Investigation of Rhabdomyosarcoma (RMS) Cases in the Rye Area

February 2, 2016

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SUMMARY

In March 2014, the Department of Health and Humans Services (DHHS) was contacted by residents of Rye, NH, reporting concern about the number of cases of rhabdomyosarcoma (RMS) among children living in, or connected with, the Rye area. DHHS followed standard practices using standardized incidence ratios (SIRs) to determine whether a higher than expected number of RMS cases were present in the combined New Hampshire area of Rye and the surrounding four towns of New Castle, Portsmouth, Greenland and North Hampton (five-town area). Other adult and childhood cancers were also evaluated as part of the investigation.

The results of the analyses showed that there was a small number of excess pediatric RMS cancer cases (<5 total cases) in the five-town area of investigation, and that number was above what would be expected based on comparison with the rest of Rockingham County (SIR 6.0, 95% CI: 1.9-18.5). The cases within the five-town area did not appear to cluster geographically within any particular town or in relation to areas of concern mentioned during reporting. We reviewed the literature on RMS and found that several inherited or genetic conditions could predispose to RMS. We did not find any convincing scientific evidence that development of RMS was linked to environmental or behavioral risk factors.

During our evaluation of other pediatric and adult cancers in the five-town area, the only other significant finding was a small excess (<5 total cases) of pediatric lung cancer cases (SIR 20.3, 95% CI: 5.1-81.0); all cases were of a single rare type called pleuropulmonary blastoma (PPB). We conducted a literature review of PPB and found a strong genetic and familial connection to PPB, sometimes occurring as part of a familial cancer syndrome associated with other tumors including RMS. We did not find any environmental or behavioral risk factors identified in the literature that have been linked with development of PPB. Based on our investigation combined with information from the community, we believe the excess of PPB cases likely is attributable to familial or genetic factors that have been described in the scientific literature.

While we suspect a genetic or familial role in the finding of excess PPB cancer cases, we do not know whether genetic or familial conditions have played a role in the development of RMS in the five-town area, but several inherited or genetic conditions can predispose individuals to RMS. Under New Hampshire law, data on such conditions are not collected by the State Cancer Registry. Therefore, while we are not able to definitively say what the cause is for the elevated small number of RMS cases, our investigation and the published scientific literature do not support a connection to any specific behavioral or environmental factors. Any further epidemiological investigation is very unlikely to reveal environmental or behavioral risk factors given the very small number of cases involved and absence of any clear risk factors identified in the scientific literature. DHHS will review and re-evaluate the number of RMS cases reported to the State Cancer Registry in January 2017 when a full additional year of cancer registry data will be complete, and we will reassess the need for ongoing monitoring at that time. The findings described in this report will be discussed with the reporting community members.

CANCER CLUSTER IDENTIFICATION PROCESS

Cancer is not just one single disease but many, each associated with a specific set of possible causes that may relate to a person's genetic make-up, personal behaviors (e.g., diet, inactivity, smoking and alcohol consumption) and the environment (e.g., radon, arsenic, exposure to secondhand smoke). Cancer diagnoses are becoming increasingly common; as people continue to live longer their risk for cancer increases. Additionally, improvements in cancer treatments have led people to live longer after a cancer diagnosis, which in turn means that the number of people in a community who have experienced cancer is higher than it was before these advances in medical care. Because cancer is such a common illness and occurs in so many people, it's not surprising that, when observed casually, cancer cases sometimes appear to cluster in neighborhoods, but what is observed may not be abnormal or represent a larger number of cases than expected when compared with other similar populations or geographic areas. To help determine whether an observed number of cancer cases may represent a higher number than would normally be expected, epidemiologists (scientists who study the patterns and causes of diseases in populations) can look at the number of actual reported cases in a certain area, and compare that number with what would be expected based on the number of cancer cases seen in another similar population or geographic area, taking into account differences in age among the different populations. This comparison can give an idea about whether the observed number of cancer cases is within a normal range, or whether there may be an excess of cancer cases.

The Centers for Disease Control and Prevention (CDC) defines a cancer cluster as "a greater than expected number of cancer cases occurring within a group of people, in a geographic area, or over a period of time." According to the National Cancer Institute (NCI), a suspected cancer cluster is more likely to be a true cluster, rather than a coincidence, if it involves:

1) A large number of cases of a similar type of cancer, rather than several different types;
2) A rare type of cancer, rather than common types; or
3) An increased number of cases of a certain type of cancer in an age group that is not usually affected by that type of cancer.

If there is found to be an excess of cancer cases based on statistical calculations, the next step is to consider and, if appropriate, evaluate the possibility of a common exposure based on what is known in the scientific literature about causes of the cancer under investigation, also taking into account concerns expressed by community members. Sometimes a statistically significant excess number of cancers are found without any identifiable cause.

REPORTED CONCERN

In March 2014, the New Hampshire Department of Health and Human Services (DHHS) received a letter of concern from a resident of Rye, NH, which is in Rockingham County, regarding a

small number of pediatric rhabdomyosarcoma (RMS) cancer cases among children who live in Rye or who may have visited the area. Subsequently, DHHS received additional reports from two other community members expressing the same concern. These reports also mentioned other cases of more common cancers, including lung, colon, pancreas, and acute lymphoblastic leukemia. These additional cancer reports were not confined to children only, and were mentioned in the context of concern for cancer in general, but the main concern expressed was for RMS in the Rye area.

RMS appears to have come to the attention of community members because it is a rare cancer, Rye is a small town, and there were community efforts to help the families affected by RMS with the financial cost of treatment. During the reporting of this potential cancer cluster, community members mentioned concern that the Seabrook Station nuclear power plant, the Schiller Station coal-fired power plant, and the Pease Tradeport drinking water contamination with Perfluorochemicals (PFCs), might be contributing to, or a source of exposure leading to, the perceived greater number of cancer cases.

BACKGROUND

Rhabdomyosarcoma (RMS) is a rare type of soft tissue cancer (sarcoma) that resembles bone and muscle and arises from early developmental skeletal muscle cells. It is the most common soft tissue tumor of childhood and represents about 3-4% of all childhood cancers. Two-thirds of cases are diagnosed in children under the age of six, and more boys are affected than girls. The incidence rate of RMS in children under 20 years of age is approximately 4.3 cases per million per year, and about 350 new cases of RMS occur each year in the United States.[1] RMS can arise anywhere in the body and the common sites are head and neck, genitourinary tract, and the extremities. The predominant histologic types are embryonal (60%) and alveolar RMS (20%), and these histologic subtypes have important implications for treatment and prognosis.

Most cases of RMS appear to be random without any identifiable cause, but there do appear to be connections between RMS and different familial (inherited) conditions and specific genetic mutations.[2-14] Up to one-third of children with soft tissue sarcomas have been estimated to have a genetic predisposition.[9] No definite environmental exposures or behavioral risk factors for RMS have been identified, and a number of studies have evaluated parental exposures and habits, and the prenatal environment, without any consistent or clearly identified risk factors.[15-27]

METHODS

Case Ascertainment

At the time the report was initiated in 2014, the DHHS, Division of Public Health Services (DPHS), set out to identify cases of RMS in New Hampshire residents through use of the New Hampshire State Cancer Registry (NHSCR), which is one of the most complete and reliable sources of cancer data for the State. Initially, however, only an analysis of RMS cases through 2012 could be conducted because registry data are not considered complete until 24 months after diagnosis. New

Hampshire residents who are diagnosed or treated outside of New Hampshire (e.g., 15% of New Hampshire residents are reported to us by Massachusetts) are generally identified later than those reported by New Hampshire hospitals. Registry counterparts in Massachusetts and Maine, therefore, were contacted to alert them to the investigation and request their help in identifying New Hampshire cases as rapidly as possible. Because some RMS diagnoses were made in 2014, the DPHS investigators decided to wait until registry data would be at least 90% complete (12 months after the close of a calendar year), and then conduct a more complete analysis. This delayed the final analysis and report, but it was felt that given the small number of cancer cases, having the most complete data would be critical for interpreting the findings. Although there is the potential that additional cases of RMS identified in 2014 could be newly reported to the State Cancer Registry over the coming months, at the time this report was finalized, the NHSCR was considered 95% complete for reporting of 2014 cancer cases. Therefore, the analysis and evaluation reported here should be considered final.

Geographic Area

Small numbers of reported cases from a small geographic area make it difficult to calculate the necessary statistical measures for comparison. To conduct a more useful analysis with a greater number of cases, the geographic area was extended to include Rye and the neighboring four towns of Newcastle, Portsmouth, Greenland, and North Hampton (Figure 1). A 10-year time period (2005-2014) was also used to capture a greater number of cases for analysis.

Cancer Data and Reference Data

All cancer data for New Hampshire residents were provided by the NHSCR, as discussed above. The CDC provided national data on the number of new RMS cases in the U.S. by year.[28] Demographic data for these analyses were obtained from Claritas,[29] which provides population-based demographic data for New Hampshire.

Statistical Analyses

Standard practices recommended by the CDC and the National Program for Cancer Registries (NPCR) were followed. Data were analyzed on invasive cancers (i.e., cancers that have spread from their site of origin to surrounding tissue) obtained through the NHSCR, which collects population-based data (i.e., all cancers for the whole population). NHSCR data are certified as being of high quality, and are collected through reports from New Hampshire hospitals, clinics, and doctors' offices, as well as from neighboring states through a data exchange agreement.

Standardized Incidence Ratios (SIRs) were calculated using 'R' statistical software.[30] The SIR is a statistical measure that compares the actual observed number of cancer cases in an area with what would be expected based on the number of cancer cases reported in a similar comparison population, taking into account differences in age distributions of the populations. The SIR calculation requires that every individual be classified according to their place of residence so that cancer cases are expressed as a proportion of the population from which they arose. The SIR calculation cannot be used to estimate, for example, the rate of RMS in children who have visited Rye but who live outside New Hampshire

because we cannot know the number of visitors to Rye during 2005-2014, nor identify all subsequent diagnoses of RMS; New Hampshire does not have the authority to collect cancer data outside the State. Therefore, the analysis outlined below focuses on residents of an identifiable geographic region within the State.

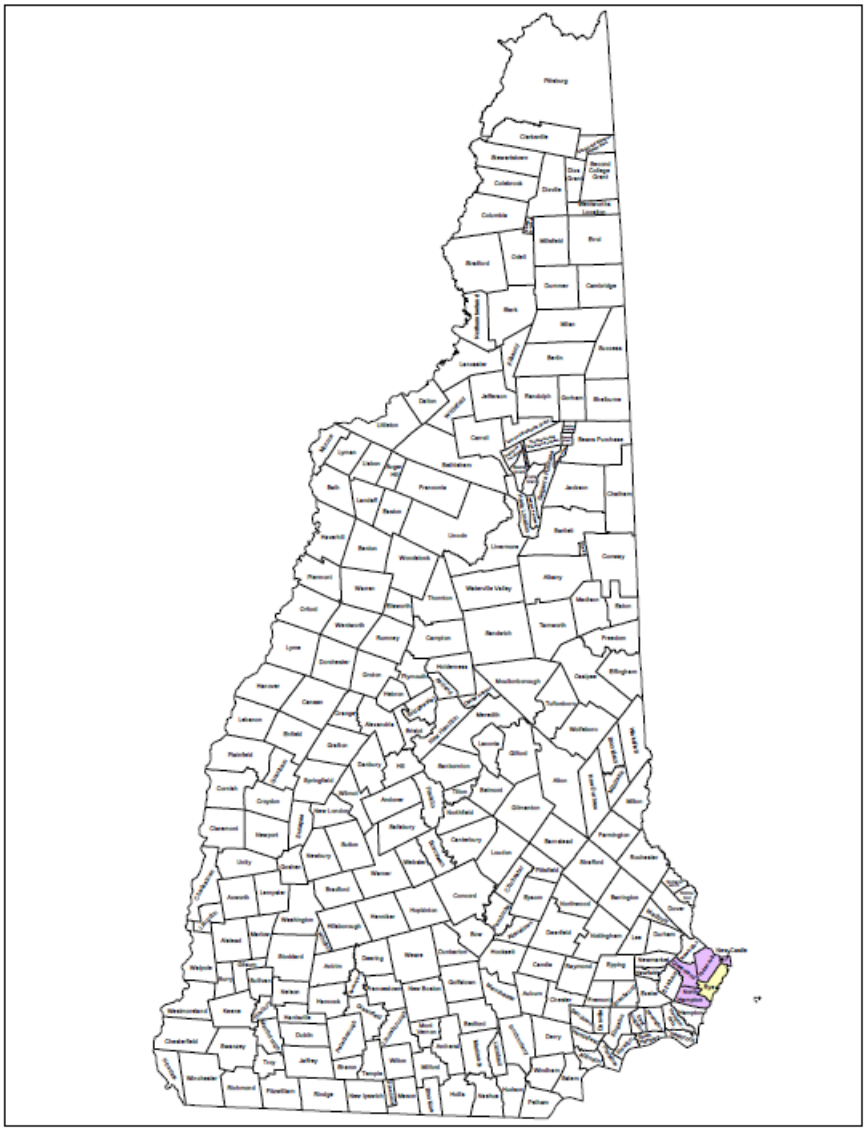
In the primary analysis, the number of cancer cases reported in the five-town geographic area of Rye and the surrounding towns was compared with the number of cancer cases that would be expected based on the population of the rest of Rockingham County (i.e., Rockingham minus the five-town area). In addition, the Maine and Massachusetts Cancer Registries each provided an SIR estimate for their bordering county (adjacent to the Rye area) during the period 2005 to 2012, using the remainder of their state as a comparison population.

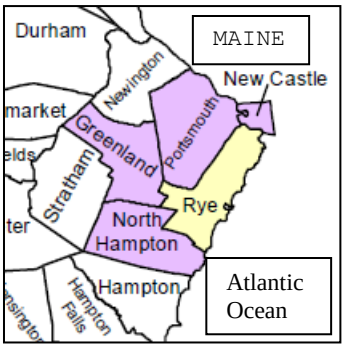
To help with interpretation, an SIR of 1.0 means the incidence of cancer in the community of concern is the same as what would be expected if the population was similar to the comparison population (e.g., the rest of Rockingham County). An SIR greater than 1.0 suggests a higher incidence of cancer than expected, and an SIR less than 1.0 suggests a lower incidence of cancer. Most of the time an SIR will not be exactly 1.0, and additional information is needed to help interpret whether the calculated SIR shows a significant difference in the number of observed vs. expected cancer cases. Any calculated SIR reflects only an estimate of this difference, and therefore, the 95% Confidence Intervals (CIs) are needed to help interpret whether the estimate represents a significant excess or deficit of cancer cases. The 95% CIs are a measure of the variability associated with the estimated/calculated SIR. The lower and upper ends of the 95% CI reflect the range where there is a 95% certainty that the true SIR value will fall within. The narrower the 95% CI range, the more precise, or sure we are, of the calculated SIR estimate; the larger the CI range, the less sure we are of the estimate. When the range between the lower and upper confidence intervals includes 1.0, then the SIR is not statistically significant, and we cannot conclude that there is a true difference between the two populations being compared; the differences are considered to be due to normal, or random, variation. Conversely, if the lower and upper CIs do not include 1.0, the estimated SIR is said to be “statistically significant;” however, there is still a 5% chance that the observed difference in the number of cases is due to chance and part of normal population variation.

The data provided in this report are constrained by New Hampshire law, which protects the confidentiality of individuals with cancer by placing restrictions on the publication of small numbers of cancer cases. Where fewer than five individuals are affected, the number of cases is not published.

Figure 1:

Map of New Hampshire highlighting the area of Rye and the surrounding four towns





RESULTS

Overview of New Hampshire RMS Cases

The incidence of RMS in New Hampshire is similar to that of the U.S. white population (Table 1). During 2005-2014, there were 14 cases of pediatric RMS among New Hampshire residents, including 8 cases of pediatric RMS in Rockingham County, and <5 cases in the five-town area under investigation. For confidentiality reasons, we cannot report the exact number of cases if it is fewer than five.

Table 1. Incidence of rhabdomyosarcoma (RMS) in New Hampshire (2005-2014) and in the United States (2005-2012).

Age Group	**New Hampshire** cases/100,000 (95% CI)	**USA** cases/100,000 (95% CI)
Age-adjusted RMS incidence rates		
Adult (Age 20+ years)	0.2 (0.1 – 0.3)	0.1 (0.1 – 0.1)
Pediatric (Age <20 years)	0.4 (0.2 – 0.7)	0.5 (0.4 - 0.5)
Age-specific RMS incidence rates		
0-4 years	0.6 (0.2 – 1.4)	0.7 (0.7 – 0.8)
5-9 years	0.5 (0.1– 1.3)	0.5 (0.4 – 0.5)
10-14 years	0.6 (0.2 – 1.4)	0.3 (0.3 – 0.3)
15-19 years	0.1 (0.003-0.6)	0.3 (0.3 – 0.4)

RMS = Rhabdomyosarcoma
CI = Confidence Interval

Five-Town Area RMS Analyses

Using the rest of Rockingham County as a reference population, the number of all adult cancers in the five-town area is not significantly different than expected (Table 2; SIR 0.9, 95% CI: 0.9-1.0), and the number of all pediatric cancers is not significantly different than expected (Table 2; SIR 1.1, 95% CI: 0.7-1.8).

For the five-town area, the number of adult RMS cases was zero, so an SIR was not calculated. The number of pediatric RMS cases, however, was higher than expected when compared with the rest of Rockingham County (Table 2; SIR 6.0, 95% CI: 1.9-18.5). The small number of RMS cases involved in the analysis is reflected in the wide confidence interval and causes uncertainty in interpretation of the result. The cases within the five-town area did not appear to cluster geographically within any particular town or in relation to the Schiller Station coal-fired power plant, Pease Tradeport, or the Seabrook Station nuclear power plant. All reported cases occurred within the last five years of analysis.

Table 2. Standardized Incidence Ratios (SIRs) for all cancers and rhabdomyosarcoma in the five-town area using the rest of Rockingham County as a reference population.

Cancer Type	Expected # of Cases	Observed # of Cases	SIR	95% Lower CI	95% Upper CI
All cancers 2005-2014					
Adult (age 20+ years)	2,555	2,363	0.9	0.9	1.0
Pediatric (age 0-19 years)	16.2	18	1.1	0.7	1.8
Rhabdomyosarcoma 2005-2014					
Adult (age 20+ years)	<1*	0	NC	NC	NC
Pediatric (age 0-19 years)	<1*	<5*	6.0	1.9	18.5

* When the number of observed cases is less than 5, data that would allow that number to be calculated cannot be published.
SIR = Standardized Incidence Ratio
CI = Confidence Interval
NC = Not Calculated. A value was not calculated because the observed number of cases was zero.

Maine and Massachusetts County RMS Analyses

Maine reported that the SIR for pediatric RMS cases in York County (2005-2012) relative to the rest of the State of Maine was 0.7 (95% CI: 0.01-3.95). Massachusetts reported that the SIR for pediatric RMS cases in Essex County (2005-2012) relative to the rest of the Commonwealth of Massachusetts was 1.2 (95% CI: 0.5-2.3).

Five-Town Area Additional Cancer Analyses

Additional calculations were performed to evaluate other pediatric cancers in the five-town area. During 2005-2014, there were a total of 18 pediatric cancer cases reported. SIR values were calculated for the more common pediatric cancers, which include leukemia, brain and other central nervous system cancers, and lymphoma, in addition to lung and bronchus cancer, which is relatively rare in children, but a small number of cases were noted. The total number of reported pediatric cancer cases in the five-town area was small, sometimes with fewer than 5 cases depending on the type of cancer, and most SIR values were not statistically significant (Table 3). The SIR for cancers of the lung and bronchus was significantly elevated (Table 3; SIR 20.3, 95% CI: 5.1-81.0), but all of these reported cases of lung cancer were a single rare type (pleuropulmonary blastoma) and considered attributable to familial or genetic factors that have been described in the scientific literature.

Table 3. Standardized Incidence Ratios (SIRs) for non-RMS pediatric cancers in the five-town area using the rest of Rockingham County as a reference population.

Pediatric cancers 2005-2014	Expected # of Cases	Observed # of Cases	SIR	95% Lower CI	95% Upper CI
Brain and Other CNS	2.7	6	2.2	1.0	5.0
Leukemia	<5*	<5*	1.3	0.4	3.9
Lung and Bronchus	<1*	<5*	20.3	5.1	81.0
Non-Hodgkin's Lymphoma	<5*	<5*	0.5	0.1	3.3

* When the number of observed cases is less than 5, data that would allow that number to be calculated cannot be published.
CNS = Central Nervous System
SIR = Standardized Incidence Ratio
CI = Confidence Interval

SIR values were also calculated for other types of cancer for all ages (children and adults) based on the cancers mentioned during the reporting of the RMS cases. These cancers included lung and bronchus, colorectal, pancreatic, and acute lymphoblastic leukemia. None of the SIR values showed any statistically significant excess of cancer in the five-town area. In fact, there were fewer cases of lung and bronchus cancer than expected (Table 4).

Table 4. Standardized Incidence Ratios (SIR) for additional cancers (all ages) in the 5-town area using the rest of Rockingham County as a reference population.

Cancer Type (all ages), 2005-2014	Expected # of Cases	Observed # of Cases	SIR	95% Lower CI	95% Upper CI
Lung and Bronchus	377	279	0.7	0.7	0.8
Colorectal	212	216	1.0	0.9	1.2
Pancreas	66.1	71	1.1	0.9	1.4
Acute Lymphocytic Leukemia	<5*	<5*	0.4	0.1	1.7

* When the number of observed cases is less than 5, data that would allow that number to be calculated cannot be published.
SIR = Standardized Incidence Ratio
CI = Confidence Interval

DISCUSSION

The observed number of pediatric RMS cases in the area of Rye and the surrounding four towns is higher than expected when compared with the population in the rest of Rockingham County; however, interpretation of the SIR must take into account that: (1) the number of actual cases observed during 10 years is small (<5 cases); (2) the estimated SIR is based on a fraction of a single expected case (e.g., if the expected number of cases per year was 0.4 and the observed number was two, then the SIR would be five); and (3) the SIR estimate is not precise, which is reflected in the very wide confidence intervals. Additionally, the cases were diagnosed over a several year time frame, were not localized to a single town, and do not appear to be clustered around any areas of perceived environmental concern. An

elevated SIR alone does not indicate an exposure or risk factor causing the greater number of observed cancer cases.

There has been some local concern expressed over potential environmental contaminants and exposure related to proximity to the Schiller Station coal-fired power plant, Seabrook Station nuclear power plant, and Pease Tradeport. There are no studies that convincingly support a link between RMS and radiation exposure. A few studies have evaluated parental exposure to radiation either through diagnostic imaging or occupational exposure, but the findings have not been consistent or strongly suggestive of radiation as a cause for RMS in children.[17, 20, 22-26] There are also no studies linking RMS to radiation or other emission exposures from nuclear power plants or coal-fired power plants. Routine environmental monitoring around the Seabrook Station nuclear power plant and the Schiller Station coal-fired power plant has not shown any increased levels or exceedances of any health-based standards of radiation or coal emissions, respectively.

Regarding concern over the Pease Tradeport public drinking water contamination with perfluorochemicals (PFCs), there have been inconsistent studies linking PFC exposure to a variety of health problems, but RMS is not one of the diseases that has been linked to PFC exposure. The U.S. Air Force has also been conducting routine monitoring of surveillance wells located on the Pease Tradeport, as well as testing private wells around the Tradeport, and has only identified a single private well with PFC levels higher than the provisional health advisory levels established by the U.S. Environmental Protection Agency (EPA) for drinking water. The PFC well water contamination on the Pease Tradeport, therefore, is very unlikely to have any connection to the increased number of RMS cases. Further information about PFCs and the DHHS blood testing program may be found at the following link: http://www.dhhs.state.nh.us/dphs/investigation-pease.htm.

After finding the elevated SIR for RMS cases in the five-town area, we investigated other cancers in the same area (both child and adult cancers), including cancers mentioned by the reporting community members. The only statistically significant finding was a higher than expected number of pediatric lung cancers, specifically pleuropulmonary blastoma (PPB). PPB is another rare cancer, usually occurring in young children, and appears to have a strong familial and genetic component, sometimes occurring as part of a familial cancer syndrome associated with many other tumors including RMS; it has been estimated that up to 60-70% of PPB cases have a specific genetic predisposition.[31-39] There have been no environmental or behavioral risk factors identified in the literature that have been linked with development of PPB.

While DHHS and NHSCR are not permitted to record information on genetic mutations that predispose to cancer, based on information from the community combined with scientific literature, it seems likely that the excess of PPB cases in the five-town area can be explained by familial or genetic factors and not an environmental exposure. Likewise, because the registry is not permitted to record specific genetic mutations underlying any RMS case, we do not know whether inherited conditions have

played a role in the development of RMS in the five-town area, but we know that several inherited or genetic conditions predispose individuals to RMS and other cancers within affected families. Therefore, while we are not able to definitively say what the cause is for the elevated small number of RMS cases in the five-town area, our investigation and the published scientific literature do not support a connection to any specific behavioral or environmental factors. It should also be noted that during the course of our investigation, one of the cases of RMS identified was reclassified to a different type of cancer, effectively decreasing the number of RMS cases in the five-town area.

Understandably, individuals and communities want an explanation for the cause of a suspected cluster of cancer cases, but given the small number of RMS cases involved over a lengthy 10-year period, any study of potential risk factors or environmental exposures affecting the number of RMS cases is very unlikely to provide any answers. We have discussed these findings with the experts at the Centers for Disease Control and Prevention (CDC), and we have concluded that conducting a more detailed epidemiologic investigation is not likely to identify a cause primarily because:

1) Previous studies with dozens (or hundreds) of patients have failed to clearly identify environmental exposures or other risk factors that lead to the development of RMS. This makes a study in New Hampshire extremely difficult as there are potentially hundreds of environmental exposures that could be evaluated, all with an equal probability of being responsible since there is currently little evidence to implicate any of them.

2) Assessing so many risk factors in a study of fewer than five cases is not scientifically sound and could lead to spurious associations that don’t have any actual relationship to RMS. Further, some of these children could have a known or unknown genetic predisposition that led to RMS whether or not any environmental exposures occurred. This would further complicate the analysis and reduce our ability to identify any true environmental or behavioral risk factors.

These findings will be discussed with the community members who reported the cancer cases, and DPHS will continue to engage with community stakeholders to provide education around the prevention and detection of cancer. DPHS will review and re-evaluate RMS cases reported to the NHSCR in January 2017 when a full additional year of cancer registry data will be complete, and DPHS will reassess the need for ongoing monitoring at that time. We appreciate the assistance given by individuals in the community in reporting the issue to the New Hampshire Department of Health and Human Services. Should there be any questions or concerns about this report, individuals may contact the Division of Public Health Services at 603-271-4959, toll free at 1-800-852-3345 ext. 4959, or by email at whitney.hammond@dhhs.state.nh.us.

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