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Division of Public Health

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Ewing Sarcoma Investigation in Wake County, North Carolina

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Introduction

The North Carolina Central Cancer Registry (CCR) conducted a review of cancer case reports in October 2012 after a citizen expressed concern of a possible Ewing sarcoma cluster in the Wake Forest area of Wake County. CCR did not observe an excess of Ewing sarcoma cancers above what would be expected for the time frame and location. The North Carolina Occupational and Environmental Epidemiology Branch (OEEB) initiated an epidemiologic investigation in April 2013 after local residents expressed continued concern about the potential cluster. The goal of the investigation was to look for common environmental exposures among the cases of Ewing sarcoma in the Wake Forest vicinity and address environmental issues of concern expressed by parents and local residents.

For the purpose of this investigation, the cluster was defined as three cases of Ewing sarcoma and one case of undifferentiated sarcoma (which the case patient's oncologist determined was clinically compatible with Ewing sarcoma) diagnosed between 2009 and 2012 in one ZIP code (Wake Forest area) in Wake County. Additionally, one case of Ewing sarcoma diagnosed internationally who had resided in the same ZIP code during this time period was included in the cluster investigation. CCR's analysis included three cases of Ewing sarcoma diagnosed in North Carolina but did not include the case diagnosed internationally or the case diagnosed with undifferentiated sarcoma due to the criteria for inclusion utilized in the CCR's protocol.

Methods

OEEB addressed the potential cluster of Ewing sarcoma and also addressed the citizens' concerns about possible environmental contamination in the community. To investigate this potential cancer cluster, OEEB:

- utilized the OEEB standard non-infectious disease cluster protocol,
- investigated risk factors for Ewing sarcoma identified in the scientific literature, and
- addressed environmental concerns expressed by the parents of the cases and the public.

During the initial steps of the investigation, OEEB contacted Centers for Disease Control and Prevention (CDC) staff to discuss the possible cluster of Ewing sarcoma and seek guidance to begin an investigation of this possible cluster (1). Both OEEB and CDC staff performed an independent literature review searching for known causes of Ewing sarcoma. Next, OEEB staff met with oncologists from Duke and UNC to discuss the approach and methodology to be used for the investigation. OEEB utilized its standard non-infectious disease cluster protocol to continue the investigation, which included asking the CCR to calculate a standardized incidence ratio and confidence interval for cases of Ewing sarcoma in Wake County (Attachment 1).

To obtain more occupational/environmental information on the cases and their families, OEEB mailed a standardized pediatric cancer questionnaire (Attachment 2) to the parents to gather information on potential chemical exposures at home or in their environment that the cases may have had in common. Names were obtained from the CCR of all persons living in the Wake Forest ZIP code (27587) of concern who were diagnosed with Ewing sarcoma between 2008 and 2012. Because three of the cases were in the same high school graduating class, OEEB engaged in a discussion with Wake County Public School System Environmental and Grounds Department (EGD) staff to gather information about possible environmental exposures at the high schools the students had attended in Wake County. OEEB evaluated results of radon testing in the schools and discussed with EGD staff the issues of damaged carpet and renovation work at Wake Forest-Rolesville High School, which were issues of concern to several parents.

To investigate possible environmental contamination in the area of concern, OEEB conducted a site visit to the community and discussed potential hazardous waste sites and environmental contamination in the area with North Carolina Department of Environment and Natural Resources (DENR) staff.

Results

Literature review

According to the American Cancer Society (2), the Ewing family of tumors (EFT) is a group of cancers that start in the bones or nearby soft tissues and share some common features. They can develop at any age, but these tumors are most common in early teenage years. There are three main types of Ewing tumors:

- Ewing sarcoma of bone: Ewing sarcoma that starts in the bone is the most common tumor in this family.

- Extraosseous Ewing tumor (EOE): Extraosseous Ewing tumors start in soft tissues around bones, but they look and act very much like Ewing sarcomas in bones. They are also known as Ewing sarcomas.

- Peripheral primitive neuroectodermal tumor (PPNET): This rare childhood cancer also starts in the bone or soft tissue and shares many features with Ewing sarcoma of bone and EOE. Peripheral PNETs that start in the chest wall are known as Askin tumors.

The cells that make up Ewing sarcoma, EOE, and PPNET are very similar. They tend to have the same DNA (gene) abnormalities and share similar proteins, which are rarely found in other types of cancers. For this reason, these three cancers are thought to develop from the same type of cells in the body.

The following epidemiology and risk factor information comes from the National Cancer Institute's website: http://www.cancer.gov/cancertopics/types/ewing

Epidemiology

Primary bone tumors are responsible for 6 percent of all childhood cancers. Although rare, the EFT represents the second most common primary bone malignancy affecting children and adolescents, after osteosarcoma. Despite this, EFT is responsible for only 3.5 percent of cancers in American children 10 to 14 years old, and 2.3 percent of those arising among 15 to 19 year olds. In the United States, 650 to 700 children and adolescents younger than 20 years old are diagnosed with bone tumors every year, of which 200 are EFT and the remainder osteosarcomas. The peak incidence is between 10 to 15 years of age. However, 30 percent of cases arise in children under the age of 10, and another 30 percent are in adults over the age of 20. As with many pediatric tumors, there is a slight male predominance.

Racial and ethnic factors are of epidemiologic importance. For unclear reasons, the EFT affect mainly Caucasians and are extremely uncommon among blacks (both in the United States and Africa) and Asians. The reason for this ethnic distribution is not known.

Risk factors

The cause of tumors in Ewing sarcoma is unknown. Cases are thought to be sporadic, although it has been found that relatives of patients with Ewing sarcoma have an increased incidence of neuroectodermal and stomach malignancies. In rare cases, Ewing sarcomas have been reported as a second malignancy, being found after a patient has been treated for another cancer.

EFT have not been consistently associated with any familial or congenital syndromes. Specific environmental exposures have not been identified as causal, although associations have occasionally been found (Table 1). EFT develop rarely after treatment of a primary cancer during childhood, but most cases do not appear to be related to radiation therapy.

Ewing sarcoma may be more common in children who have hernias. The mechanism underlying a possible association between hernias and Ewing sarcoma is unclear, but suggesting possible in-utero developmental exposure.

Several studies had found that living on a farm was a potential risk factor, but no specific agent on a farm was consistently found in the literature. An association has been suggested between a parental occupation of farming (particularly if the mother farmed) and the development of Ewing sarcoma. Maternal smoking or x-ray exposure during pregnancy have also been shown to be potential risk factors, although the literature is inconsistent.

Table 1. Selected environmental exposures and relevant findings in the scientific literature

Exposure	Possible association with Ewing sarcoma in the literature*
Asbestos	– (no association has been found, to our knowledge)
Biosolids	–
Carpet materials/cleaners	–
Fluoride	–
Hazardous waste	+ / – (some studies have shown a possible association with solvents which are often found in hazardous waste, while other studies have not found an association)
Maternal exposure to X-rays	+/ –
Maternal smoking during pregnancy	+ / –
Mold	–
Parent worked on a farm	+ / –
Pesticides	+ / –
Radon	–
Solvents	+ / –
TCE	–
Vinyl chloride	–

*A possible association does not imply that the agent causes Ewing sarcoma, only that those diagnosed with Ewing sarcoma may be more likely to have been exposed to the agent than those who have not been diagnosed with Ewing sarcoma.

– No association has been found, to our knowledge

+ / – Possible association shown in some but not all studies

Centers for Disease Control and Prevention involvement

OEEB sent the cancer questionnaire to the CDC for review, as well as the non-infectious disease cluster investigation protocol that OEEB uses. CDC supported OEEB's method of investigation and recommended that a standardized incidence ratio (SIR) of Ewing sarcoma be calculated to compare the observed and the expected number of cases in the county. The CCR performed this calculation and did not find an elevated incidence of Ewing sarcoma in Wake County. They were unable to calculate an SIR at the Census block group level due to small numbers (Attachment 1). CDC also did a literature review and was unable to find any specific environmental risk factors for Ewing sarcoma or any information on the latency period for this disease.

UNC/Duke Oncology meeting

On May 16, 2013, staff from OEEB and the CCR met with oncologists from UNC and Duke University to discuss the investigation. As a result of the discussion, the UNC pediatric oncology department indicated willingness to do DNA analysis on cases of Ewing sarcoma as part of a research study.

Cancer questionnaire

All five questionnaires were promptly completed by the parents and/or the cases and returned to OEEB (Table 2). Most of the cases reported living in Wake Forest for at least seven years prior to diagnosis.

Three of the cases were in the same graduating class and attended Heritage Middle School and Wake Forest-Rolesville High School together. All three also attended Jones Dairy Elementary School for at least one year, but not simultaneously. During their four years of high school, they attended three different locations due to school renovations (Wake Forest-Rolesville Ninth Grade Center, Wake Forest-Rolesville High School and Heritage High School). The fourth case attended different schools, and the fifth case was an older adult whose school years would not have overlapped with the other four cases.

Four of the cases were on city water, and one was on community well water. City water and community wells are required to be periodically monitored for chemical content each year. Testing results for City of Raleigh public water, which serves Wake Forest, showed no chemical/bacterial violations in the past ten years, with the exception of three coliform violations in 2007 and one insufficient level of chloramine disinfectant violation in 2008, which were all corrected. None of the cases or their parents reported having any jobs or hobbies that involved chemical exposures. None of the cases reported smoking or chewing tobacco on a regular basis. None of the parents of the four young adult cases reported that they had lived or worked on a farm prior to their child's diagnosis. Two cases reported that one of their parents had smoked while their mother was pregnant or before the case was diagnosed.

Table 2. Summary of completed questionnaire data

	Number (%)
Completed questionnaires returned	5 (100%)
School history	
Attended Jones Dairy Elementary School	3 (60%)
Attended Heritage Middle School	3 (60%)
Attended Wake Forest-Rolesville High School	3 (60%)
Parental history	
Case's mother had a job or hobby while pregnant that involved exposure to chemicals or radiation	0 (0%)
Case's mother or father worked in a job involving chemicals	0 (0%)
Case or their parents lived or worked on a farm	0 (0%)
Patient history	
Age at diagnosis	
≥ 18 years	3 (60%)
< 18 years	2 (40%)
Drinking water source	
Public water	4 (80%)
Community well water	1 (20%)
Had a job or hobby in which chemicals were used	0 (0%)
Smoked or chewed tobacco on a regular basis	0 (0%)
Aware of any hazardous or toxic waste sites, leaking underground storage tanks, chemical plants, waste incinerators or landfills near their home before they developed cancer	0 (0%)

Environmental investigation of Wake Forest-Rolesville High School

Several parents expressed concern about possible exposures that may have occurred during renovations at Wake Forest-Rolesville High School (WFRHS) while their children were attending the school.

OEEB contacted the Director of the Environmental and Grounds Department for the Wake County Public School System and the Assistant Superintendent for Facilities to inquire about the renovation work that had occurred at WFRHS in recent years. It was reported that the school had undergone a major renovation during 2008–2009. According to the AHERA Reinspection report from 03/26/13, all identified asbestos in the building was removed between 2009 and 2010, with the exception of asbestos fire doors (confirmed through

documentation provided by the Health Hazards Control Unit, OEEB, NC Division of Public Health, reviewed October 2013).

Mobile classroom units (trailers) are very common in Wake County schools. These are monitored for water leaks and mold, and work orders are submitted to repair or replace them as needed. There were nine mobile units on the site of WFRHS during the 2007–2008 school year. All units were inspected by the Town of Wake Forest Inspections Department and complied with all applicable building codes. All nine units were no longer present after 2009.

OEEB was provided the maintenance history for WFRHS from 2007–2011. OEEB staff reviewed the list of repairs, which appeared to consist of routine maintenance issues.

While carpet materials have not been associated with Ewing sarcoma, concerns about carpet issues at the high school were investigated. Wake County Public School System Environmental and Grounds Department (EGD) staff reported that the carpet was replaced in the school's media center in December 2012. The underlying concrete slab had not been thoroughly dried, and when glue was applied, the backing of the carpet began to break down and school employees complained of a "chemical odor." The carpet, which had been installed one year prior, was subsequently removed, the underlying slab dried out, and the carpet replaced with no further odor complaints.

According to EGD staff, an integrated pest management system is utilized, and pesticides are not routinely used. Occasional crack and crevice treatment in a specific area may be used for certain situations like roaches, or outside the building to treat fire ants and wasps. Some studies have shown a possible association between pesticide exposure and Ewing sarcoma, although the literature is inconsistent. There is no indication that the students would have direct contact with pesticides applied in the school.

All Wake Forest area public schools are on City of Raleigh water. Public water supplies are required to be routinely monitored for chemical content by Wake county. WFRHS was built on the former site of Wake Forest College after it moved to Winston Salem in the 1950's and became Wake Forest University. There is no history of any hazardous waste disposal at the site.

OEEB staff traveled to Wake Forest on July 3, 2013, to view the school properties where the three cases had attended. OEEB staff did not see any industries nearby that may be a source of pollution. They observed the following:

- site of a former landfill on North White Street that has been turned into a park

- a former power plant near the intersection of North Avenue and Wingate Street (according to facilities management staff at Southeastern Baptist Theological Seminary, there had previously been two boilers in the facility, but the facility was closed one year ago)
- old trailers behind Heritage Middle School
- small gas tanks and an electric company next to Jones Dairy Elementary School
- a small farm with a large silo across from Jones Dairy Elementary.

Any potential contaminants from these sources would not affect the public drinking water supply, and there is no evidence of active air contaminant releases at these sites.

Radon levels statewide were checked in the late 1980's and early 1990's at various schools in each county. In Wake County, 323 samples were taken at different schools throughout the county for routine testing. During the initial testing in the early 1990's, four samples were taken at WFRHS. Three of the four samples were lower than the EPA action level of 4 picocuries/liter (pCi/L). One sample, taken in the music room, was at 4.5 pCi/L (www.ncradon.org/Testing_Data.html). The school did not consider this level to be of immediate concern at that time. Radon has not been shown to be associated with Ewing sarcoma.

In 2007, Jones Dairy Elementary School and Heritage Middle School were tested for radon, and levels found were below 4 pCi/L. In 2009, WFRHS was tested again for radon in all occupied spaces (approximately 70 rooms), and the levels for eight of the sampled rooms were between 4 pCi/L and 10 pCi/L. EGD staff felt that the levels found did not require immediate action and verified that the HVAC system was operating correctly.

Environmental Investigation of the Community

OEEB spoke with several DENR staff to inquire about underground storage tanks or hazardous waste sites in the area where the cases lived. DENR's Division of Waste Management (DWM) reported that there had been a leaking underground storage tank containing heating oil at WFRHS. In 1997, the tank was closed in place by emptying it and filling it with concrete, as is commonly done. The tank is located under what is now a paved parking lot. DWM was not aware of any oil contamination of ground water in the area.

The former North White Street landfill is located about one mile from the former Wake Forest-Rolesville Ninth Grade Center and about two miles from WFRHS (Attachment 3). This site is inactive and was closed around 1989. The facility was permitted to receive municipal solid waste. Ground water and surface water sampling is occurring at the site. A small amount of vinyl chloride has been found in one monitoring well, but it has not migrated off-site (personal communication from DENR Solid Waste Section on 9/19/2013). The site has been turned into a park. Vinyl chloride has not been shown to be associated with Ewing sarcoma.

According to the Aquifer Protection Section of DENR's Division of Water Quality, the nearest permitted biosolid application fields are located about four miles from WFRHS and about 2.5 miles from Heritage High School. Biosolids have not been shown to be associated with Ewing sarcoma.

The Superfund Section of DENR's DWM reported that there are 11 drycleaners located in the Wake Forest area, and none reported soil or ground water contamination issues. There is one Resource Conservation and Recovery Act (RCRA) site within the five by six mile area where the cases lived. This site is located about one mile from WFRHS and about three miles from the residence of the nearest case. The site is undergoing well monitoring, and there is some indication of trichloroethylene (TCE) contamination in the water and soil at the site. This is a common contaminant found in many of the approximately 2,000 inactive hazardous sites that DENR is tracking throughout North Carolina. TCE has not been shown to be associated with Ewing sarcoma.

DENR's Division of Air Quality reported that they were not aware of any indicators of pollutant releases to the air in the Wake Forest area that would be exposures of concern.

DENR's Hazardous Waste Section confirmed that there are no known releases from hazardous waste generators in the 27587 ZIP code area.

While radon has not been associated with Ewing sarcoma (3), concern about radon exposure was expressed by the parents of the cases and community members. The State Radon Program provided information about radon levels in Wake County (Attachment 4). The average radon level is 1.6 pCi/L, which is slightly higher than the national average indoor radon concentration in homes of 1.3 pCi/L. For Wake County, 75% of samples were below 2 pCi/L, 15% were between 2 and 3.9 pCi/L and 10% were at or above 4.0 pCi/L (http://county-radon.info/NC/Wake.html). In Wake Forest ZIP code 27587, 182 homes were tested. Levels ranged from 0.1 pCi/L to 12.9 pCi/L, with an average level of 1.7 pCi/L. Nineteen homes (approximately 10%) were over the EPA recommended level of 4 pCi/L. According to the EPA's website (www.epa.gov/radon/aboutus.html), "Lung cancer is the only known effect on human health from exposure to radon in air." This is also supported in scientific literature.

Discussion

In the U.S., it is estimated that cancer will affect approximately 1 in 2 men and 1 in 3 women in their lifetime. Cancer is not a single disease but is a group of more than 100 different types of conditions characterized by the uncontrolled growth and spread of abnormal cells. Different cancers have different causes and are likely to be caused by a combination of factors acting together over many years. Both hereditary and environmental factors have a role in cancer development. It is estimated that about 75–80% of cancer cases have an environmental factor as an underlying cause. Of the identified environmental factors, tobacco smoking is estimated to be responsible for 30%; nutrition, physical activity and obesity for 30%; occupational (work

exposures) for 4% and environmental pollutants for 2% (4). However, for many cancers, such as Ewing sarcoma, the cause is unknown. If a cancer cluster is suspected, OEEB will begin a preliminary investigation, working with the CCR, to see if an elevated rate of cancer is detected and if so, to determine if exposure to a known environmental pollutant is occurring.

Investigations of cancer clusters have rarely found an etiologic agent to explain the cancer cluster. In a review of cancer clusters nationwide during the last 20 years, only 1 of 428 investigations revealed a clear cause (5). In fact, most clusters appear to be chance events (occurring at random), especially those that involve common cancer types or all cancers combined (6). Cancer cluster investigations are difficult for many reasons, including the small number of cases often involved (making statistical analyses problematic), failure to account for latency, and issues of in-migration to a community where a person may have a similar cancer but the exposure to an agent associated with that cancer occurred years before the person moved into that community. It is recognized that there is a length of time (usually years to decades) from exposure to a carcinogen to the development of the cancer (known as the latency period) (1). This gives the appearance that there may be a common environmental exposure in the community, when in reality the cases are not related. Additionally, there is often a lack of clinical or molecular tests that can determine the cause of cancer. From the time the oncogenic process begins until the person first shows symptoms, many years have usually passed and there is no evidence of the cancer-causing chemical in the person's body. However, as research advances, new genetic markers are being found for certain cancers which may have a hereditary basis.

OEEB performed a cancer cluster investigation of 4 individuals who developed Ewing sarcoma and one individual who developed undifferentiated sarcoma but had clinical characteristics of Ewing sarcoma. The investigation involved multiple steps, and OEEB was provided information by various local, state and federal agencies. Among these agencies, assistance was provided by the Wake County Public School System Environmental and Grounds Department, Wake County Public Health staff, various sections within the North Carolina Department of Environment and Natural Resources, the Central Cancer Registry in the North Carolina Department of Health and Human Services, and the Centers for Disease Control and Prevention National Center for Environmental Health**.**

Independent literature reviews by OEEB and CDC did not reveal a specific etiologic agent that is known to lead to the development of Ewing sarcoma. Potential risk factors such as living on a farm were not reported by the high school students. OEEB was not able to find a shared unusual environmental exposure that possibly may be associated with Ewing sarcoma. The Central Cancer Registry did not find an elevated SIR for Ewing sarcoma in Wake County from 2008–2012.

OEEB's investigation of Wake Forest-Rolesville High School did not find any imminent health risk to students or staff. A leaking underground storage tank was remediated years ago. There were no obvious sites in close

proximity to WFRHS that would pose an environmental health risk to students as far as OEEB could determine, based on their site visit and discussions with DENR. Short term testing results showed that eight classrooms had radon levels above 4 pCi/L. Long term testing in these areas should be conducted to determine if remediation is needed.

Concern was expressed by several community members about environmental contamination and radon in the Wake Forest area. While radon has not been associated with Ewing sarcoma, it has been associated with lung cancer (3). The average radon level in Wake County is 1.6 pCi/L, which is slightly higher than the national average indoor radon concentration in homes of 1.3 pCi/L. Fortunately, in Wake County, 75% of samples were below 2 pCi/L, and 15% were between 2 and 3.9 pCi/L. However, 10% were at or above 4.0 pCi/L (http://county-radon.info/NC/Wake.html). In the Wake Forest ZIP code 27587, approximately 10% were over the EPA recommended level of 4 pCi/L.

Conclusion/Recommendations

Ewing sarcoma is a rare and serious disease which affects mainly young people. OEEB staff were saddened to learn of the potential cluster of four persons diagnosed with Ewing sarcoma and one person diagnosed with undifferentiated sarcoma (clinically compatible with Ewing sarcoma) who resided within the same ZIP code in Wake Forest and felt that it was important to investigate all potential exposures of concern, particularly since three of the cases attended the same schools for a number of years prior to being diagnosed. OEEB staff investigated the concerns of the cases and their parents with the goal of either identifying and eliminating any harmful exposures to persons in the community or providing reassurance that no imminent hazards exist in the community.

Based on analysis of the completed questionnaire data, review of potential sources of environmental contamination by DENR, risk factors identified from the literature and investigation of issues raised by the public, OEEB was not able to identify any common environmental exposures that were likely to be associated with Ewing sarcoma. In addition, the CCR did not find a higher incidence of Ewing sarcoma in Wake County compared to what would be expected for 2008–2012. This finding suggests that the five cancer cases occurred within the same Wake Forest ZIP code by chance.

OEEB staff did not identify any environmental exposures of immediate concern in the area. Although this finding will hopefully be reassuring to the Wake Forest community, OEEB acknowledges that the lack of a common environmental exposure or explanation for the cancer diagnoses is frustrating for the cases and their families. Unfortunately, the majority of cancer cluster investigations across the United States do not find a common environmental exposure that is likely to be associated with the cases. Although many types of cancer are associated with behavioral or environmental risk factors which can be changed (e.g. smoking), based on

our current state of knowledge, the cause of Ewing sarcoma remains unknown so specific behavioral or environmental recommendations to decrease the risk are not available.

Because slightly elevated radon levels were detected in some WFRHS classrooms, OEEB recommends long term radon testing in the 8 classrooms in WFRHS with radon levels > 4 pCi/L. In addition, OEEB recommends that Wake Forest residents test their homes for radon, as up to 10% of the Wake Forest homes tested previously were higher than the EPA recommended level and the U.S. Surgeon General and EPA recommend that all homes be tested for radon (www.epa.gov/radon/aboutus.html).

As the etiology of Ewing sarcoma remains unknown, OEEB would encourage the families of the cases to contact the UNC Pediatric Oncology Division to participate in a DNA research study on Ewing sarcoma.

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Attachment 1

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Report on Standard Incidence Ratio for Ewing Sarcoma Cases
Wake County, North Carolina
November 2013

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Background

The residents of Wake Forest expressed concern about the high incidence of Ewing Sarcoma in their neighborhood to the North Carolina Central Cancer Registry. The initial investigation using N.C. CCR's standard procedure did not find any excess cases of Ewing Sarcoma in Wake County. Per recommendation by the Centers for Disease Control and Prevention (CDC), standard incidence ratios (SIR) were used to further examine whether there was unusually high incidence of Ewing Sarcoma in Wake County.

Standard incidence ratios have been widely used to evaluate whether the incidence of disease, such as cancer, is a statistically significant excess for one selected area, such as a county, over a period of time, such as 10 years. It is assessed by calculating the ratio of the *observed number of cases* over the *expected number of cases* in the selected area during the study period. The expected number of cases is estimated by multiplying North Carolina age-specific incidence rates of the disease and the denominator population of the area during the study period. This is based on the assumption that the State rate of the disease is what would be the average rate expected throughout the state. Thus, we can "expect" a certain number of cases in the selected area by using the State rates as a standard. The standard incidence ratio is calculated to compare *the observed and the expected number of cases* in the area. A 95% confidence interval (CI) calculated around the SIR assesses the statistical significance and the stability of an SIR. If the 95% CI range does not include the value one, it is an indication that the incidence in the study population is significantly different from the 'normal' population.

Material and Method

Data source

Data used for this investigation were based on cases diagnosed during 2008 – 2012 and reported to the North Carolina Central Cancer Registry (N.C. CCR) as of October 2013 for patients whose address at the time of diagnosis was in North Carolina. This time period was used to be consistent with the cases being investigated. Cases were selected based on diagnosis codes as reflected in the pathology and medical reports reported from the hospitals and facilities. Further, 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 N.C. CCR. The N.C. CCR receives cancer diagnosis and treatment information from hospitals and other facilities at least six months after the diagnosis. The reason for this is that General Statute 130A-209 requires facilities to report complete first course of treatment data and many cases have an extended period of first course of treatment. The patient may have surgery, followed by multiple courses of chemotherapy, followed by radiation therapy. In order to obtain complete and accurate data from the facilities, there is a lag time of at least six months. For some cases, N.C. CCR receives multiple reports from different facilities, which are reviewed and consolidated on an ongoing basis. N.C. CCR continues to receive reports

from the hospitals for cases diagnosed in 2011, 2012, 2013 and prior years. Therefore, there may be cases diagnosed in 2011 or 2012 that have not been reported and included in this report.

Selection criteria for observed Ewing sarcoma cases

According to standard procedure county-level data were used to calculate standard incidence ratios (SIR) for the county; hence, Wake County was selected as the unit of analysis for this investigation. Observed cases of Ewing Sarcoma Family of Tumors (ESFT) selected for this investigation were diagnosed between 2008 and 2012 in Wake County, North Carolina. In this investigation, two definitions of Ewing sarcoma were considered: 1) Ewing Sarcoma only, based on histology code 9260; and 2) Ewing Sarcoma Family of Tumors, based on histology codes 9260, 9364, 9365 and 9473.

Estimation of expected cases

In order to estimate expected Ewing sarcoma and ESFT cases for Wake County between 2008 and 2012, North Carolina 2008-2012 age-specific (in 10-year intervals) incidence rates for Ewing Sarcoma, as well as ESFT were used. It should be noted that the incidence rates may be underestimated because the N.C. CCR does not have complete cases for 2012 (see Data Source section). The denominator population of Wake County was the total population in Wake County for each age group from 2008 to 2012. The annual age-specific populations for Wake County came from the National Center for Health Statistics.[1]

Data Analysis

Data were analyzed using formula-based calculations with Microsoft Excel. The formulas used in this report were based on those listed on the National Cancer Institute website for the standard incidence ratios and exact confidence limits.[2]

Denominator population of an age group:

Wake County population between 2008 and 2012 for each age group

Expected number of cases of an age group:

N.C. age-specific incidence rate (per 100,000) x Denominator population

Standard incidence ratio (SIR):

Observed number of cases / Sum of expected number of cases from all age groups

Exact 95% Confidence Interval:

$$\text{Lower limit} = \frac{\chi^2_{2x(\#observed),\alpha/2}}{2x(\#Expected)} \qquad \text{Upper Limit} = \frac{\chi^2_{2x(\#observed+1),1-\alpha/2}}{2x(\#Expected)}$$

Where $\chi^2_{v,\alpha}$ is the 100α percentile of the chi-square distribution with v degrees of freedom and α is 0.05.

The 95% confidence interval indicates that the "true" value of the standard incidence ratio would be within the interval 95 percent of the time, and is calculated to indicate whether the standard incidence ratio is statistically significant, i.e., the upper and lower bound does not include the value of one.

Results

During 2008-2012, there were 9 observed cases of Ewing Sarcoma and 12 were statistically expected to occur and 10 observed cases of Ewing Sarcoma Family of Tumors (ESFT) and 17 were expected to occur in Wake County. The standard incidence ratios for both case definitions were less than one, indicating that the incidence of Ewing Sarcoma or ESFT between 2008 and 2012 in Wake County was not higher than expected (See Table 1). The confidence intervals further confirmed that any differences between observed and expected number of cases, for

both Ewing Sarcoma and ESFT, were not statistically significant as both confidence intervals included one. In order for the number of cases to have been significantly greater (i.e., less than 5% probability the observed value occurred by chance) than the expected level, we would need to have observed 22 Ewing Sarcoma cases during this time-frame.

Table 1. Observed and Expected Cases, 2008–2012

	Observed	Expected	SIR	95% C.I.
Ewing Sarcoma (9260)	9	12	0.8	(0.3-1.4)
ESFT (9260, 9364, 9365, 9473)	10	17	0.6	(0.4-1.2)

Additional analysis was also performed at the 2010 U.S. Census block group level. Census block groups were aggregated to form an area encompassing the Ewing Sarcoma cases from the initial inquiry. Census 2010 block groups were chosen for inclusion in an initial study area, based on whether they included at least one Ewing Sarcoma case, for the time period studied. However, there were too few cases (less than five) for the analysis to assess the standard incidence ratios as well as the 95% confidence intervals. Therefore results from this analysis are not reported.

Conclusions

The standard incidence ratios were estimated for both Ewing Sarcoma and Ewing Sarcoma Family of Tumors to investigate whether the incidence of Ewing Sarcoma was unusually high in Wake County between 2008 and 2012. As of October 2013, the result of the analysis failed to indicate a higher than expected number of Ewing Sarcoma cases in Wake County during this time period.

One limitation of this investigation is that age-specific incidence rates, hence the number of expected cases, for Ewing Sarcoma and ESFT were under-estimated. This is because the N.C. CCR is still receiving 2012 cases from medical facilities. Similarly, the number of observed cases for Ewing Sarcoma and ESFT could also be under-counted due to the lag time in reporting. Therefore, this analysis will be repeated by the end of 2013 when it is determined that 2012 incidence reporting is at least 98 percent complete.

References

1. Bridged-Race Population Estimates: Data Files and Documentation. The National Center for Health Statistics. URL: www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm#vintage2009. Updated on June 13, 2013. Accessed on June 18, 2013.

2. Standardized Incidence Ratio and Confidence Limits. The National Cancer Institute: Surveillance, Epidemiology and End Results. URL: http://seer.cancer.gov/seerstat/WebHelp/Standardized_Incidence_Ratio_and_Confidence_Limits.htm. Accessed on June 18, 2013.

Attachment 2

Pediatric Cancer Cluster Report Form

1. Name of Person Completing Form_____

2. Date Form Completed_____

Informant Information (informant is the person completing the form)

3. Address: Street_____
(For address, please list physical street name and number)

4. City_____ State_____ Zip_____

5. Telephone Number: _____

6. Relationship to Patient: _____

Patient Information

7. Name_____

8. Current Mailing Address: Street_____
(For addresses, please list street name and not PO Box number)

9. City_____ State_____ Zip_____

10. Telephone Number_____

11. Residence address at time of cancer diagnosis (if different from current mailing address above)
Street: _____
(For addresses, please list street name and not PO Box number)

City_____ State_____ Zip_____

How long did the patient live at this address before diagnosis? (yrs)_____

Please list previous addresses of patient and dates (year) of residence prior to diagnosis:

_____
_____
_____
_____
_____
_____
_____

12. Did the patient live with anyone besides the parents for a significant length of time prior to being diagnosed? (circle) Yes No Don't Know
If yes, please list address and dates (year)

_____
_____
_____
_____

13. What schools did your child attend and dates before diagnosis?
Preschool_____
_____
_____
Grade School_____
_____
_____
Middle School_____
_____
_____
High School _____
_____
_____

14. Location of primary cancer (example lung, brain):_____

15. Type of Cancer (example: glioma, meningioma)_____

16. Age at diagnosis (yrs) _____

17. Approximate date when patient first developed symptoms_____

18. Date of Diagnosis (month/year)_____

19. Physician and facility where the patient was diagnosed and treated?
_____

20. Race (circle one) White Black American Indian Asian Other (list)_____

20. Patient's current age (yrs) _____

21. If deceased, age at death (yrs) _____

22. Parents' Occupation and Industry
Father's job at time when patient diagnosed with cancer
Industry_____
Job Title_____
Dates Worked _____
Any chemical or radiation exposures at work (circle) yes no don't know
If yes, please list types

Past jobs (company and job title)
1) _____
2) _____
3) _____

Mother's job at time when patient diagnosed with cancer
Industry_____
Job Title_____
Dates worked_____
Any chemical or radiation exposure at work (circle) yes no
If yes, please list types

Past Jobs 1) _____
2) _____
3) _____

23. Did the patient have a job before being diagnosed with cancer? (circle) yes no
If yes, describe_____
_____
_____

24. Did the mother have any jobs or hobbies while she was pregnant with the patient that involved exposure to chemicals or radiation? (circle) Yes No
If yes, describe_____
_____
_____

25. Family History of cancer: list all close blood relatives who have had cancer and give the site and type of cancer (do not give site to where cancer has spread)

Relationship to Patient	Site of Cancer	Type of Cancer
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

26. Did the patient ever smoke tobacco on a regular basis? (circle) Yes No Don't know
If yes, how often and how much_____

27. Did the patient chew tobacco? (circle) Yes No Don't Know
If yes, how often and how much_____

28. Did either parent smoke while the mother was pregnant or before the patient developed cancer? (circle)
Yes No Don't Know

29. Did the patient have any hobbies in which chemicals were used? (Examples: photography, staining of furniture, gardening) (Circle) Yes No Don't Know
If yes, list the chemicals used_____

30. Did either parent have hobbies where chemicals were used <u>before</u> the patient was diagnosed with cancer? (circle) Yes No Don't Know
If yes, list the chemicals used_____
_____

31. List any activities the patient had outside the home: (list activities and location)
_____
_____
_____

32. Did the mother use well water or public water <u>while</u> pregnant?
_____
_____

33. Did the patient use well water or public water <u>before</u> the patient developed cancer?
_____
_____

34. Did you live close to any hazardous or toxic waste sites, leaking underground storage tanks, chemical plants, waste incinerators or landfills before the patient developed cancer?
(circle) Yes No Don't Know

If yes, describe the site, location of the source of potential exposure, the dates the exposure has been present and the contaminants that were present.

A. Source_____
Location_____
Date from_____ to _____
Contaminants_____
_____

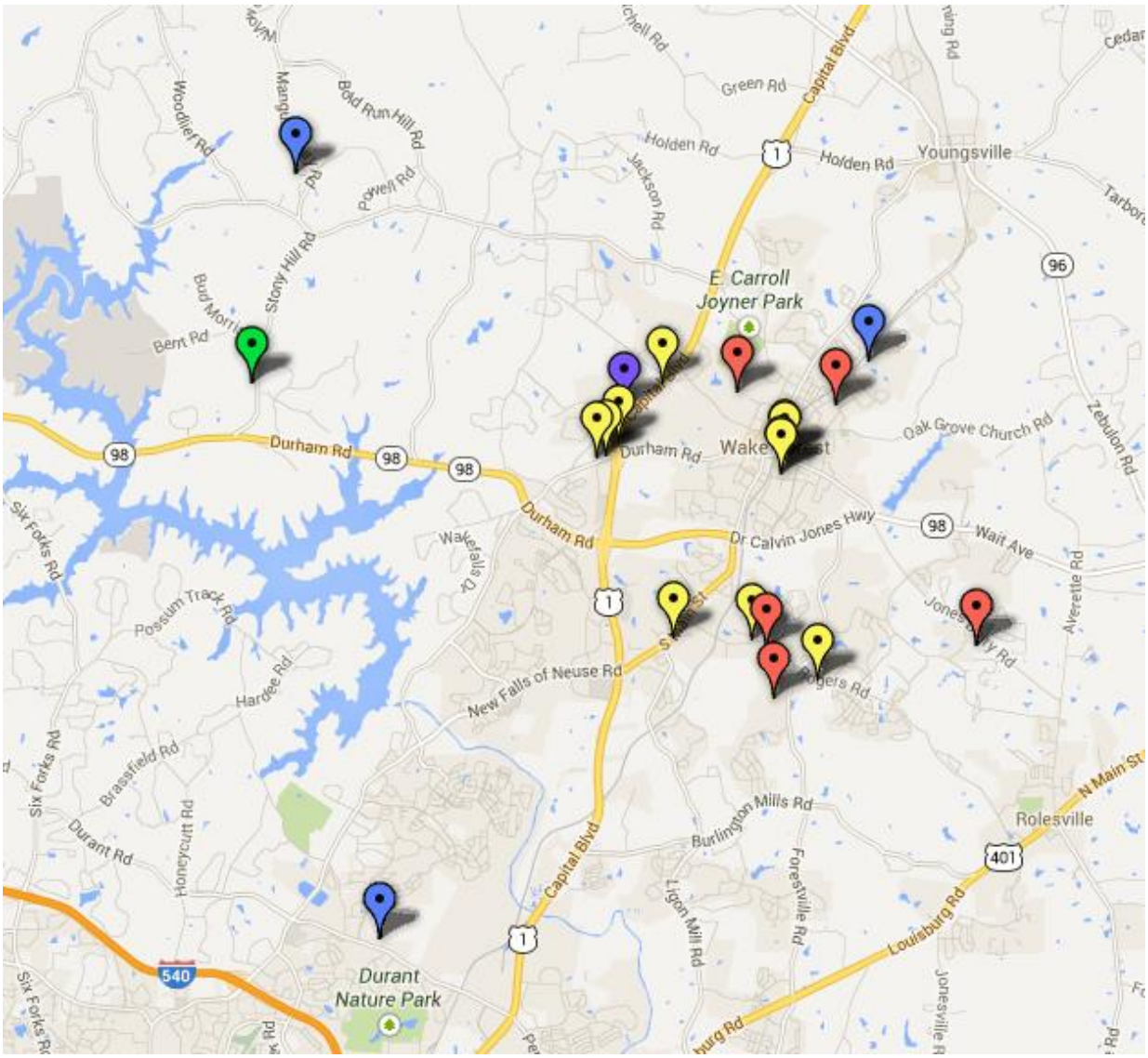
B. Source_____
Location _____
Date from _____to _____
Contaminants_____
_____

C. Source _____
Location _____
Date from_____ to _____
Contaminants_____
_____

35. Are there any other things that you can think of that may help us with this investigation?

Attachment 3

Map of Wake Forest showing public schools, dry cleaners, former landfills, and hazardous sites

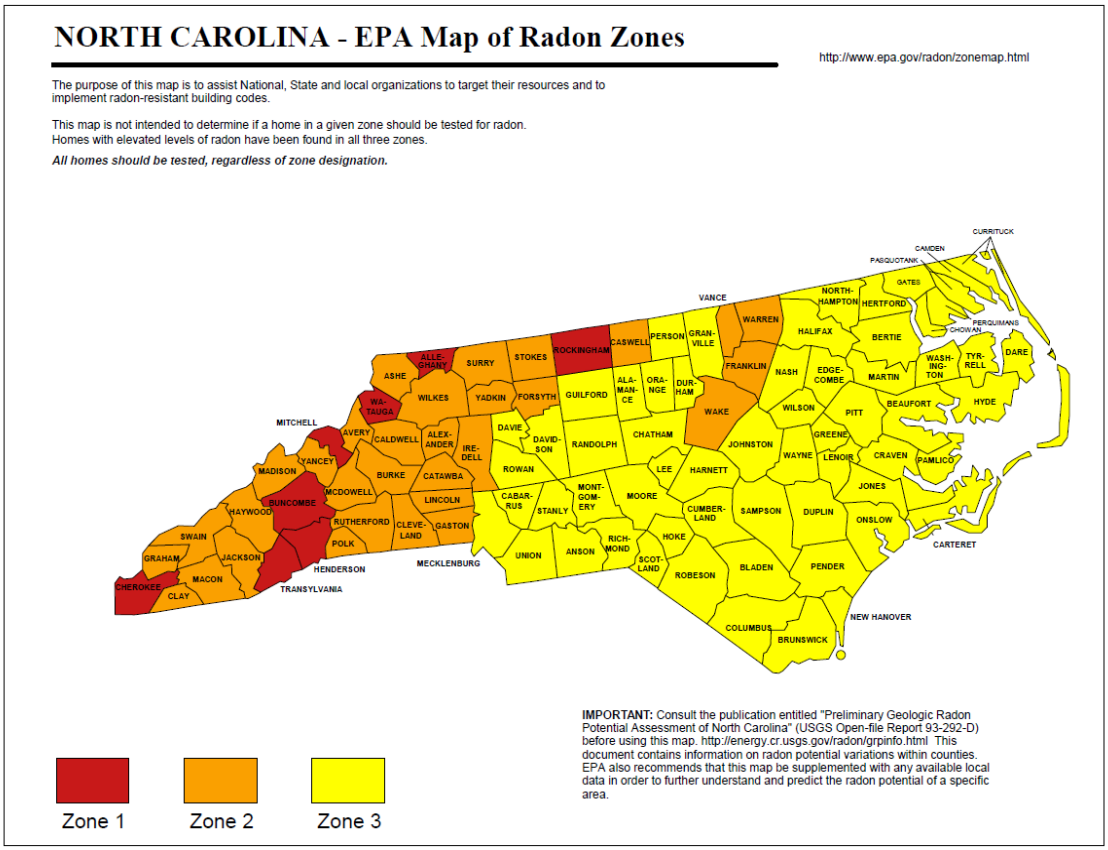


Legend

- Schools
- Dry cleaners
- Former landfills
- Stony Hill site
- RCRA site

Attachment 4

North Carolina Radon Map from EPA website



What do the colors mean?

Zone 1 counties have a predicted average indoor radon screening level greater than 4 pCi/L (picocuries per liter) **(red zones)**	**Highest Potential**
Zone 2 counties have a predicted average indoor radon screening level between 2 and 4 pCi/L **(orange zones)**	**Moderate Potential**
Zone 3 counties have a predicted average indoor radon screening level less than 2 pCi/L **(yellow zones)**	**Low Potential**

Source: http://www.epa.gov/radon/states/northcarolina.html