were available due to a lag time in reporting. Finally, it was reported that "cases diagnosed out of the state and country but that may be receiving treatment in facilities in North Carolina were not included as they are not required to be reported to the North Carolina CCR."

Importantly, of the 5 index cases, none were included as observed cases in the North Carolina CCR report based on the inclusion criteria initially set forth by the state. One patient's UM was diagnosed in 2014, 2 lived out of state at the time of diagnosis, and although living in North Carolina at the time of diagnosis, 2 cases were diagnosed and treated out of state.

To further illustrate the discrepancies between actual cases and those captured by the state cancer registry, a chart review performed by Dr. Kitty Gordon, an ophthalmologist in North Carolina, found that nearly one-third of the cases of ciliary body or choroidal melanoma evaluated at the University of North Carolina (UNC) between 2010 and 2015 were not reported to the North Carolina CCR. Based

TABLE 1. Geospatial Accumulation of Patients With UM in Huntersville, NC

Patient	Sex	Age at Diagnosis (y)	Date of Diagnosis	Residence at Diagnosis	Location of UM	Diagnosing and Treating Institution	Residence at Time of Suspected Clustering
1	F	22	4/2009	Aiken, SC	Choroid	Wills Eye Philadelphia, PA	Huntersville, NC
2	F	24	12/2008	Charleston, SC	Cilio-choroid	Duke Eye Center Durham, NC	Huntersville, NC
3	F	20	7/2013	Charlotte, NC	Choroid	Wills Eye Philadelphia, PA	Huntersville, NC
4	F	31	2/2011	Charlotte, NC	Choroid	Wills Eye Philadelphia, PA	Huntersville, NC
5	F	30	2/2014	Concord, NC	Choroid	Duke Eye Center Durham, NC	Huntersville, NC

F = female; NC = North Carolina; PA = Pennsylvania; SC = South Carolina; UM = uveal melanoma.

TABLE 2. SIR Calculation Mecklenburg County, NC 2000-2013

	Observed	Expected	SIR	95% C.I
All UM cases	56	79	0.7	0.5-0.9

SIR = standard incidence ratio; UM = uveal melanoma.

on International Classification of Diseases editions 9 (ICD)-9 and -10 codes, there were 66 patients with UM diagnoses, followed and/or treated with ciliary body or choroidal melanomas at UNC between 2010 and 2015. Of those cases, only 41 (62%) were on the list of cases reported through the UNC Cancer Registry to the North Carolina CCCR. The State Registrars reviewed the missing cases and identified 2 of them in their database that might have been reported through another entity. Therefore, at least 23 of the present 66 cases were not reported to the North Carolina CCCR (unpublished data).

• **ALABAMA:** We initially identified 4 young women (Patients 1-4) all of whom attended Auburn University, AL, during 1989 to 1993 and had diagnoses of UM in 2000, 2001, and 2012 at ages 31, 31, 42, and 50. It is notable that Patients 1, 2, and 3 lived in dormitories in close proximity to each other whereas they studied at Auburn University. We subsequently identified 2 male patients who stayed on the Auburn University campus during the time when the above female patients attended Auburn University. Patient 5 was a student in a master's degree program, and Patient 6 was employed at Auburn and was involved in reconstruction of dormitories. (Table 3)

A request for an investigation was submitted to the Alabama state cancer registry. A brief data analysis was provided that reported SIR calculations for malignant ocular tumors in white females stratified by age. When considering ages 30-44, the SIR calculation was 1.15 (95% CI, 0.989-1.328), although a ratio of more than 1 was not found to be statistically significant (Table 4).

Similar to the investigation in North Carolina, there was concern that observed cases were under-reported due to patients receiving diagnoses out of state or living out of state at the time of diagnosis, despite their living near one another during the time of possible mutual exposure.

• **NEW YORK:** Fourteen patients who resided within a 15-mile radius of each other along the Susquehanna River in the towns of Owego, Apalachin, Vestal, Endicott, Johnson City, and Binghamton were identified (Table 5, Figure). These towns bridge 2 counties, Broome and Tioga. The median age at diagnosis in this group of patients was 53 years old and was slightly higher than that of the patients identified in North Carolina and Alabama. Eight of the 14 patients were women.

A request for investigation was submitted to the New York state cancer registry, and SIR calculations were provided for Broome and Tioga counties individually and combined for years 2005-2015. The expected numbers of cases were computed by applying age- and sex-specific rates for a standard population (New York State, exclusive of New York City) to the age- and sex-specific populations of the 2 counties, as provided by the National Cancer Institute's Surveillance, Epidemiology and End Results program. Considering both males and females across both counties, the SIR calculation was 0.93 and was not statistically significant. SIR calculations for Broome county across sexes was also not significant. However, SIR calculations for males and females and females alone in Tioga county noted ratios of 2.00 (95% CI, 0.91-3.9) and 3.33 (95% CI, 1.34-6.87), respectively (Table 6).

TABLE 3. Geospatial Accumulation of Patients With UM in Auburn, AL

Patient	Sex	Age at Diagnosis (y)	Date of Diagnosis	Residence at Diagnosis	Location of Uveal Melanoma	Diagnosing and Treating Institution	Residence/Employment at Time of Suspected Clustering
1	F	31	10/2001	Birmingham, AL	Cilio-choroid	Wills Eye Philadelphia, PA	Auburn, AL Auburn University
2	F	31	1/2000	Birmingham, AL	Choroid	Eye Foundation Birmingham, AL	Auburn, AL Auburn University
3	F	42	7/2012	Memphis, TN	Iris	Hamilton Eye Institute Memphis, TN	Auburn, AL Auburn University
4	F	50	12/2013	Guntersville, AL	Choroid	Retinal Consultants Birmingham, AL	Auburn, AL Auburn University
5	M	31	3/5/2002	Greenville, AL	Choroid	Retinal Consultants Birmingham, AL	Auburn, AL Auburn University
6	M	39	9/2009	Birmingham, AL	Cilio-choroid	Wills Eye Philadelphia, PA	Auburn, AL Auburn University

F = female; M = male; Al = Alabama; TN = Tennessee; PA = Pennsylvania; UM = uveal melanoma.

TABLE 4. SIR Calculation Alabama White Females 2002-2011

Age Group	Observed	Expected	SIR	95% CI
30-34 y	5	2.45	2.04	0.625-4.283
35-39 y	2	3.74	0.53	0.046-1.558
40-44 y	11	6.62	1.66	0.811-2.814
30-44 y	18	12.8	1.41	0.821-2.147
All ages	185	160.5	1.15	0.989-1.328

CI = confidence interval; SIR = standard incidence ratio.

DISCUSSION

ALTHOUGH AWARENESS OF UM HAS INCREASED, DIAGnostic methods have improved, insight into molecular pathogenesis is better, and there is a greater understanding of prognostic factors, there remains limited understanding surrounding the cause of the disease. There have been numerous publications investigating the role of host risk factors such as iris and skin color, geographic residence, occupation, hormones, access to fluoridated water, exposure to ultraviolet light, cell phone use, electromagnetic fields, blue light, arc welding, and pesticides.[14–24] However, other than iris and skin color and arc welding, none of the other factors have been shown to be statistically significant when subsequently studied.

As noted previously, there have been only 2 suspected UM "clusters" documented in the medical literature.[10,11] Although in both clusters an environmental or occupational exposure was suspected, no candidate exposures were identified. In the 1980 report,[10] as all patients were chemical workers at the same plant, the potential for chemical exposures as a cause was discussed. That paper notes that the workers might have been exposed to 13 substances with known carcinogenic properties. However, the authors also noted that, because exposure histories were incomplete for all of the cases, they did not feel it was appropriate to discuss specific exposures as possible cause.[10] In the 1982 publication,[11] which reported on cases in a small Pennsylvania community, the authors administered water obtained from the town with suspected clustering and water from a town that acted as a control to mice. Interestingly, 9 of 60 mice (15%) of the mice given water from the town with the increased incidence developed ocular lesions that were described as an abnormal bilateral monolayer of cells on the outer surface of the anterior outer lens capsule. None of the mice were found to have developed choroidal lesions of any kind.

A publication by Schwartz[19] correlated the incidence of eye cancer with access to fluorinated water. The investigation began with an attempt to correlate the incidence of eye cancer, including UM, with geographic and demographic features such as latitude, longitude, population density, ophthalmologist density, and percentage receiving fluorinated water. After data analysis, incidence rates were only significantly correlated with access to fluorinated water ($P = .01$). The discussion noted that the state with the highest incidence of eye cancer was Oregon, which happened to have a state-wide long-standing opposition to the fluorination of water. Furthermore, the author considered a publication by Watzke and associates[25] that noted an increase in histoplasmosis-like choroiditis in Oregon, which is a nonendemic area. Given the significant correlation between the incidence of UM incidence and the lack of fluorination of water in Oregon, coupled with the documented occurrence of potentially infectious histoplasmosis-like condition causing choroidal inflammation, the authors postulated that fluorination might have protected against UM by its antimicrobial properties.

TABLE 5. Geospatial Accumulation of Patients With UM in NY

Patient	Sex	Age at Diagnosis (y)	Date of Diagnosis	Residence at Time of Suspecting Clustering and Diagnosis	Location of Uveal Melanoma	Diagnosing and Treating Institution
1	M	57	1/2014	Binghamton, NY	Choroid	Wills Eye; Philadelphia, PA
2	F	56	6//2005	Vestal, NY	Choroid	Wills Eye Philadelphia, PA
3	F	50	5/2015	Endicott, NY	Iris	Wills Eye Philadelphia, PA
4	M	37	2004	Johnson City, NY	Unknown	Wills Eye Philadelphia, PA
5	F	50	9/2007	Owego, NY	Choroid	Wills Eye Philadelphia, PA
6	F	65	5/2014	Owego, NY	Choroid	Wills Eye Philadelphia, PA
7	F	48	12/2005	Vestal, NY	Choroid	Wills Eye Philadelphia, PA
8	F	49	4/2000	Binghamton, NY	Cilio-choroid	Wills Eye Philadelphia, PA
9	M	67	4/2017	Apalachin, NY	Choroid	Wills Eye Philadelphia, PA
10	F	61	1997	Endicott, NY	Choroid	Wills Eye Philadelphia, PA
11	M	60	2/2008	Owego, NY	Cilio-choroid	Wills Eye Philadelphia, PA
12	M	29	9/2016[a]	Endicott, NY	Choroid	Wills Eye Philadelphia, PA
13	F	35	12/2017	Binghamton, NY	Choroid	Wills Eye Philadelphia, PA
14	M	56	11/2016	Binghamton, NY	Choroid	Retinal Consultants Birmingham, AL

AL = Alabama; F = female; M = male; NY = New York; PA = Pennsylvania.
[a]Initial diagnosis with amelanotic choroidal nevus in 2011.

Although there are no definitive data to show that a history of ocular histoplasmosis or histoplasmosis-like infection causing choroiditis were risk factors for UM, this hypothesis is intriguing, given the geographic accumulations discussed in this paper.

In addition to the "infectious" hypothesis mentioned above, another hypothesis is highlighted that involves exposure to known carcinogenic polychlorinated biphenyls (PCBs). Behrens and associates[26] sought to study the association between hormonal factors and occupational PCB exposure with UM risk. PCBs have been shown to possibly interfere with estrogen and antiandrogenic pathways and may influence melanogenesis.[27–30] Behrens and associates concluded that exposure to PCBs, notably pyralene, was associated with a more than 6-fold increased risk for UM. Although there have been no reports directly linking PCB contamination to increased UM in a population, a report of 117 patients with PCB poisoning noted unique ocular manifestations, including abnormal pigmentation of the eyelids and conjunctiva.[31] The report did not comment on abnormal pigmentation of the iris, ciliary body, or choroid. Concerns for PCB contamination in North Carolina and Alabama have been suggested for further investigation.

One other hypothesis that should be considered is that of exposure to electromagnetic fields (EMF) as a risk factor for development of UM. Behrens and associates previously reported on possible association between occupational EMF and the risk of UM.[21] Analysis of a case-control study noted positive associations between EMF exposure and risk of UM, especially in dark-eyed women. Similar to his hypothesis of PCB driven melanogenesis, Behrens and associates also proposed that EMF exposure might have influenced risk of UM development through hormonal alterations.[26] The suggestion that EMF exposure correlates with a higher risk of UM, especially among women with brown eyes, is particularly interesting given the predominance of female cases in the geographic accumulations noted in this paper.

The present study had a number of limitations due mostly to the relatively unprecedented nature of this type of investigation. First, cluster analyses of any disease can be difficult and certainly more so for rare cancers that

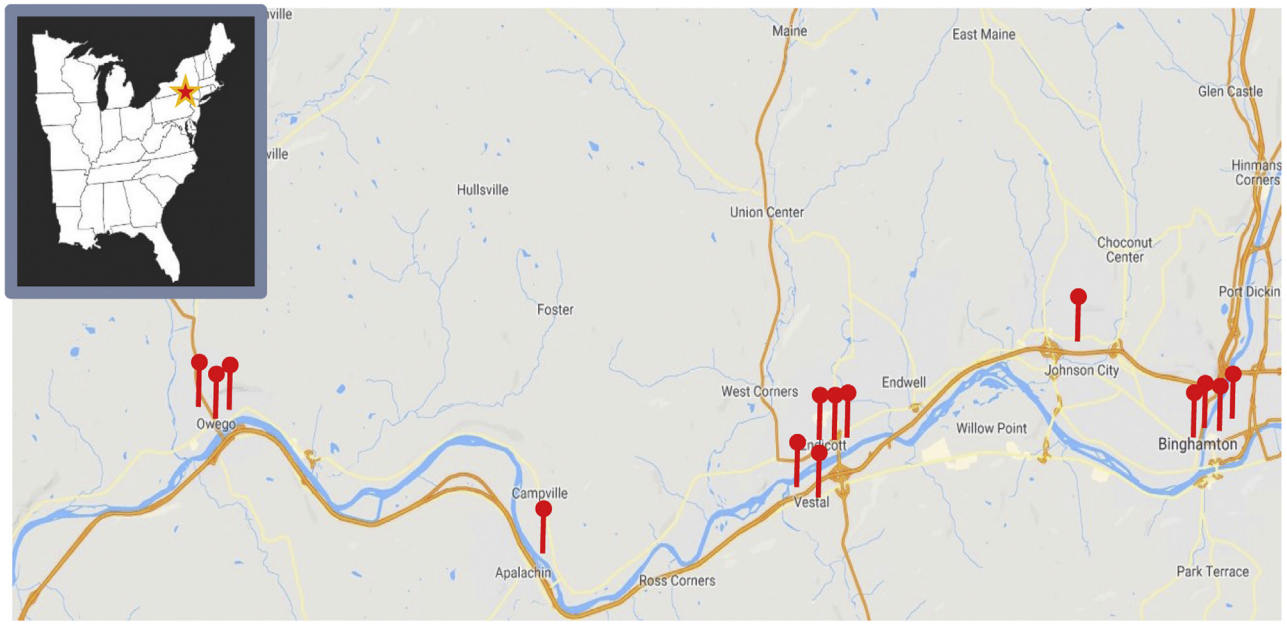

FIGURE. Map of Broome and Tioga Counties with Cases.

TABLE 6. SIR Calculations for Broome and Tioga Counties

Counties	Observed	Expected	SIR	95% CI
Males and Females				
Broome and Tioga	20	21.5	0.93	(0.57-1.44)
Broome	11	17.0	0.64	(0.32-1.16)
Tioga	9	4.5	2.00	(0.91-3.9)
Males				
Broome and Tioga	8	11.1	0.72	(0.31-1.42)
Broome	6	8.7	0.69	(0.25-1.50)
Tioga	2	2.4	0.83	(0.10-3.01)
Females				
Broome and Tioga	12	10.4	1.15	(0.60-2.02)
Broome	5	8.3	0.6	(0.20-1.41)
Tioga	7	2.1	3.33	(1.34-6.87)

CI = confidence interval; SIR = standard incidence ratio.

may not be accurately reported to the respective state cancer registries. Beyond requesting SIR calculations from state cancer registries, there is a lack of guidance on how to further investigate unique accumulations especially if the definition of a statistical "cancer cluster" is not met. Second, although the authors represent a number of academic centers that attend a good number of UM cases, there may be cases that the authors were unaware of that could have impacted the observations. Third, in identifying patients that met our criteria, the study relied on patients or families in the instance the patient was deceased to accurately report where they lived and when. Often subjects were recalling their geographic locations and details of dates and diagnoses greater than 10 years prior.

Notably, the authors thoroughly investigated the family histories of cases reported in this paper. The authors failed to identify the clear evidence to suggest "founder effect" in reported cases. There were no blood relations up to the third generation of individual patients. Germ-line mutation in *BAP1* is reported to cause familial *BAP1* cancer syndrome including UM, mesothelioma, and meningioma.[32] There were no such accumulations of cancers in their family members.

We are currently collecting tissue and blood specimens from patients and family members to investigate the germline mutation of the *BAP1* gene and other genes of interest.

The main purpose of this paper was to describe the unique accumulation of UM cases. All patients were white, and they did not have a known occupational risk factors. From the authors' standpoint, there were no lifestyle factors in common in the reported cases. Results of more extensive analysis including geospatial analysis are being conducted and will be presented in a separate report.

Although there have been no definitive epidemiologic studies regarding the cause of UM, a review of the literature summarized in this discussion may aid in ongoing investigations. In the absence of a known cause and as a result of the initial responses from the state cancer registries, it was suspected that the conventional approach to cancer cluster investigation would not be beneficial in rare cancers such as UM. Although the accumulation of cases had not met the criteria for a "cluster," the number of cases reported here warranted further investigation. A comprehensive

investigation that includes environmental toxicology, clinical genetics, geospatial association, and molecular epidemiology evaluation has been subsequently initiated.

More importantly, development of reliable and timely national tumor registry system for UM is critical to the investigation into the epidemiology of this disease.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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