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Evaluation of Childhood Cancer Incidence in Sandwich, MA: 1995-Present

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I. INTRODUCTION/BACKGROUND

At the request of a concerned resident of Sandwich, Massachusetts, the Community Assessment Program (CAP) of the Massachusetts Department of Public Health (MDPH), Center for Environmental Health (CEH), reviewed the incidence of childhood cancer (i.e., ages 0-19) for the town of Sandwich as a whole and in each of its four census tracts (CTs) (see Figure 1). Specific concerns focused on a suspected increase in the incidence of cancer among children in the town with particular concerns focused on more recent years. Written correspondence to the CEH from the Sandwich resident provided some information on 23 children from Sandwich reported to have a diagnosis of cancer (some children were listed with an estimated year of diagnosis but no other information; others had full names, addresses, cancer type, and diagnosis dates).

The following review provides an evaluation of childhood cancer (all types) for all children living in Sandwich who were diagnosed between 1995 – present to determine if childhood cancer may be occurring in an unexpected pattern in the town of Sandwich as a whole or in any particular area of the town.

II. METHODS FOR ANALYZING CANCER INCIDENCE

To investigate concerns about childhood cancer in Sandwich, the most recent data available from the Massachusetts Cancer Registry (MCR) for Sandwich residents between the ages of 0 and 19 years were reviewed in an effort to confirm cancer diagnoses that were reported to the CEH, identify any additional diagnoses, and to determine whether an atypical pattern of childhood cancer may be occurring in the town as a whole or in any particular area of the town. [Coding for cancer types in this report follows the International Classification of Childhood Cancer (ICCC) system. See Appendix A for the incidence coding definitions used in this report.]

The MCR, a division within the MDPH Center for Health Information, Statistics, Research and Evaluation, is a population-based surveillance system that has been monitoring cancer incidence in the Commonwealth since 1982. All new diagnoses of cancer among Massachusetts residents

are required by law to be reported to the MCR within six months of the date of diagnosis (M.G.L. c.111. s 111b). This information is kept in a confidential database. Data are collected on a daily basis and are reviewed for accuracy and completeness on an annual basis. This process corrects misclassification of data (i.e., city/town misassignment) and deletes duplicate case reports. Once these steps are finished, the data for that year are considered "complete." Due to the volume of information received by the MCR, the large number of reporting facilities, and the six-month period between diagnosis and required reporting, the most current registry data that are complete will inherently be a minimum of two years prior to the current date. At the time of this analysis, complete data records available from the MCR include diagnoses that occurred from 1/1/1982 – 12/31/2002. Although the MCR data are currently complete through 2002, this is an on-going surveillance system that collects reports on a daily basis. Therefore, it is possible to review case reports for more recent years (i.e., 2003-present), which can provide a qualitative review of cancer patterns in a given area.[1] To determine whether there may be additional recent diagnoses not yet reported to the MCR, staff from the MCR contacted the five medical centers in Massachusetts that routinely treat pediatric oncology patients (i.e., Dana Farber/Children's Hospital, Massachusetts General Hospital, New England Medical Center, University of Massachusetts Medical Center, and Baystate Medical Center) and requested the registrars to review hospital databases for any records of pediatric cancer patients residing in Sandwich. In addition, MCR staff contacted the central registry in Rhode Island in an effort to identify patients who may have traveled to Rhode Island for treatment.

It is important to note that although some non-cancerous (i.e., benign) tumors are reported to the MCR (e.g., those diagnosed in the brain and central nervous system), these cases are not included in the data summarized here. Also, only primary site (original location in the body) cancers are included in the MCR. Cancers that occur as the result of a primary site cancer spreading to another location in the body (i.e., metastasis) are not considered separate cancers. Therefore, this analysis includes only diagnoses of invasive (i.e., malignant) primary cancers.

[1] The data summarized here are drawn from data entered on MCR computer files before December 31, 2005. The numbers presented may differ slightly from those published in previous or future reports, reflecting late reported cases, address corrections, or other changes based on subsequent details from reporting facilities.

In order to determine whether cancer incidence in a community is occurring at a higher or lower rate than expected, a statistic called the standardized incidence ratio (SIR) is calculated using data from the MCR. More specifically, an SIR is the number of observed cancer cases in a town divided by the number of expected cases based on the population of the town and the state's cancer rates.[2] An SIR greater than 100 indicates that more cancer cases occurred than expected; an SIR less than 100 means that fewer cases occurred than expected. For example, an SIR of 150 is interpreted as 50 percent more cases than expected; an SIR of 90 indicates 10 percent fewer cases than expected. When an SIR is statistically significant, as indicated by an asterisk symbol (*), there is less than a 5% chance that the observed number of cases is due to chance alone. SIRs and 95% confidence intervals (CIs), statistics used to help interpret the SIR, are not calculated when the observed number of cases is fewer than five. A more detailed explanation of SIRs and 95% CIs is provided in Appendix B.

SIRs for childhood cancer (all types) for the town of Sandwich as a whole as well as for each CT within Sandwich were calculated for the 8-year time period 1995 – 2002. Because statewide data for the years 2003 – present are not considered complete, expected numbers of diagnoses and incidence ratios cannot be calculated for this more recent time period.

Accurate age group and gender-specific population data are required to calculate SIRs. Therefore, the CT is the smallest geographic area for which cancer rates can be accurately calculated. Specifically, a CT is a smaller statistical subdivision of a county as defined by the U.S. Census Bureau. CTs usually contain between 2,500 and 8,000 persons and are designed to be homogeneous with respect to population characteristics (U.S. DOC, 1990). As stated above, an SIR and 95% CIs are not calculated when the observed number of cases is fewer than five.

To better characterize the pattern of childhood cancer incidence in Sandwich, case-specific information available from the MCR relating to type of cancer, date of diagnosis, age at diagnosis, and gender was also reviewed for each child diagnosed with cancer in Sandwich. This information is discussed in the context of known or established cancer risk factors and incidence

[2] Using different population estimates or statistical methodologies, such as grouping ages differently or rounding off numbers at different points during calculations, may produce results slightly different from those published here.

patterns in the general population. In addition, place of residence at the time of diagnosis for each individual between the ages of 0 and 19 with cancer was "mapped" [using a computerized geographic information system (ESRI, 2005)]. This allowed for a qualitative evaluation of the spatial distribution of the addresses of children diagnosed with cancer and an assessment of any possible geographic concentration of diagnoses in specific neighborhoods in Sandwich. For confidentiality reasons, maps of the residences of individuals diagnosed with cancer cannot be provided in this report. However, a summary of this evaluation with any notable findings is presented in this report.

III. RESULTS OF CHILDHOOD CANCER INCIDENCE ANALYSES

A. Efforts to Confirm Reported Cases

As stated earlier, information on 23 children from Sandwich reported to have a diagnosis of cancer was provided to the CEH by a concerned resident of Sandwich. Name, cancer type, age at diagnosis, and/or address was provided for 20 of the 23 children. The year of diagnosis was the only information reported to the CEH for the other three children.

From 1995 – 2002 (the most recent time period for which complete data is available from the MCR), 10 children from Sandwich were reported to the MCR with a diagnosis of cancer. From January 2003 through December 2005, the MCR has received reports of seven children in Sandwich diagnosed with cancer. Staff from the MCR also contacted the five medical centers in Massachusetts that routinely treat pediatric oncology patients and the central cancer registry in Rhode Island to look for any additional children in Sandwich recently diagnosed but not yet reported to the MCR. As of January 23, 2006, no additional children from Sandwich were identified as being treated for cancer. Therefore, seven children have been reported to the MCR from 2003 through 2005.

Of the 23 children reported to the CEH by the Sandwich resident, the CAP was able to confirm 14 diagnoses using the MCR and a search of hospital databases. In some instances, case-specific information confirmed via the MCR (e.g., cancer type, age at diagnosis, year of diagnosis) was different from that reported to the CEH. Of the nine children whose diagnosis was not

confirmed, one individual was confirmed by the MCR as being diagnosed with cancer after the age of 19, i.e., not a childhood cancer. A second child was confirmed in the MCR as being diagnosed with cancer, however, this child was not a resident of Sandwich at the time of diagnosis. The remaining seven reports could not be confirmed, in part because of insufficient information (e.g., name and address were not provided for three of these seven children). It is important to note that a year of diagnosis was provided for six of these seven individuals. All six individuals were reported as being diagnosed between 2001 and 2004. Because MCR staff contacted hospitals in MA and the RI cancer registry for reports of more recent diagnoses, it is unlikely these individuals would have been excluded if they had been diagnosed with cancer in the town of Sandwich. However, searches of hospital databases were based on reported address at the time of diagnosis. Children whose parent or guardian reported an address other than Sandwich would not have been identified. For these reasons such individuals would not be included in the MCR data files for Sandwich. Finally, it is also possible that some of these individuals may have actually been diagnosed with a benign tumor or other pre-cancerous (e.g., aplastic anemia) or non-cancerous conditions.

B. Childhood Cancer Incidence in Sandwich, 1995-2002

1. Town-wide

Table 1 summarizes childhood cancer incidence data for the town of Sandwich for the 8-year time period 1995 – 2002. Overall, cancer occurred more often than expected among children aged 0-19 years in Sandwich during this time period (10 diagnoses observed vs. 7.5 expected, SIR = 133). This elevation was not statistically significant (95% CI = 64-245). A separate evaluation of these data by gender revealed that the incidence among males was slightly less than expected, while female children were diagnosed more often than expected in the town. Specifically, three males in Sandwich were diagnosed with cancer during this time period compared to four children that would have been expected to have a diagnosis of cancer. As explained previously, an SIR and 95% CI were not calculated for males due to the small number of observed diagnoses (i.e., less than five). Among females in the town, seven diagnoses were

observed compared to 3.5 expected (SIR = 200). This elevation did not achieve statistical significance (95% CI = 80-412).

Table 1: Childhood cancer incidence in Sandwich, MA: 1995-2002

	Observed	Expected	SIR	95% CI
Males	3	4.0	NC	NC
Females	7	3.5	200	80-412
Total	10	7.5	133	64-245

Notes: 95% CI = 95% confidence interval; NC = not calculated; * = statistical significance

The cancer types diagnosed among these 10 children during 1995 – 2002 included leukemia (n = 3), Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms [CNS tumors (n = 3)], cancer of the bone (n = 1), soft tissue sarcoma (n = 2), and Hodgkin's disease (n = 1). These cancers are among the most common cancer types diagnosed among children (i.e., ages 0-19). The number of diagnoses per year varied between zero and two with at least one diagnosis occurring in seven of the eight years.

2. Census Tracts

The incidence of childhood cancer for each of the four census tracts in Sandwich is summarized in Table 2. Among males and females combined, childhood cancer incidence was close to the number of expected cases in three of the four CTs. In CT 0135, located in southeast Sandwich, 5 children were diagnosed with cancer while approximately three were expected (SIR = 192); this elevation was not statistically significant (95% CI = 62-449). The overall elevation was due to an elevation among female children in this CT (4 observed vs. 1.2 expected).

The cancer types diagnosed among the four females in CT 0135 included two diagnoses of leukemia (both lymphoid leukemia), a cancer of the bone, and a soft tissue sarcoma. Three of these four females lived within a half mile of each other and their diagnoses occurred from 1996 to 1999. It is important to note that this area of Sandwich is among the more densely populated

areas of town. Other than CT 0135, childhood cancer diagnoses during this time period were evenly distributed throughout the town.

Table 2: Childhood cancer incidence in Sandwich Census Tracts: 1995-2002

Census Tract	Total				Males				Females			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
0133	1	0.9	NC	NC-NC	0	0.4	NC	NC-NC	1	0.4	NC	NC-NC
0134	2	1.3	NC	NC-NC	1	0.7	NC	NC-NC	1	0.6	NC	NC-NC
0135	5	2.6	192	62-449	1	1.4	NC	NC-NC	4	1.2	NC	NC-NC
0136	2	2.7	NC	NC-NC	1	1.4	NC	NC-NC	1	1.2	NC	NC-NC
Town Total	10	7.5	133	64-245	3	4.0	NC	NC-NC	7	3.5	200	80-412

Notes: Obs = observed; Exp = expected; 95% CI = 95% confidence interval;
NC = not calculated

3. Incidence in Sandwich by Cancer Type

a. Leukemias

Leukemia is a group of cancers that develop in the blood-forming tissues (MDPH, 2003). Leukemia and CNS tumors were the most common cancer types diagnosed among children in Sandwich during 1995 – 2002. Of the 10 children diagnosed with cancer during this time period, three (30%) were diagnosed with leukemia. Two children were diagnosed in 1999 and one child was diagnosed in 2001.

In children, leukemia is classified into four major subtypes: lymphoid leukemia, acute myeloid leukemia (AML), chronic myelodysplastic disease, and myelodysplastic syndrome. In Massachusetts, the majority of childhood leukemia diagnoses are of the lymphoid leukemia subtype (MDPH, 2003). During 1995 – 2002, all three childhood leukemia diagnoses observed were lymphoid leukemias. According to the American Cancer Society (ACS), lymphoid leukemia is most commonly diagnosed among children 2 – 3 years old (ACS, 2005a). Two of the three children fit the pattern suggested by the ACS and the third child was between the ages of five and 10 years old at diagnosis.

b. Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms

Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms (CNS tumors) include tumors that arise from the brain, spinal cord, and other sites within the skull and spinal cord (MDPH, 2003). Statewide, these tumors are the second most common type of cancer in children. In Sandwich, three (30%) children were diagnosed with a CNS tumor from 1995 – 2002 over a period of five years (beginning in 1997).

There are several different types of CNS tumors, including astrocytomas, ependymomas, primitive neuroectodermal tumors (PNET) and medulloblastomas, as well as some rare types. In Sandwich, one child was diagnosed with an astrocytoma, one was diagnosed with an ependymoma, and one was diagnosed with a PNET during 1995 – 2002. According to the American Brain Tumor Association (ABTA), CNS tumors typically affect children under fifteen years of age and older adults (ABTA, 2005). Of the three children diagnosed with neoplasms of the CNS, all were diagnosed at ages younger than 15.

c. Soft-tissue Sarcomas

Soft-tissue sarcomas are cancers that develop in the supporting tissues, such as muscle, fat and blood vessels (MDPH, 2003). These cancers can develop at any site in the body. In Massachusetts, soft tissue sarcomas represent about 7.4% of all childhood cancer diagnoses (MDPH, 2003), similar to national trends (CDC, 2003). The most common type of childhood soft tissue sarcoma is rhabdomyosarcoma, which develops in skeletal muscle (ACS, 2005b). There are many different types of soft tissue sarcomas, which are all thought to be medically related to each other. In Sandwich, two children were diagnosed with a soft tissue sarcoma during 1995 – 2002. The diagnoses for these two children occurred over a 14-month period beginning in 1996. One child was diagnosed with a rhabdomyosarcoma and one was diagnosed with a less common type of soft tissue sarcoma found in cartilage and bone.

According to the Centers for Disease Control and Prevention (CDC), soft tissue sarcomas are most commonly diagnosed in children less than one year old and in children aged 15 – 19 (CDC,

2003). During 1995 – 2002, the incidence in Sandwich was consistent with this trend; one individual was diagnosed at less than one year old and the other was over 15 years of age at the time of diagnosis.

d. Malignant Bone Tumors

In Massachusetts, malignant bone cancers account for about 5% of all childhood cancers (MDPH, 2003). In Sandwich, one child was diagnosed with bone cancer from 1995 – 2002. This child's cancer was in the Ewing's family of tumors. Ewing's tumors are most often found in bone but can also develop in soft tissues. According to the American Cancer Society, only about 250 children and adolescents are diagnosed with Ewing's tumors (in either the bone or soft tissues) in the U.S. each year, accounting for less than three percent of all childhood cancers (ACS, 2005c). Ewing's tumors comprise about 27% of malignant bone tumors diagnosed in children in Massachusetts (MDPH, 2003). The majority occur in individuals aged 10 to 20, but Ewing's tumors can also affect children under 10 and young adults into their twenties (Gurney et al., 1999). The child diagnosed with bone cancer was diagnosed before age 10.

e. Lymphomas and Reticuloendothelial Neoplasms

Lymphomas are cancers that develop from the lymphatic or reticuloendothelial (lymphocyte supporting tissue) system, the system of the body that helps fight infection and disease (MDPH, 2003). There are two main types of lymphomas: Hodgkin's disease and non-Hodgkin's lymphoma (NHL). Although the overall incidence of each type is similar in children aged 0-19, NHL tends to occur more often in younger children, while Hodgkin's disease is more common in adolescents (ACS, 2005d). Of the 10 children diagnosed with cancer in Sandwich during 1995 – 2002, one was diagnosed with Hodgkin's disease as an adolescent (between the ages of 15-19). There were no diagnoses of NHL among children in Sandwich reported to the MCR during the time period evaluated.

C. Childhood Cancer Incidence, 2003 – 2005

As stated earlier, because statewide data for the years 2003 – present cannot be considered complete, expected numbers of diagnoses and incidence ratios cannot be calculated for more recent years. However, this section provides a qualitative review of childhood cancer in Sandwich for more recent years (i.e., 2003 – present).

From January 2003 to December 2005, seven children (four females and three males) reported to the MCR as residents of Sandwich were diagnosed with cancer. The cancer types diagnosed among these children were leukemia (n = 3), CNS tumors (n = 2) and cancer of the bone (n = 2). Of the seven diagnoses that were reported for the years 2003 – present, three occurred during 2003, one in 2004, and three in 2005.

Among the seven children reported to the MCR during 2003 – 2005, two resided in CT 0133, two were in CT 0134, and three resided in CT 0135 at the time of diagnosis. At the time of this report, no children from Sandwich CT 0136 had been reported to the MCR with a diagnosis of cancer from 2003 through 2005. The two children living in CT 0133 were both diagnosed with tumors of the CNS. Both of the individuals residing in CT 0134 were diagnosed with leukemia, and of the three children living in CT 0135, one was diagnosed with leukemia and the other two were diagnosed with bone cancer.

Of note, the child diagnosed with leukemia in CT 0135 was living in the same neighborhood of southeast Sandwich at diagnosis where three other children diagnosed with cancer during 1995 – 2002 were living. Therefore, during the nine-year time period between 1996 and 2005, four children (3 with leukemia and 1 soft tissue sarcoma) were diagnosed with cancer in this area of Sandwich. In addition, in a different neighborhood of CT 0135, one of the children diagnosed with bone cancer during 2003 – 2005 was living in close proximity to another child diagnosed with bone cancer during 1995 – 2002. Although these children were diagnosed with similar types of bone cancer (i.e., Ewing's family of tumors), they were different ages at the time of diagnosis and were diagnosed about five years apart from each other. The other child diagnosed

with bone cancer in Sandwich during 2003 – 2005 was a resident of CT 0135 but was living approximately two and one-half miles away from these two children at the time of diagnosis.

1. Incidence by Cancer Type

a. Leukemias

Leukemia was the most common type of cancer (43%) diagnosed among children in Sandwich during 2003 – 2005. Of the three children diagnosed with leukemia during this time period, two were diagnosed before age 10 and the third was over age ten at the time of diagnosis. All three children were diagnosed with lymphoid leukemia.

b. Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms

Two children were diagnosed with a CNS tumor during 2003 – 2005. One child was between the ages of five and ten at diagnosis while the second child was between 10 and 14 years old at the time of diagnosis. Each child was diagnosed with a different type of tumor of the CNS. One child was diagnosed with a PNET (diagnosed in 2003) and the other was diagnosed with a medulloblastoma (diagnosed in 2005).

c. Malignant Bone Tumors

Two of the seven children were diagnosed with bone cancer; both were classified in the Ewing's family of tumors. One child (diagnosed in 2005) was between 10 and 15 years of age at the time of diagnosis, and the other child (diagnosed in 2003) was over the age of 15 at diagnosis.

D. Residential History

In general, many adult cancers have latency periods (i.e., the interval between first exposure to a disease-causing agent and the appearance of symptoms of the disease [Last, 1995]) that can range from 10 to 30 years and in some cases may be more than 40 or 50 years (Bang, 1996; Frumkin, 1995). While not much is known about the latency period for cancers that occur in

children (other than latency is assumed to be considerably shorter), the length of time in which an individual lived in a specific area may help determine the importance that their place of residence might have in terms of exposure to a potential environmental source. Therefore, a residential history of each child diagnosed with cancer in Sandwich was constructed, with particular attention paid to the children mentioned earlier in this report who are living in close proximity to each other in two different areas of CT 0135 in Sandwich.

Residential histories were constructed by consulting Massachusetts birth records from the Registry of Vital Records and Statistics and the Town of Sandwich annual street listings. For 16 of the 17 children, length of residence at the address reported at diagnosis was determined. Review of this information indicated that six children had lived at their reported address since birth. Ten children were not born at the same residence reported to the MCR as their residence at diagnosis. These families moved to the MCR-reported address between one and eleven years after birth. Length of residence at the address reported at diagnosis varied between two to fifteen years.

With respect to the one area of Sandwich where four children were diagnosed with cancer since 1996, two individuals were born at the address reported to the MCR at the time of diagnosis. Both of these children were diagnosed with leukemia, however, their diagnoses were approximately six years apart. The remaining two children were not born at the address reported to the MCR at diagnosis. One child, diagnosed with leukemia lived at this address less than three years before diagnosis. The other child, diagnosed with a soft tissue sarcoma, lived at their address between five and seven years before diagnosis.

In regard to the other area of Sandwich where two children with bone cancer were living, neither of these two children was born at the address reported to the MCR at diagnosis. Both of these children lived at their residence at diagnosis in Sandwich between five and 10 years before being diagnosed with bone cancer. As stated earlier, the diagnoses of these children occurred approximately five years apart.

IV. ENVIRONMENTAL FACTORS

In addition to reviewing the pattern of cancer incidence among children in Sandwich, available information regarding Sandwich drinking water, and data for any groundwater contamination from the Massachusetts Military Reservation (MMR) was also reviewed.

A. Sandwich Municipal Drinking Water

Under the Federal Safe Drinking Water Act, all public water suppliers nationwide are required by the U.S. Environmental Protection Agency (EPA) to test for a wide variety of substances. The Massachusetts Department of Environmental Protection (MDEP) requires local water suppliers to perform over 100 tests for the presence of different organic and inorganic contaminants. The MDEP has also established Massachusetts' Maximum Contaminant Levels (MMCLs) which are regulatory limits for contaminants in public drinking water supplies. According to information collected by the 1990 US Census, the percentages of households using public drinking water varied for each of Sandwich's four CTs. Most or all households in CTs 0133 and 0136 (See Figure 1) were reportedly using municipal drinking water in 1990 (100% in CT 0133 and 90% in CT 0136). Approximately half (55%) of households in CT 0134 were supplied by public drinking water, while 36% of household in CT 0135 were using public drinking water. The number of households served by public drinking water was not collected in the 2000 Census.

MDEP provided information on any violations of drinking water standards for the Sandwich municipal drinking water system during the period 1993 to present. With the exception of total coliform (TC), no violations of health-based drinking water standards have been reported for the Sandwich drinking water supply during this time period. From 1995 to 1997 four instances have occurred in Sandwich where the MCL for TC has been exceeded. Total coliforms are a group of related bacteria that are generally harmless, are common in the environment, and serve as an indicator of the presence of other potentially harmful bacteria (EPA, 2001; MDEP, 2005). According to the MDEP, follow-up sampling as required did not indicate the presence of harmful bacteria (Thompson, 2005).

B. Groundwater Contamination from MMR

To date, a total of 14 groundwater contaminant plumes from various areas of the MMR have been identified in Bourne, Sandwich, Mashpee, and Falmouth (AFCEE, 2005). A plume is a body of groundwater containing contaminants exceeding the state and/or federal MCLs based on sampling from various locations. Review of the location of these plumes indicated that no children diagnosed with cancer in Sandwich were living near any of these plumes.

V. DISCUSSION

Although most cancer types occur more frequently in older populations (i.e., age 50 and over), cancer can affect people of all ages. When evaluating cancer patterns in adults, different cancers are treated as different diseases, each with different causes and risk factors. However, some childhood cancers may have similar etiologies and are often grouped together to reflect similarities in histology or cell type [e.g., leukemias, lymphomas (including Hodgkin's disease and NHL), tumors of the central nervous system, and soft tissue sarcomas] (Birch and Marsden, 1987; MDPH, 2003). Unfortunately, very little is known about the etiology of childhood cancer. In addition, some of the risk factors for childhood cancers may differ from the risk factors for adult cancers.

Between 1995 and 2002, 2182 Massachusetts children between the ages of 0 and 19 were diagnosed with cancer. Leukemia is the most common type of childhood cancer in Massachusetts children aged 0 to 19 years, followed by cancers of the CNS. Other common childhood cancers include non-Hodgkin's lymphoma (NHL), Hodgkin's disease, soft tissue sarcoma, Wilms' tumor (a type of kidney cancer), neuroblastoma, and some bone cancers. For the most part, the distribution of cancer types diagnosed among children in Sandwich during 1995 – 2005 was consistent with state and national trends. Specific information on each of the five cancer types diagnosed among children in Sandwich is discussed below. Appendix C of this report provides more information regarding risk factors for the types of cancer diagnosed among children in Sandwich.

Three children from Sandwich were reported to the MCR with leukemia during the eight year time period 1995 – 2002. Since 2003, three other children from Sandwich have been reported to the MCR with leukemia. While it appears that the incidence of this cancer type is increasing among children in Sandwich, this is consistent with a slight rise in leukemia incidence among children both statewide and across the country (MDPH, 2003; Ries et al., 2005). A few risk factors for the development of childhood leukemia have been identified. Some children with certain genetic diseases (e.g., Down's syndrome and Klinefelter's syndrome) have an increased risk of developing this cancer (Chow et al., 1996; ACS, 2005a). An MDPH study published in 2002 showed that maternal exposure to drinking water contaminated with solvents and metals during pregnancy was likely associated with their children's development of leukemia (Costas et al., 2002). While Sandwich drinking water was not found to contain these contaminants above MDEP guidelines, information from the 1990 US Census indicates that only 36% of households in CT 0135 were on public water. In addition, high-dose radiation exposure, including prenatal exposure to x-rays, has been associated with an increased risk of leukemia in children (Chow et al., 1996; ACS, 2005a). As noted in this report, three of the six children diagnosed with leukemia were living in a neighborhood of southeast Sandwich (in CT 0135) at the time of diagnosis. These three children were diagnosed with leukemia over a 6-year period. Two of the three children were born at the address reported to the MCR at diagnosis. The remaining child was not born at the same address as he/she was living at diagnosis; this child had lived at his/her residence at diagnosis two years before being diagnosed with leukemia.

During 1995 – 2005, four different subtypes of CNS tumors commonly found in children were diagnosed among five children in Sandwich. Some causes of CNS tumors in children have been identified. The only known environmental risk factor for CNS tumors is treatment with ionizing radiation (e.g., from radiation therapy to the head and neck) (ACS, 2005e; Chow et al., 1996). In addition, rare cases of CNS tumors run in some families. Some types have also been associated with certain rare genetic disorders, such as neurofibromatosis type 1, von Hippel-Lindau disease, and Li-Fraumeni syndrome (ACS, 2005e; Chow et al., 1996). Environmental exposures, such as vinyl chloride, aspartame (a sugar substitute), and electromagnetic fields, have been suggested as risk factors for brain cancer, but the evidence to support these associations is inconsistent (ACS, 2005e). Two of the five children diagnosed with CNS tumors were born at the address listed at

diagnosis. Of the remaining three children, two were not born at the address they were living at when diagnosed. These two children had been at their address between zero and two years before diagnosis. A residential history for the fifth child from Sandwich diagnosed with a CNS tumor could not be confirmed. Therefore, it is likely this child's family only lived at this address for a short time (e.g., less than one year) prior to diagnosis.

In general, the causes of bone cancer are unknown. However, a small number of children with certain rare inherited syndromes (e.g., Li-Fraumeni syndrome and Rothmund-Thompson syndrome) or certain non-cancerous bone diseases (e.g., Paget's disease) may be at an increased risk of developing some types of bone cancer. Also, exposure to large doses of ionizing radiation (e.g., radiation therapy to treat another cancer) poses an increased risk of developing bone cancer (ACS, 2005f). There are no known risk factors for Ewing's tumors. Moreover, studies of children with Ewing's tumors have not linked this cancer to radiation, chemicals, or any other environmental exposures (ACS, 2005c). The three children diagnosed with bone cancer in Sandwich were diagnosed with a Ewing's related tumor. While two of the three children diagnosed with bone cancer were living in the same neighborhood in the southern part of town, their diagnoses were 5 years apart. Neither of these two children were born at the address at diagnosis reported in the MCR, but they had been at their address at diagnosis in Sandwich between five and 10 years before being diagnosed with bone cancer. The third child, diagnosed with bone cancer in 2005, was living in a neighborhood approximately two and one-half miles from the other two children at diagnosis.

Since the second of two children in Sandwich was diagnosed with a soft tissue sarcoma in 1997, no other Sandwich children have been reported to the MCR with this type of cancer. No pattern with respect to residence at diagnosis emerged when reviewing the residential history and geographic distribution for each child diagnosed with a soft tissue sarcoma. The family of one child had been at the residence at diagnosis less than a year between the date of birth and the date of diagnosis. The second child was not born at the address listed in the MCR and had been living at this address for approximately 6 years before being diagnosed with soft tissue sarcoma. The places of residence at diagnosis for these two children were approximately four and one-half miles apart from one another, and in different CTs. Some causes of soft tissue sarcoma among

children have been identified. Certain inherited conditions (e.g., neurofibromatosis, Gardner's syndrome, and Li-Fraumeni syndrome) are associated with an increased risk of soft tissue sarcoma (ACS, 2005g; Chow et al., 1996). In addition, exposure to ionizing radiation (e.g., for the treatment of other cancers) is a risk factor for soft tissue sarcoma (Zham et al., 1996). The average time between radiation exposure and diagnosis of a sarcoma in adults is approximately 10 years (ACS, 2005g). However, it is estimated that this risk factor accounts for less than five percent of all diagnoses. Some studies have suggested possible links between soft tissue sarcoma and occupational exposure to high doses of certain pesticides (ACS, 2005g). Pesticide exposure has also been associated with childhood rhabdomyosarcoma (Chow et al., 1996).

Hodgkin's disease has been associated with immune deficiencies (Mueller, 1996; Scherr and Mueller, 1996). While environmental factors have been considered in some epidemiological studies, they are not thought to be strongly associated with Hodgkin's disease. An increased risk of Hodgkin's disease has been associated with Epstein-Barr virus (EBV) infection (the virus that causes infectious mononucleosis) (Mueller, 1996). Although the disease is relatively rare among children, two peaks in the age distribution have been observed for this cancer type. The first peak occurs in young adults usually between the ages of 15 to 40 (typically ages 25-30) and the second peak occurs in adults aged 55 years and above. The child diagnosed with Hodgkin's disease in Sandwich was between the ages of 15 and 19 at diagnosis which is consistent with patterns observed for this cancer type. Occupational exposures to workers in the chemical industry and woodworkers have also been suggested in several epidemiologic studies to be associated with the development of Hodgkin's disease. However, specific chemical exposures related to the development of this disease have not been identified and results of studies investigating occupational exposures are inconsistent (Mueller, 1996). Although specific genetic factors have not been identified, some studies of twins with Hodgkin's disease have suggested that family history may play a role in the development of this disease among some individuals (ACS, 2005d; Percy et al., 1999).

According to statistics from the American Cancer Society, cancer is the second leading cause of death in Massachusetts and the United States. Not only will one out of three people develop cancer in their lifetime, but also this disease will affect three out of every four families. For this

reason, cancers often appear to occur in "clusters," and it is understandable that someone may perceive that there are an unusually high number of cancer cases in their surrounding neighborhood or town. Upon close examination, many of these "clusters" are not unusual increases, as first thought, but are related to such factors as local population density, variations in reporting or chance fluctuations in occurrence. In other instances, the "cluster" in question includes a high concentration of individuals who possess related behaviors or risk factors for cancer. Some, however, are unusual; that is, they represent a true excess of cancer in a workplace, a community, or among a subgroup of people. A suspected cluster is more likely to be a true cancer cluster if it involves a large number of cases of one type of cancer diagnosed in a relatively short time period rather than several different types diagnosed over a long period of time (i.e., 20 years), a rare type of cancer rather than common types, and a large number of cases diagnosed among individuals in age groups not usually affected by that cancer. These types of clusters may warrant further public health investigation.

In general, the geographic distribution of children diagnosed with cancer closely matched the pattern of population density in Sandwich. However, an atypical geographic pattern in SE Sandwich was observed during this time period.

VI. CONCLUSIONS

- For the eight-year period of 1995 through 2002, the incidence of childhood cancer in Sandwich was slightly elevated (10 diagnoses observed versus 7.5 diagnoses expected), but this elevation was not statistically significant. The elevation was due primarily to an elevation among female children in CT 0135 (4 diagnoses observed versus 1.2 diagnoses expected);

- Within CT 0135, four females were diagnosed with cancer between 1996 and 1999. Among these four children, two were diagnosed with leukemia, and there was one diagnosis of bone cancer, and a soft tissue sarcoma;

- For the three-year period of 2003 through 2005, the period for which an expected number of diagnoses cannot yet be calculated using statewide incidence rates, seven children in Sandwich were reported to the MCR with a diagnosis of three different types of cancer;

- When age at diagnosis and cancer type was examined for each child in Sandwich diagnosed with cancer from 1995 – 2005, the distribution of both variables was consistent with the epidemiologic literature for the types of cancer reported;

- When the timing and geographic distribution of childhood cancer in Sandwich was examined, two observations were noted:
    - One observation involved two children with the same type of cancer, bone cancer, living in fairly close proximity to one another in southern Sandwich. Although geographically close, they were diagnosed approximately five years apart;

    - The second observation involved four children living in close proximity (within a half-mile radius) to each other in southeastern Sandwich. Three of the four children were diagnosed with leukemia and the fourth child was diagnosed with a soft tissue sarcoma. Two of the three children with leukemia were diagnosed within five months of one another. The residential history of these three children revealed that two of the children resided in their homes for approximately 3 to 3.5 years before diagnosis, the same homes that they were born in. The other child had moved from the home that he/she was born in and lived in their residence at diagnosis for two years. Because of the uncertainties about the roles of latency periods and potential exposures during pregnancy for childhood cancer, and the small number of cases, it is difficult to assess how unusual this pattern may be.

- The distribution of childhood cancer did not appear to correspond to areas of Sandwich where there might be greater opportunities for exposure to MMR groundwater plumes. In addition, since 1993, no violations in Sandwich public drinking water supplies (other than TC) have been reported by the MDEP;

- Several types of cancers diagnosed among children in Sandwich have been associated with certain genetic diseases and familial disorders. The MCR does not contain information on an individual's medical history. Therefore, it is unknown if any children diagnosed with cancer in Sandwich had any pre-existing medical conditions that might increase their risk for certain types of cancer.

VII. RECOMMENDATIONS

Based on the observed geographic pattern of childhood cancer diagnoses in southeast Sandwich during 1995 – 2005, the MDPH recommends the following steps:

- Conduct in-person interviews with the biological mother or primary care-givers of all children diagnosed with cancer in Sandwich during 1995 – present. Topics of interest include closer scrutiny of pregnancy history, family medical history, and parental occupational history. Parents of children who provide informed consent will be asked to participate in personal interviews and a medical records review by a physician to determine any possible environmental or other factors that may have contributed to their diagnosis;

- Review childhood cancer incidence in census tracts adjacent to Sandwich CT 0135. This would include CT 0131 in Barnstable and CT 0150 in Mashpee;

- Review additional environmental factors including but not limited to review of available private well data.

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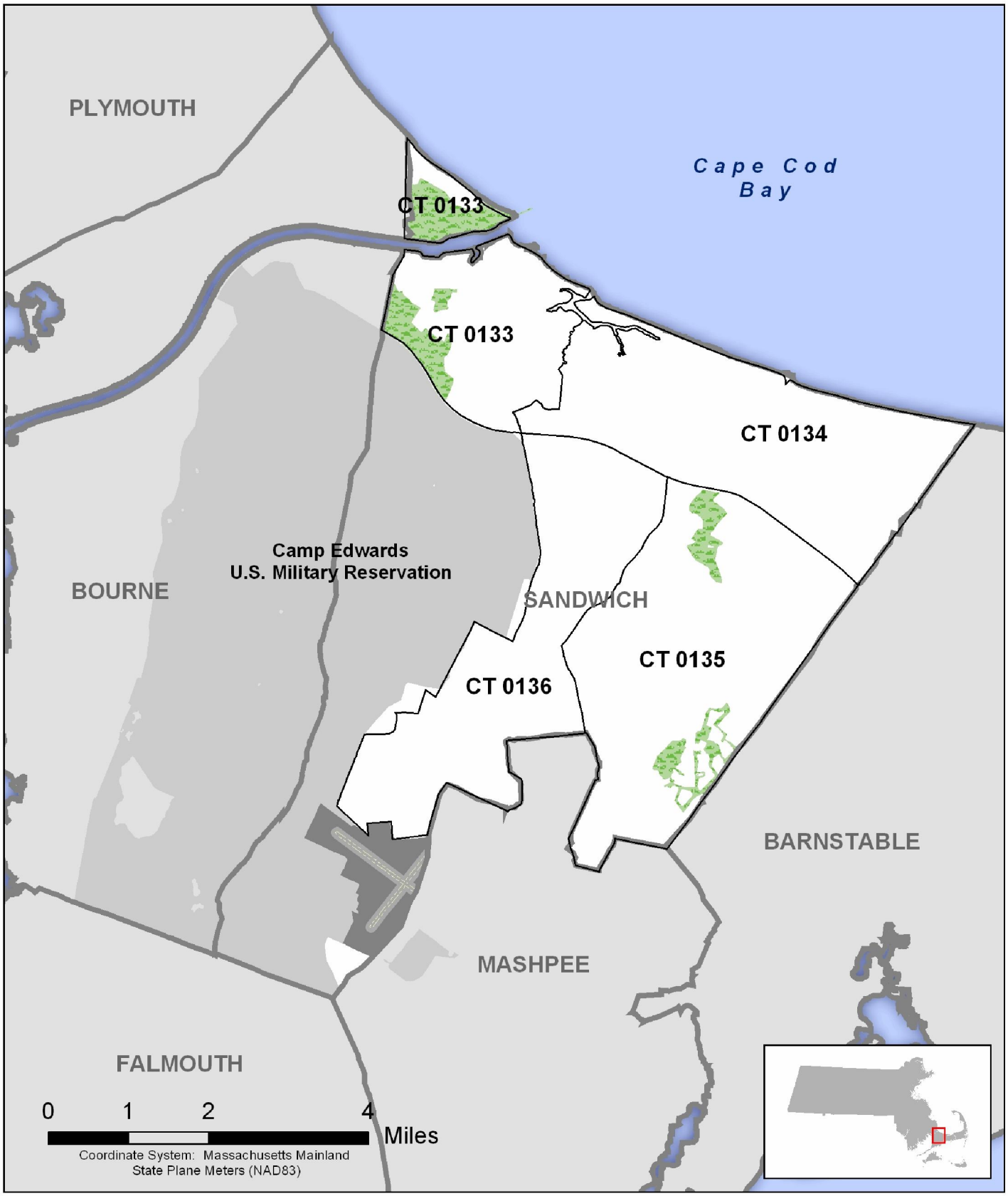
Figure 1
Location of Census Tracts (CTs)
Sandwich, Massachusetts



Center for CEH Environmental Health

Geographic data supplied by:
Massachusetts Executive Office of Environmental Affairs, MassGIS;
Geographic Data Technology, Inc.; U.S. Bureau of the Census.

N W E S

CT Boundary
City/Town Boundary
Recreation Area
Runway
Airport

Appendix A

Appendix A
Coding Definitions of Childhood Cancer

ICCC Diagnostic Group	ICD-O-3** codes	
	Morphology	**Topography**
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases		
a. Lymphoid leukemias	9820, 9823, 9826, 9827, 9831-9837, 9940, 9948	
b. Acute myeloid leukemias	9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931	
c. Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960-9964	
d. Myelodysplastic syndrome and other myeloproliferative diseases	9945, 9946, 9975, 9980, 9982-9987, 9989	
e. Unspecified and other specified leukemias	9800, 9801, 9805, 9860, 9930	
II. Lymphomas and reticuloendothelial neoplasms		
a. Hodgkin Lymphomas	9650-9655, 9659, 9661-9665, 9667	
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	9591, 9670, 9671, 9673, 9675, 9678-9680, 9684, 9689-9691, 9695, 9698-9702, 9705, 9708, 9709, 9714, 9716-9719, 9727-9729, 9731-9734, 9760-9762, 9764-9769, 9970	
c. Burkitt lymphomas	9687	
d. Miscellaneous lymphoreticular neoplasms	9740-9742, 9750, 9754-9758	
e. Unspecified lymphomas	9590, 9596	
III. Central nervous system and miscellaneous intracranial and intraspinal neoplasms		
a. Ependymomas and choroid plexus tumors	9383, 9390-9394[a]	
b. Astrocytomas	9380[a]	C72.3
	9384, 9400-9411, 9420, 9421-9424, 9440-9442[a]	
c. Intracranial and intraspinal embryonal tumors	9470-9474, 9480, 9508[a]	
	9501-9504[a]	C70.0-C72.9
d. Other gliomas	9380[a]	C70.0-C72.2, C72.4-C72.9, C75.1, C75.3
	9381, 9382, 9430, 9444, 9450, 9451, 9460[a]	
e. Other specified intracranial and intraspinal neoplasms	8270-8281, 8300, 9350-9352, 9360-9362, 9412, 9413, 9492, 9493, 9505-9507, 9530-9539, 9582[a]	

* Chart from: Steliarova-Foucher E, Stiller C, Lacour B & Kaatsch P. International classification of childhood cancer, third edition. 2005. *Cancer*, **103**, 1457-1467.

** *International Classification of Diseases for Oncology, 3rd Ed.*

Appendix A
Coding Definitions of Childhood Cancer

f. Unspecified intracranial and Intraspinal neoplasms	8000-8005[a]	C70.0-C72.9, C75.1-C75.3
IV. Neuroblastoma and other peripheral nervous cell tumors		
a. Neuroblastoma and ganglioneuroblastoma	9490, 9500	
b. Other peripheral nervous cell tumors	8680-8683, 8690-8693, 8700, 9520-9523	
	9501-9504	C00.0-C69.9, C73.9-C76.8, C80.9
V. Retinoblastoma	9510-9514	
VI. Renal Tumors		
a. Nephroblastoma and other nonepithelial renal tumors	8959, 8960, 8964-8967	
	8963, 9364	C64.9
b. Renal carcinoma	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8231, 8240, 8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C64.9
	8311, 8312, 8316-8319, 8361	
c. Unspecified malignant renal tumors	8000-8005	C64.9
VII. Hepatic Tumors		
a. Hepatoblastoma	8970	
b. Hepatic carcinoma	8010-8041, 8050-8075, 8082, 8120-8122, 8140, 8141, 8143, 8155, 8190-8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244-8246, 8260-8264, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C22.0, C22.1
	8160-8180	
c. Unspecified malignant hepatic tumors	8000-8005	C22.0, C22.1
VIII. Malignant bone tumors		
a. Osteosarcomas	9180-9187, 9191-9195, 9200	C40.0-C41.9, C76.0-C76.8, C80.9
b. Chondrosarcomas	9210, 9220, 9240	C40.0-41.9, 76.0-76.8, 80.9
	9221, 9230, 9241-9243	
c. Ewing tumor and related sarcomas of bone	9260	C40.0-C41.9, C76.0-76.8, C80.9
	9363-9365	C40.0-C41.9
d. Other specified malignant bone tumors	8810, 8811, 8823, 8830	C40.0-C41.9
	8812, 9250, 9261, 9270-9275, 9280-9282, 9290, 9300-9302, 9310-9312, 9320-9322, 9330, 9340-9342, 9370-9372	C40.0-C41.9
e. Unspecified malignant bone tumors	8000-8005, 8800, 8801, 8803-8805	C40.0-C41.9

Appendix A
Coding Definitions of Childhood Cancer

IX. Soft tissue and other extraosseous sarcomas		
a. Rhabdomyosarcomas	8900-8905, 8910, 8912, 8920, 8991	
b. Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms	8810, 8811, 8813-8815, 8821, 8823, 8834-8835	C00.0-C39.9, C44.0-76.8, C80.9
c. Kaposi sarcoma	9140	
d. Other specified soft tissue sarcomas	8587, 8710-8713, 8806, 8831-8833, 8836, 8840-8842, 8850-8858, 8860-8862, 8870, 8880, 8881, 8890-8898, 8921, 8982, 8990, 9040-9044, 9120-9125, 9130-9133, 9135, 9136, 9141, 9142, 9161, 9170-9175, 9231, 9251, 9252, 9373, 9581	
	8830	C00.0-C39.9, C44.0-C76.8, C80.9
	8963	C00.0-C63.9, C65.9-C69.9, C73.9-C76.8, C80.9
	9180, 9210, 9220, 9240	C49.0-C49.9
	9260	C00.0-C39.9, C47.0-C75.9
	9364	C00.0-C39.9, C47.0-C63.9, C65.9-C69.9, C73.9-C76.8, C80.9
	9365	C00.0-C39.9, C47.0-C63.9, C65.9-C76.8, C80.9
e. Unspecified soft tissue sarcomas	8800-8805	C00.0-C39.9, C44.0-C76.8
X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads		
a. Intracranial and Intraspinal germ cell tumors	9060-9065, 9070-9072, 9080-9085, 9100, 9101[a]	C70.0-C72.9, C75.1-C75.3
b. Malignant extracranial and extragonadal germ cell tumor	9060-9065, 9070-9072, 9080-9085, 9100-9105	C00.0-C55.9, C57.0-C61.9, C63.0-C69.9, C73.9-C75.0, C75.4-C76.8, C80.9
c. Malignant gonadal germ cell tumors	9060-9065, 9070-9073, 9080-9085, 9090, 9091, 9100, 9101	C56.9, C62.0-C62.9
d. Gonadal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8190-8201, 8210, 8211, 8221-8241, 8244-8246, 8260-8263, 8290, 8310, 8313, 8320, 8323, 8380-8384, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573, 9000, 9014, 9015	C56.9, C62.0-C62.9
	8441-8447, 8450, 8451, 8460-8473	
e. Other and unspecified malignant gonadal tumors	8590-8671	
	8000-8005	C56.9, C62.0-C62.9

Appendix A
Coding Definitions of Childhood Cancer

XI. Other malignant epithelial neoplasms and malignant melanomas		
a. Adrenocortical carcinomas	8370-8375	
b. Thyroid carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8510, 8560-8573	C73.9
	8330-8337, 8340-8347, 8350	
c. Nasopharyngeal carcinomas	8010-8041, 8050-8075, 8082, 8083, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8576	C11.0-C11.9
d. Malignant melanomas	8720-8780, 8790	
e. Skin carcinomas	8010-8041, 8050-8075, 8078, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940, 8941	C44.0-C44.9
f. Other and unspecified carcinomas	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C00.0-C10.9, C12.9-C21.8, C23.9-C39.9, C48.0-C48.8, C50.0-C55.9, C57.0-C61.9, C63.0-C63.9, C65.9-C72.9, C75.0-C76.8, C80.9
XII. Other and unspecified malignant neoplasms		
a. Other specified malignant tumors	8930-8936, 8950, 8951, 8971-8981, 9050-9055, 9110	
	9363	C00.0-C39.9, C47.0-C75.9
b. Other unspecified malignant tumors	8000-8005	C00.0-C21.8, C23.9-C39.9, C42.0-C55.9, C57.0-C61.9, C63.0-C63.9, C65.9-C69.9, C73.9-C75.0, C75.4-C80.9

ICD-0-3: International Classification of Diseases for Oncology, third edition; CNS: Central Nervous System
[a] Tumors with nonmalignant behavior are included for all morphology codes on the line.

Appendix B

Appendix B
Explanation of a Standardized Incidence Ratio (SIR)
And 95% Confidence Interval

In order to evaluate cancer incidence a statistic known as a standardized incidence ratio (SIR) was calculated for each cancer type. An SIR is an estimate of the occurrence of cancer in a population relative to what might be expected if the population had the same cancer experience as some larger comparison population designated as "normal" or average. Usually, the state as a whole is selected to be the comparison population. Using the state of Massachusetts as a comparison population provides a stable population base for the calculation of incidence rates. As a result of the instability of incidence rates based on small numbers of cases, SIRs were not calculated when fewer than five cases were observed.

Specifically, an SIR is the ratio of the observed number of cancer cases to the expected number of cases multiplied by 100. An SIR of 100 indicates that the number of cancer cases observed in the population evaluated is equal to the number of cancer cases expected in the comparison or "normal" population. An SIR greater than 100 indicates that more cancer cases occurred than expected and an SIR less than 100 indicates that fewer cancer cases occurred than expected. Accordingly, an SIR of 150 is interpreted as 50% more cases than the expected number; an SIR of 90 indicates 10% fewer cases than expected.

Caution should be exercised, however, when interpreting an SIR. The interpretation of an SIR depends on both the size and the stability of the SIR. Two SIRs can have the same size but not the same stability. For example, an SIR of 150 based on 4 expected cases and 6 observed cases indicates a 50% excess in cancer, but the excess is actually only two cases. Conversely, an SIR of 150 based on 400 expected cases and 600 observed cases represents the same 50% excess in cancer, but because the SIR is based upon a greater number of cases, the estimate is more stable. It is very unlikely that 200 excess cases of cancer would occur by chance alone.

To determine if the observed number of cases is significantly different from the expected number or if the difference may be due solely to chance, a 95% confidence interval (CI) was calculated for each SIR. A 95% CI assesses the magnitude and stability of an SIR. Specifically, a 95% CI is the range of estimated SIR values that has a 95% probability of including the true SIR for the population. If the 95% CI range does not include the value 100, then the study population is significantly different from the comparison or "normal" population. "Significantly different" means there is less than 5% percent chance that the observed difference is the result of random fluctuation in the number of observed cancer cases.

For example, if a confidence interval does not include 100 and the interval is above 100 (e.g., 105-130), then there is statistically significant excess in the number of cancer cases. Similarly, if the confidence interval does not include 100 and the interval is below 100 (e.g., 45-96), then the number of cancer cases is statistically significantly lower than expected. If the confidence interval range includes 100, then the true SIR may be 100, and it cannot be concluded with sufficient confidence that the observed number of cases is not the result of chance and reflects a real cancer increase or decrease. Statistical significance is not assessed when fewer than five cases are observed.

In addition to the range of the estimates contained in the confidence interval, the width of the confidence interval also reflects the stability of the SIR estimate. For example, a narrow confidence interval (e.g., 103--115) allows a fair level of certainty that the calculated SIR is close to the true SIR for the population. A wide interval (e.g., 85--450) leaves considerable doubt about the true SIR, which could be much lower than or much higher than the calculated SIR. This would indicate an unstable statistic.

Appendix C

Appendix C
Risk Factor Information for Bone Cancer

The occurrence of bone cancer is extremely rare; fewer than 2,600 primary cancers of the bone and joints will be diagnosed in the U.S. in 2005, accounting for less than 0.2% of all cancer types (ACS, 2005). There are several different types of malignant or cancerous bone tumors: osteosarcoma (about 35% of all cases), chondrosarcoma (26%), Ewing's sarcoma (or Ewing's tumor) (16%), chordoma (8%), and malignant fibrous histiocytoma/fibrosarcoma (6%). Several rare types account for the remainder of cases (ACS, 2000). Osteosarcoma affects the bones themselves and primarily occurs in young people between the ages of 10 and 30. However, about 10% of cases develop in people aged 60 to 80. Chondrosarcoma is a cancer of the cartilage cells and is uncommon in people under the age of 20. After age 20, the risk of this disease increases with age. Ewing's sarcomas most often develop in the cavity of the bone and are usually diagnosed in children and adolescents (ACS, 2000). Among the major bone cancer types, males experience a higher incidence of bone cancer than females. Similar incidence rates for osteosarcoma have been observed among whites and blacks. However, in the United States and Africa, the occurrence of Ewing's sarcoma among black individuals is almost non-existent. The incidence of Ewing's sarcoma among the Asian population is also very low (Miller et al., 1996).

Very little is known about factors associated with the development of bone cancer. In fact, most people with bone cancer do not have any known risk factors (ACS, 2000). Several pre-existing medical conditions are associated with the development of certain primary bone cancers. For example, osteosarcomas develop in about 5% to 10% of severe cases of Paget's disease, which primarily affects people over the age of 50 and results in the formation of abnormal bone tissue (ACS, 2000). The presence of multiple exostoses (overgrowth of bone tissue) increases the risk of osteosarcoma, as does the presence of multiple osteochondromas (benign tumors formed by bone and cartilage). In addition, an increased risk of chondrosarcoma has been observed among people with multiple enchondromas (benign cartilage tumors), although this risk is very low (ACS, 2000).

Very few bone cancers appear to have a hereditary basis. However, an elevated risk of developing bone cancer (especially osteosarcoma) has been associated with a family history of Li-Fraumeni syndrome. In addition, children with an inherited form of retinoblastoma, a rare eye cancer, have an increased risk for developing osteosarcoma due to an abnormal mutation of the retinoblastoma gene (ACS, 2000).

Ionizing radiation has been identified as one of the only environmental factors known to play a role in the development of certain types of bone cancer (e.g., osteosarcoma and chondrosarcoma). A typical x-ray of a bone does not pose a significant risk, but exposure to high-dose radiation (e.g., radiation therapy to treat another type of cancer) and ongoing exposure to internally deposited radionuclides (used to treat bone disease or for diagnostic radiography) may increase the risk of bone cancer (ACS, 2000; Miller et al., 1996). Although the use of high dose radiation has been identified as a risk factor, it is likely that less than 0.2% of patients treated develop bone cancer (Miller et al., 1996). However, children with certain cancers seem to be particularly susceptible to radiogenic

bone cancer and it appears that radiotherapy may interact with genetic susceptibility (e.g., due to a mutation in the retinoblastoma gene) (Miller et al., 1996).

Some studies have suggested that injury to a bone can cause cancer, but this has not been corroborated and most doctors do not believe that trauma is a significant risk factor. It is more likely that a diagnosis prompts patients to remember an injury to a site or that an injury draws their attention to a pre-existing bone mass (ACS, 2000).

Limited information is available regarding bone cancer and occupational risk factors (Hoppin et al., 1999). In the past, occupational exposure to radium was found to increase the risk of developing bone cancer. One study revealed that prior to 1930, women employed as radium dial painters in the United States were found to be ingesting radium orally by licking their paintbrushes to produce finer tips for finer lines. Of the 1,474 women in the study, 4% developed bone cancer (Miller et al., 1996). Some studies have suggested that certain woodworking occupations (e.g. carpenters, furniture workers) are associated with increased bone cancer mortality, but findings are inconsistent (Hoppin et al., 1999).

Metal implants (e.g., hip replacement) are also thought to play a causal role in the development of bone cancer. This is thought to be due to the use of metals such as chromium (a known human carcinogen) and nickel (a suspected human carcinogen), or the use of bone cement. While an association between bone cancer and metal implants is suggested, no definitive links in humans have been identified (Miller et al., 1996).

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Appendix C
Risk Factor Information for Brain and Central Nervous System (CNS) Cancers

Brain and central nervous system (CNS) tumors can be either malignant (cancerous) or benign (non-cancerous). Primary brain tumors (i.e., brain cancer) comprise two main types: gliomas and malignant meningiomas. Gliomas are a general classification of malignant tumors that include a variety of types, named for the cells from which they arise: astrocytomas, oligodendrogliomas, and ependymomas. Meningiomas arise from the meninges, which are tissues that surround the outer part of the spinal cord and brain. Although meningiomas are not technically brain tumors, as they occur outside of the brain, they account for about 50% of all reported primary brain and spinal cord tumors. The majority of meningiomas (about 85%) are benign and can be cured by surgery. Therefore, approximately 7.5% of brain and CNS tumors are malignant meningiomas. In addition to these main types, there are a number of rare brain tumors, including medulloblastomas, which develop from the primitive stem cells of the cerebellum and are most often seen in children. Also, the brain is a site where both primary and secondary malignant tumors can arise; secondary brain tumors generally originate elsewhere in the body and then metastasize, or spread, to the brain (ACS, 1999a). The American Cancer Society estimates that 18,500 Americans (10,620 men and 7,880 women) will be diagnosed with primary brain cancer (including cancers of the central nervous system, or spinal cord) and approximately 12,760 people (7,280 men and 5,480 women) will die from this disease in 2005 (ACS, 2005).

Brain and spinal cord cancers account for over 20% of all cancer types diagnosed among children aged 0-14 (ACS, 2005). About half of all childhood brain tumors are astrocytomas and 25% are medulloblastomas (ACS, 1999b). After a peak in childhood (generally under 10 years of age), the risk of brain cancer increases with age from age 25 to age 75. In adults, the most frequent types of brain tumors are astrocytic tumors (mainly astrocytomas and glioblastoma multiforme). Incidence rates are higher in males than in females for all types. In general, the highest rates of brain and nervous system cancer tend to occur in whites. However, this varies somewhat by type; the incidence of gliomas is lower among black men and women than whites, but for meningiomas, the reverse is true (Preston-Martin and Mack, 1996).

Despite numerous scientific and medical investigations, and analyses, the causes of brain cancer are still largely unknown. Among the possible risk factors investigated in relation to this type of cancer are ionizing radiation, electromagnetic fields, occupational exposures, exposure to N-nitroso compounds, head trauma, and genetic disorders.

The most established risk factor (and only established environmental risk factor) for brain tumors (either cancerous or non-cancerous) is high-dose exposure to ionizing radiation (i.e., x-rays and gamma rays). Most radiation-induced brain tumors are caused by radiation to the head from the treatment of other cancers (ACS, 1999a). Meningiomas are the most common type of tumors that occur from this type of exposure, but gliomas may also occur (Preston-Martin and Mack, 1996). Among adults, the risk of developing meningiomas has been associated with full-mouth dental x-rays taken decades ago when radiation doses were higher than today. Although the relationship between low-dose radiation exposure and increased risk of brain tumors has been debated in several studies,

prenatal exposure from diagnostic x-rays has been related to an increase in childhood brain tumors (Preston-Martin and Mack, 1996).

In recent years, there has been increasing public concern and scientific interest regarding the relationship of electromagnetic fields (EMF) to brain cancer. However, results from recent epidemiological investigations provide little or no evidence of an association between residential EMF exposure (e.g., from power lines and home appliances) and brain tumors (Kheifets, 2001). Studies also suggest that the use of handheld cellular telephones is not associated with an increased risk of primary brain cancer (Muscat et al., 2000). However, given the relatively recent use of cellular phones, evidence is preliminary and few studies have been conducted.

Other environmental factors such as exposure to vinyl chloride (used in the manufacturing of some plastics) and aspartame (a sugar substitute) have been suggested as possible risk factors for brain cancer but no conclusive evidence exists implicating these factors (ACS, 1999a). Although some occupational studies have suggested that electrical and electric utility workers may be at a slightly increased risk of brain cancer, these studies have important limitations, such as exposure misclassifications and a lack of dose-response relationships (Kheifets, 2001). Some researchers have also reported an increased risk of brain tumors in adults among veterinarians and farmers. Exposure to farm animals and pets have been considered as possible risk factors because of their association with bacteria, pesticides, solvents, and certain animal oncogenic (cancer-related) viruses (Yeni-Komshian and Holly, 2000). However, the relationship between farm life and brain cancer remains controversial.

Recent reports have proposed a link between occupational exposure to lead and brain cancer risk, but further analytic studies are warranted to test this hypothesis (Cocco et al., 1998). In a recent case-control study, the concentrations of metal and non-metal compounds in brain biopsies from patients with primary brain tumors were compared to results from an analysis of tumor-free brain tissue. Statistically significant associations were observed between the presence of brain tumors and the concentrations of silicon, magnesium, and calcium (Hadfield et al., 1998). However, further research using a larger sample size is needed to determine whether exposure to these elements plays a role in the development of brain cancer. Other occupations that may be associated with elevated risks include workers in certain health professions (e.g., pathologists and physicians), agricultural workers, workers in the nuclear industry, and workers in the rubber industry, although specific exposures have not been established (Preston-Martin and Mack, 1996). Studies investigating the possible association between occupational exposure of parents (in particular, paper or pulp-mill, aircraft, rubber, metal, construction, and electric workers) and the onset of brain tumors in their children have provided inconsistent results (Preston-Martin and Mack, 1996).

The association between the development of brain cancer and nitrites and other N-nitroso compounds, among the most potent of carcinogens, has been heavily researched. N-nitroso compounds have been found in tobacco smoke, cosmetics, automobile interiors, and cured meats. A recent study concluded that an increased risk of pediatric brain tumor

may be associated with high levels of nitrite intake from maternal cured meat consumption during pregnancy (Pogoda and Preston-Martin, 2001). However, the role of nitrites and cured meats in the development of brain cancer remains controversial (Blot et al., 1999; Bunin, 2000). Because most people have continuous, low level exposure to N-nitroso compounds throughout their lives, further studies, especially cohort studies, are needed to determine if this exposure leads to an increased risk of brain tumors (Preston-Martin, 1996).

Injury to the head has been suggested as a possible risk factor for later development of brain tumors but most researchers agree that there is no conclusive evidence for an association (ACS, 1999b). Head trauma is most strongly associated with the development of meningiomas compared with other types of brain tumor. Several studies have found an increased risk in women with histories of head trauma; in men who boxed; and in men with a previous history of head injuries. Gliomas are the most common type of childhood brain tumor and have been positively associated with trauma at birth (e.g., Cesarean section, prolonged labor, and forceps delivery). However, other studies have found no association (Preston-Martin and Mack, 1996).

In addition, rare cases of brain and spinal cord cancer run in some families. Brain tumors in some persons are associated with genetic disorders such as neurofibromatosis types I and II, Li-Fraumeni syndrome, and tuberous sclerosis. Neurofibromatosis type I (von Recklinghausen's disease) is the most common inherited cause of brain or spinal cord tumors and occurs in about one out of every 3,000 people (Preston-Martin and Mack, 1996). The disease may be associated with optic gliomas or other gliomas of the brain or spinal cord (ACS, 1999b). Of those afflicted with the disease, about 5-10% will develop a central nervous system tumor (Preston-Martin and Mack, 1996). In addition, von Hippell-Lindau disease is associated with an inherited tendency to develop blood vessel tumors of the cerebellum (ACS, 1999a). However, malignant (or cancerous) brain tumors are rare in these disorders; inherited syndromes that predispose individuals to brain tumors appear to be present in fewer than 5% of brain tumor patients (Preston-Martin and Mack, 1996).

Other possible risk factors investigated for brain cancer have included alcohol consumption, use of barbiturates, smoking and exposure to second-hand smoke, pesticides, and infectious diseases (i.e., tuberculosis and chicken pox). To date, studies on these risk factors have yielded inconclusive results. Further, the majority of individuals diagnosed with brain cancer have no known risk factors (ACS, 1999a).

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Appendix C
Risk Factor Information for Hodgkin's Disease

Hodgkin's disease (or Hodgkin's lymphoma) is a form of cancer that involves the lymphatic system and can be distinguished from non-Hodgkin's lymphomas by cancer cell type. The American Cancer Society estimates that there will be approximately 7,350 new cases of this disease in the U.S. in 2005, accounting for less than 1% of all cancer types, and approximately 1,410 deaths (ACS, 2005). Because of substantial improvement in effective therapy for this disease, mortality rates have decreased approximately 60% since the early 1970s (ACS, 1999).

Epidemiologic studies have shown that Hodgkin's disease is more common among men than women and more common among whites than blacks. People of Jewish descent appear to be at higher risk of Hodgkin's disease compared to people of non-Jewish descent (Mueller, 1996). Although the disease is relatively rare among children, two peaks in the age distribution have been observed for this cancer type. The first peak occurs in young adults usually between the ages of 15 to 40 (typically ages 25-30) and the second peak occurs in adults aged 55 years and above.

No major risk factors for Hodgkin's disease have been found (ACS, 1999). However, the clinical and cellular features of Hodgkin's disease suggest a chronic infectious process (Mueller, 1996). The bimodal age distribution of this disease suggests that two distinct etiologies (or causes) for Hodgkin's disease may be involved for each group. Researchers have proposed that among young adults, Hodgkin's disease is caused by a biological agent of low infectivity. Among individuals of older ages, the cause is probably similar to those of other lymphomas (Mueller, 1996). The virus that has been linked most specifically to this disease is the Epstein-Barr virus (EBV). EBV, a herpesvirus, is common in the general population and causes mononucleosis or "mono." Approximately 40% to 50% of Hodgkin's disease cases are associated with EBV (Weiss, 2000). In addition, several studies have also shown that young adults who have developed infectious mononucleosis have a significantly higher risk of developing Hodgkin's disease (ACS, 1999). However, the absence of EBV infection in about half the cases and the high prevalence of EBV in the general population suggest that EBV may be only one of several factors in the development of this cancer. Although cytomegalovirus (CMV) and the more recently identified human herpesvirus type 6 have been considered as possible factors in the development of Hodgkin's disease, results of antibody studies are inconsistent and these viruses do not appear to be related to risk of Hodgkin's disease (Mueller, 1996).

Slightly higher rates of Hodgkin's disease occur among people with reduced immunity, such as those with AIDS, people with congenital immune deficiencies, and individuals on immunosuppressant medication following organ transplants. However, Hodgkin's disease occurs at a much lower rate than non-Hodgkin's lymphomas among this group of individuals (ACS, 1999).

Hodgkin's disease trends in the young adult population reveal that the disease has become increasingly associated with populations both of middle to higher socioeconomic status and small family size. These factors are consistent with susceptibility to late infections with common childhood viruses, supporting the theory that Hodgkin's disease

is associated with an infectious agent (Mueller, 1996). Occupational exposures to workers in the chemical industry and woodworkers have also been suggested in several epidemiologic studies to be associated with the development of Hodgkin's disease. However, specific chemical exposures related to the development of this disease have not been identified and results of studies investigating occupational exposures are inconsistent (Mueller, 1996). Based on an examination of medical and scientific literature, the American Cancer Society concludes that although the exact cause remains unknown, Hodgkin's disease does not seem to be caused by genetic, lifestyle (e.g., dietary), or environmental factors (ACS, 1999).

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Appendix C
Risk Factor Information for Leukemia

Leukemia is the general term that includes a group of different cancers that occur in the blood forming organs and result in the formation of abnormal amounts and types of white blood cells in the blood and bone marrow. Individuals with leukemia generally maintain abnormally high amounts of leukocytes or white blood cells in their blood. This condition results in an individual's inability to maintain certain body functions, particularly a person's ability to combat infection.

In 2005, leukemia is expected to affect approximately 34,810 individuals (19,640 males and 15,170 females) in the United States, resulting in 22,570 deaths. In Massachusetts, approximately 770 individuals will be diagnosed with the disease in 2005, representing more than 2% of all cancer diagnoses. There are four major types of leukemia: acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), and chronic myeloid leukemia (CML). There are also a few rare types, such as hairy cell leukemia. In adults, the most common types are AML and CLL. Leukemia is the most common type of childhood cancer, accounting for about 30% of all cancers diagnosed in children. The majority of these cases are of the ALL type (ACS, 2005).

While ALL occurs predominantly among children (peaking between ages 2 and 3 years), an elevation in incidence is also seen among older individuals. The increase in incidence among older individuals begins at approximately 40-50 years of age, peaking at about age 85 (Linet and Cartwright, 1996). ALL is more common among whites than African Americans and among males than females (Weinstein and Tarbell, 1997). Exposure to high-dose radiation (e.g., by survivors of atomic bomb blasts or nuclear reactor accidents) is a known environmental risk factor associated with the development of ALL (Scheinberg et al., 1997). Significant radiation exposure (e.g., diagnostic x-rays) before birth may carry up to a 5-fold increased risk of developing ALL (ACS, 2000b). However, few studies report an increased risk of leukemia associated with residing in proximity to nuclear plants or occupational exposure to low-dose radiation (Linet and Cartwright, 1996; Scheinberg et al., 1997). It is unclear whether exposure to electromagnetic fields (EMF) plays a role in the development of ALL, however, most studies to date have found little or no risk (ACS, 2000b).

Few other risk factors for ALL have been identified. There is evidence that genetics may play an important role in the development of this leukemia type. Studies indicate that siblings of twins who develop leukemia are at an increased risk of developing the disease. Children with Down's syndrome are 10 to 20 times more likely to develop acute leukemia (Weinstein and Tarbell, 1997). In addition, other genetic diseases, such as Li-Fraumeni syndrome and Klinefelter's syndrome, are associated with an increased risk of developing leukemia. Patients receiving medication that suppresses the immune system (e.g., organ transplant patients) may be more likely to develop ALL (ACS 2000b). ALL has not been definitively linked to chemical exposure, however, childhood ALL may be associated with maternal occupational exposure to pesticides during pregnancy (Infante-Rivard et al., 1999). Certain rare types of adult ALL are caused by human T-cell leukemia/lymphoma virus-I (HTLV-I) (ACS, 2000a). Some reports have linked other viruses with various types of leukemia, including Epstein-Barr virus and hepatitis B virus. Still others propose that leukemia may develop as a response to viral infection.

However, no specific virus has been identified as related to ALL (Linet and Cartwright, 1996). Recent reports also suggest an infectious etiology for some childhood ALL cases, although a specific viral agent has not been identified and findings from studies exploring contact among children in day-care do not support this hypothesis (Greaves MF, 1997; Kinlen and Balkwill, 2001; Rosenbaum et al., 2000).

Although AML can occur in children (usually during the first two years of life), AML is the most common leukemia among adults, with an average age at diagnosis of 65 years (ACS, 2000a and 2000b). This type of leukemia is more common among males than among females but affects African Americans and whites at similar rates (Scheinberg et al., 1997). High-dose radiation exposure (e.g., by survivors of atomic bomb blasts or nuclear reactor accidents), long-term occupational exposure to benzene, and exposure to certain chemotherapy drugs, especially alkylating agents (e.g., mechlorethamine, cyclophosphamide), have been associated with an increased risk of developing AML among both children and adults (ACS, 2000a and 2000b; Linet and Cartwright, 1996). The development of childhood AML is suspected to be related to parental exposure to pesticides and other chemicals, although findings are inconsistent (Linet and Cartwright, 1996). Recent studies have suggested a link between electromagnetic field (EMF) exposure (e.g., from power lines) and leukemia (Minder and Pfluger, 2001; Schuz et al., 2001). However, there is conflicting evidence regarding EMF exposure and leukemia and it is clear that most cases are not related to EMF (ACS, 2000a; Kleinerman et al., 2000).

Other possible risk factors related to the development of AML include cigarette smoking and genetic disorders. It is estimated that approximately one-fifth of cases of AML are caused by smoking (Scheinberg et al., 1997). Also, a small number of AML cases can be attributed to rare inherited disorders. These include Down's syndrome in children, Fanconi's anemia, Wiskott-Aldrich syndrome, Bloom's syndrome, Li-Fraumeni syndrome, and ataxia telangiectasia (ACS, 2000a and 2000b). Recently, scientists have suggested that a mutation in a gene responsible for the deactivation of certain toxic metabolites may have the ability to increase the risk of acute myeloid leukemia in adults. However, further research is necessary in order to confirm the findings of this study (Smith et al., 2001).

CLL is chiefly an adult disease; the average age at diagnosis is about 70 years (ACS, 1999). Twice as many men as women are affected by this type of leukemia (Deisseroth et al., 1997). While genetics and diseases of the immune system have been suggested as playing a role in the development of CLL, high-dose radiation and benzene exposure have not (ACS, 1999; Weinstein and Tarbell, 1997). It is thought that individuals with a family history of CLL are two to four times as likely to develop the disease. Some studies have identified an increased risk of developing CLL (as well as ALL, AML, and CML) among farmers due to long-term exposure to herbicides and/or pesticides (Linet and Cartwright, 1996). In addition, many researchers believe that cigarette smoking plays a role in some chronic leukemias. The role of EMF in the development of chronic leukemia remains controversial (ACS, 1999). Although viruses have been implicated in

the etiology of other leukemias, there is no evidence that viruses cause CLL (Deisseroth et al., 1997).

Of all the leukemias, CML is among the least understood. While this disease can occur at any age, CML is extremely rare in children (about 2% of leukemias in children) and the average age of diagnosis is 40 to 50 years (ACS, 1999). Incidence rates are higher in males than in females, but unlike the other leukemia types, rates are higher in blacks than in whites in the U.S. (Linet and Cartwright, 1996). High-dose radiation exposure may increase the risk of developing CML (ACS, 1999). Finally, CML has been associated with chromosome abnormalities such as the Philadelphia chromosome (Weinstein and Tarbell, 1997).

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Appendix C
Risk Factor Information for Rhabdomyosarcoma

What Are The Risk Factors for Rhabdomyosarcoma?

A risk factor is anything that increases your child's chance of getting a disease such as cancer. Different cancers have different risk factors. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for cancers of the lung, mouth, larynx, bladder, kidney, and several other organs. But having a risk factor, or even several, does not mean that your child will get the disease. Lifestyle-related risk factors have little or no significance in childhood cancers.

Rhabdomyosarcoma is unlike most adult cancers in that there are no known environmental conditions that increase your child's chance of getting the disease. No association has ever been documented between rhabdomyosarcoma and toxic substances, air or water pollution, use of drugs or x-rays during pregnancy, or trauma (injury).

Inherited Conditions

There is evidence suggesting that people with certain conditions may inherit an increased risk of developing rhabdomyosarcoma. Some families have an inherited tendency for developing not only rhabdomyosarcoma, but also other tumors, including breast cancer and brain tumors.

- Members of families with *Li-Fraumeni syndrome* are more likely to develop sarcomas, breast cancer, leukemia, and other cancers.
- Children with *Beckwith-Wiedemann syndrome* have a high risk of developing Wilms' tumor, a type of kidney cancer, but children with this syndrome may also develop rhabdomyosarcoma.
- *Neurofibromatosis*, also known as von Recklinghausen disease, usually causes multiple nerve tumors but also slightly increases the risk of rhabdomyosarcoma.

These inherited conditions are very rare and account for only a small fraction of rhabdomyosarcoma cases, but they do suggest that the key to understanding rhabdomyosarcoma will come from studying genes and how they work in very early life to control cell growth and development.

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