

Investigation of Ocular Melanoma Incidence, an Aggressive Form of Rare Tumor

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Investigation of a potentially rare form of cancer cluster can be challenging for central cancer registries and traumatic for the patients and families concerned. This investigation of ocular melanoma incidence in the City of Huntersville, NC included reviews of literature, inter-state collaborations, records from building sites and construction, site visit, environmental health inspections, cancer rate analyses and community questionnaires.

The NC CCR's analyses of ocular melanoma, a rare and aggressive form of cancer, reiterates the importance of recruitment of physician offices and timely case ascertainment from facilities that diagnose and treat cancer. Diagnosis may be made in a clinic in one state but treatment may be given in a different state where specialized radiation treatment is available. Therefore, the need for timely exchange of data between registries is also strengthened. Further, there is a need for a clear case definition as the diagnosis of ocular melanoma is often based on clinical exam only, tumors are treated with radiation, and rarely is a histological evaluation available.

In November 2013, the NC CCR responded to the initial inquiry to investigate an incidence of ocular melanoma diagnosed among five young women ages 19-31 in years 2008, 2009, 2011, 2013 and 2014 and all identified as living in Huntersville, NC. Three of these young women attended the same high school. The NC CCR did not observe an excess of ocular melanoma cases above what would be expected in the concerned area for these years. The NC CCR continued to monitor the incidence of ocular melanoma in Huntersville for years 2014 - 2017 and found that no additional cases of ocular melanoma were reported.

According to the Ocular Melanoma Foundation (<http://www.ocularmelanoma.org/disease.htm>), approximately 2,500 adults are diagnosed with ocular melanoma in the United States each year. The incidence is approximately 5 to 7.5 new cases per one million people per year. Males have an increased incidence compared to females, and incidence is highest among people with lighter skin and blue eyes. The incidence rate increases with age and peaks near age 70. Further, among those who develop metastatic ocular melanoma, 90% of patients also develop liver disease. Approximately 50% of ocular melanoma patients will develop metastatic disease within 15 years of the original diagnosis; currently there is no cure for metastatic ocular melanoma.

The fact that this rare form of cancer had affected young women--under 30 years of age when diagnosed—makes it clear why the families and patients wanted answers and wanted to find the cause for this deadly disease. The Mayor of Huntersville, the Mecklenburg County Health Department, the Charlotte-Mecklenburg County School System, and the media were equally concerned about the situation. The NC CCR continued the investigation by collaborating in 2015 with the NC Occupational and Environmental Epidemiology Branch (OEEB), who initiated an epidemiologic investigation to look for common environmental exposures and risk factors for ocular melanoma. The Centers for Disease Control and Prevention (CDC) were consulted about this potential cluster of ocular melanoma, and independent literature reviews were conducted by the CDC and OEEB. As several of these ocular melanoma cases were diagnosed and/or treated at Thomas Jefferson University Hospital in Pennsylvania, Duke University Medical Center, and UNC Hospital, oncologists and physicians from these facilities were also involved and consulted about the potential cluster.

For the epidemiologic investigation, names and contact information of eight people diagnosed with ocular melanoma between 2009 and 2014 and who had lived in, worked in, or frequently

visited Huntersville prior to their diagnosis were collected by the families and provided to OEEB. Four additional cases were referred by the initial contacts, and an additional case joined after becoming aware of this investigation through the media. The OEEB, with the support of the Mecklenburg County Health Department Epidemiology Program, administered the questionnaire with these 13 families.

The OEEB's questionnaire collected information on 13 patients: their demographics, occupational and non-occupational exposures, exposure to ultraviolet (UV) light exposure and other environmental exposures, their school and medical history, where they lived, where they were diagnosed, name of the diagnosing physician and facility and name of the physician and facility where they received treatment. One out of these 13 respondents was diagnosed with benign eye tumor and not ocular melanoma, and was therefore excluded from the OEEB's analysis.

The NC CCR used the 12 questionnaire responses to identify and confirm the residence at the time of diagnosis and the diagnosing physician/facility. At the time of diagnosis, six cases were from Mecklenburg County and, of these, three lived in the city of Huntersville or in Cornelius (town adjacent). Two out of these three cases were diagnosed and treated in Pennsylvania. For the remaining six cases, two lived in South Carolina and four lived in other NC counties.

However, three of these six cases lived in Huntersville at some point prior to being diagnosed and one only worked in Huntersville. Three of these 12 total cases attended the same high school in Huntersville at different times between 2001 and 2011 and were diagnosed with ocular melanoma within six years of graduating.

In June 2015, the CCR and the OEEB presented their findings to the families at a Community Meeting in Charlotte, NC coordinated by the Mecklenburg County Health Department. The CCR

did not observe an excess of ocular melanoma cases, and the OEED reported that there were no obvious environmental causes identified. Still, perhaps due to the atypical nature of these cases, the investigation was continued to identify potential underlying etiology.

The NC CCR followed up with physicians listed in the questionnaires and as well as over 25 other physicians/ophthalmologists in the Huntersville/Charlotte area to make sure that all ocular melanoma cases diagnosed during the previous five years were reported to the NC CCR. In addition, the NC CCR reached out to the cancer registries in Pennsylvania, Georgia, and South Carolina to receive ocular melanoma cases of North Carolina residents diagnosed or treated in their state. The Pennsylvania Central Cancer Registry conducted additional follow-up on two of the missed NC cases and later reported them to our registry through the data sharing agreement.

The NC CCR staff reviewed hundreds of medical records submitted by Mecklenburg County ophthalmology offices for this special study, looking for missed ocular melanoma cases with an ICD-O-3 primary site code of C69 and histology codes of 8720-8780. This was an extremely time-intensive effort. Upon receiving the additional cases from this special case-finding study and interstate data exchange, the NC CCR updated the analysis and did not find the incidence rates to be elevated in Huntersville or Mecklenburg County. Most of the added cases were not diagnosed within this timeframe, or the patient's address at diagnosis was not Huntersville. The OEED's investigation and risk factors identified from the literature review did not find any common environmental exposures specific to the Huntersville areas that were likely associated with ocular melanoma.

In August 2016, The North Carolina General Assembly appropriated \$100,000 to the City of Huntersville to address the Ocular Melanoma Cluster in the Huntersville area and to perform environmental testing. A committee was formed consisting of Medical Oncologists and

Ophthalmologists from UNC Lineberger Cancer Center, Duke Hospital, Jefferson Hospital in Philadelphia, and Columbia University in New York, and an epidemiologist from the UNC Gillings School of Public Health, along with the families of ocular melanoma patients.

Ongoing efforts are to offer enrollment in the UNC Health Registry and Cancer Survivorship Cohort, biobanking of blood and tumor tissue, and to provide genetic testing. The medical oncologists are also investigating to close the gap between clinicians and the registries ascertainment of ocular melanoma cases, and to review the registry definition verses clinicians' definition of diagnosing ocular melanoma cases. This investigation of a rare disease has resulted in the Ocular Melanoma Cluster committee considering creating a patient centered registry for ocular melanoma patients that would help in following patients over their lifetime independent of the NC CCR.

Ocular melanoma diagnosed clinically and treated with minimal histologic confirmation, for it to strike outside of its usual demographics makes the push to see action so understandable. This ocular melanoma investigation has underscored the importance of our relationship with community physicians and their role in our case ascertainment efforts.

A final report on the Huntersville investigation of Ocular Melanoma by the committee is due to the General Assembly. The NC CCR is looking forward to presenting the findings of this report and having a thoughtful discussion of this investigation at the 2018 NAACCR Annual Conference.