CANCER INCIDENCE STUDY

Utah Statewide Investigation of Brain Cancer for Spatiotemporal Clustering Patterns Between 1973 to 2010

October 24, 2013

Prepared by the

Utah Department of Health
Division of Disease Control and Prevention
Bureau of Epidemiology
Environmental Epidemiology Program

TABLE OF CONTENTS

ACKNOWLEDGMENT....3
EXECUTIVE SUMMARY....4
INTRODUCTION....5
DATA AND METHODS....8
FINDINGS....13
DISCUSSION....15
CONCLUSIONS AND RECOMMENDATIONS....20
AUTHORSHIP, REVIEW AND CITATION....21
CERTIFICATION....22
REFERENCES....23
FIGURES....33
DEFINITIONS....41

ACKNOWLEDGMENT

Cancer data used for this investigation was obtained from the Utah Cancer Registry (UCR). The UCR is funded by contract N01-PC-35141 from the National Cancer Institute (NCI)'s Surveillance, Epidemiology and End Results (SEER) Program (NCI 2012a) with additional support from the Utah Department of Health (UDOH) and University of Utah (UCR 2013).

Other data and analytical tools used for this investigation were obtained from the Utah Environmental Public Health Tracking Network (UEPHTN). In addition, the UEPHTN provides geocoding services to UCR data. The UEPHTN is funded by a grant from the Centers for Disease Control and Prevention (CDC), Environmental Public Health Tracking Branch. The current UEPHTN award is number 1U38EH000954 (UEPHTN 2012).

EXECUTIVE SUMMARY

Cancer is a dominating environmental public health concern. A function of epidemiology is to investigate cancer incidence starting with a statistical review of cancer cases. The Environmental Epidemiology Program (EEP), a program within the Utah Department of Health (UDOH), conducts statistical reviews of cancer in Utah. During the past ten years, the EEP has received a number of requests from concerned citizens to investigate brain cancer incidence in Utah.

This report presents a statistical review of the spatial and temporal distribution of invasive primary neuromas and gliomas (two types of brain cancer) in Utah from 1973 to 2010 using a spatiotemporal scan methodology. The purpose of this review was to identify regions of Utah with a historical or ongoing excess occurrence of brain cancers. Identified regions were characterized with respect to the cancer cluster. Eight historical cancers were identified by the scanning tool. No current cancer clusters were found. In addition, the eight cancer clusters could not be definitively distinguished as true clusters. The clusters could be natural patterns of random excess that appear as clusters. Details of these eight potential clusters are presented along with a discussion of known risk factors for brain cancer.

The rate of brain cancer in Utah is rising and is similar to the current national rate. Nationally the rate has been declining. A comprehensive literature review of known risks factors for brain cancer revealed that brain cancer in Utah is rising, but did not reveal any significant environmental risk other than exposure to strong ionizing radiation to the head level. Other risks have been studied and the available evidence was found to be generally inconclusive. This report can be used by local and state public health officials to formulate a response to concerned citizens who perceive increased brain cancer rates in their communities.

INTRODUCTION

The Brain: The brain is the organ responsible for sensory perception, cognition, memory, arousal, muscular activation, and certain metabolic controls (Frackowiak et al. 2004). At the cellular level, the brain consists of two major types of brain cells. These cells arise from neural stem cells that differentiate initially into a progenitor cell, migrate into position, and then further mature into specific types of brain cells (Ndubaku & de Bellard 2008; Stiles & Jernigan 2010). See Figure 1 in the appendices of this report or a representation of the cellular structure of the brain showing the relationship and connectivity of neural and glial cells.

The neuron or nerve cell is an electrically excitable cell that processes or transmits information through electrical and chemical signals. The human brain has between 80 and 100 billion neurons (NINDS 2013; Nowakowski 2006; Raine 1999). The neuroglia (also called glia or glial cells) provide structural support, metabolic support, neural insulation, protection, repair, and developmental guidance to the neurons (Chedotal & Richards 2010; Ndubaku & de Bellard 2008; Raine 1999). The human brain has approximately one trillion glial cells. The major types of glial cells in the central nervous system (CNS) include astrocytes, oligodendrocytes, and the ependymal cells. A fourth type of cell, known as radial glial cells, is found in young developing brains. Radial glial cells function as neuronal progenitors and as scaffolding upon which newly differentiated neurons migrate (Howard et al. 2008; Sild & Ruthazer 2011). Ependymal cells form a thin epithelial membrane lining the ventricular system of the brain and are responsible for the production of cerebrospinal fluid (Del Bigio 2010). Oligodendrocytes form a protective coating known as the myelin sheath around neuronal axons (the long filament extending from the neuron cell that forms connections with other neurons). This sheath also enhances and accelerates the electrical activity of neurons (Baumann & Pham-Dinh 2001; Bradl & Lassmann 2010). Astrocytes are the most common type of glia cell and are involved in many processes including the blood/brain transfer of nutrients, the blood/brain barrier against harmful substances, the biochemical support of the neurons, maintenance of the extracellular electrolyte and neurotransmitter balances, structural support of neurons, the structural integrity of the brain, and the brain repair and scarring processes (Montgomery 1994; Seth & Koul 2008; Sofroniew & Vinters 2010). Microglia are considered part of the family of glial cells. Microglia are specialized white blood cells that migrate from the cardiovascular system into the nervous system to provide white blood cell functions. They do not arise from neural stem cells (Kettenmann et al. 2011; Kofler &Wiley 2011; Neumann et al. 2009).

Brain Cancer: Cancer is a broad group of more than 100 diseases that involve uncontrollable cell replication and growth. Often these cells are “undifferentiated,” meaning they have lost their tissue-specific characteristics. As these cells grow to form tumor tissue, they invade nearby healthy tissue or spread to other tissues through metastasis. This invasion, or spread, disrupts the functions of the affected healthy tissues. Cancer cells may also produce metabolic products that can be transported to other parts of the body resulting in adverse health effects (NCI 2012b). The American Cancer Society (ACS) estimates that about one in two men and one in three women will develop cancer (all invasive sites) sometime in their life (lifetime risk). The lifetime risk for U. S. men developing brain cancer is one in 143 and for women, one in 182. By way of comparison, the lifetime risk for men developing lung cancer is one in 13 and for women, one in 16 (ACS 2009; NCI 2011a, 2011b). In the U.S., cancer is the second leading cause of death

(CDC 2012). Among all causes of death, approximately one in four men and one in five women will die of cancer. The risk of dying due to brain cancer among U. S. men is one in 200 and for women, one in 250 (ACS 2009; NCI 2011a, 2011b). On average, about one in nine people will develop two or more types of cancer in his or her lifetime (Wilkins and Woodgate 2008). Brain cancer accounts for approximately 1.4% of all cancers and 2.3% of all cancer-related deaths (El-Zein et al. 2002; Fang et al. 2004). Brain cancer is the second most common cancer among children in the United States (Fang et al. 2004).

Brain cancers are first classified by the type of brain cell and the level of maturity of the brain cell from which the cancer originated:

- Neuroblastomas arise from neuronal precursor cells
- Neuromas arise from neurons
- Glioblastomas arise from glial cell precursors
- Gliomas arise from glial cells

Gliomas can further be segregated by the type of glial cell from which the cancer originated:

- Astrocytomas arise from astrocytes
- Ependymomas arise from ependymal glial cells
- Oligodendrogliomas arise from oligodendroglial cells.

In some cases, a cancer may involve more than one type of glial cell (e.g., an oligoastrocytoma involves both oligodendroglial cells and astrocytes) or a mixture of glial cells and neurons. Brain cancer can be distinguished further based on the cancer's aggressiveness and stage of progression or other cellular characteristics. These levels of distinction give rise to a variety of names (e.g., pilocytic astrocytoma, fibrillary astrocytoma, anaplastic astrocytoma, etc.) (Berger et al. 2002; Higginson et al. 1992; Preston-Martin et al. 2006).

The rate of incidence and mortality of brain and other nervous system (ONS) cancers among Utah residents has been rising since 1975. Historically, the rates of both measures have been slightly lower than the nation, but have achieved the national level in the last few years. Between 2005 and 2009, the state annual incidence rate has been 6.7 cases per 100,000 person-years [the 95% confidence interval is 6.2-7.2]. The U. S. had a similar incidence rate (6.7 [6.6-7.2]). The annual death rate due to brain and ONS cancers for Utah was 4.5 deaths [4.1-4.9] per 100,000 persons. For the nation, the death rate was 4.3 deaths [4.2-4.3] per 100,000 persons. As the confidence intervals of the state and national rates for these two metrics overlap, one can say that there is no statistical difference between the state and national incidence or death rate (NCI 2013a). Nationally, the incidence of brain and ONS cancers has been declining by 0.2% per year for the last 10 years (NCI 2013b).

Diagnosis of a brain cancer is particularly devastating for the patient and the patient's family and friends for several reasons. Brain cancer is difficult to treat with poor prognosis of survival or quality of life (Edvardsson 2008; Valentine et al. 2002). Brain function is central to self-identity. Brain cancer or the treatment of brain cancer can result in changes or loss of brain function, memory, and personality resulting in change or loss of parts of the patient's self-identity and

quality of life (Edvardsson 2008; Forman 2002; Meyers and Kayl 2002; Valentine et al. 2002). The brain is part of the endocrine regulatory system. Brain cancer or the treatment of brain cancer may disrupt or change neuroendocrine function resulting in a variety of secondary health effects including growth and developmental effects, metabolic effects, weight gain and obesity, and an increased risk for the development of chronic diseases such as diabetes (Vassilopoulon-Sellin 2002). The course of disease is unpredictable resulting in increased levels of anxiety and stress for the patient and family. Finally, brain cancer patients require a great deal of physical and emotional support which is stressful to the support givers (Edvardsson 2008; Valentine et al. 2002).

Cancer Incidence Statistical Reviews: A core function of epidemiology is to track and evaluate disease patterns. This function helps public health officials and policy makers identify and assess communities with public health challenges, define public health priorities, develop and implement informed public health policy, monitor and evaluate public health actions, discover knowledge about public health concerns, and guide public health outreach, education and intervention activities (Dicker 2002; Lawson and Kulldorff 1999; Stanbury et al. 2012; Thacker 2000; Thacker et al. 2012). Cancer is a dominating environmental public health concern (Goujon-Bellec et al. 2011; Morrone 2011; Wakefield et al. 2000). Public concerns about excess cancer risk often result in requests made to public health agencies to conduct investigations. Public health agencies conduct investigations of cancer incidence using one of several methods. The first is a cancer incidence statistical review. This method focuses on determining if a particular community is experiencing more cancer than would be expected. A cancer statistical review is usually conducted by linking cancer registry and population data, and evaluating trends. From the public health perspective, a cancer incidence statistical review is most useful in identifying community needs about cancer-related health education and awareness building, public health screening services, and other public health interventions. For the community, these kinds of studies empower the community to make improvements in governmental policymaking and health care services (Bell et al. 2006; Kingsley et al. 2007).

One of the outcomes of a statistical review is the identification of probable patterns of disease clustering. A spatial cluster (also called a hot spot) is defined as a limited area within a general study area with a significant and meaningful increase in the incidence of disease. A temporal cluster is a defined period of time within a larger range of time with a significant and meaningful increase in disease incidence. A spatiotemporal cluster is a cluster defined in both the geographic and temporal dimensions (Aamodt et al. 2006; Hinrichsen et al. 2009; Lawson and Kulldorff 1999; Wakefield et al. 2000; Wheeler 2007).

The discovery or knowledge of the presence of a possible disease cluster usually warrants additional action, either as continued monitoring or a more aggressive investigation. However, disease clusters may not always be a public health concern. Often in looking through a long period of time, historical clusters may be discovered that have resolved themselves. Clustering may be the natural result of the distribution of residential or demographic population patterns or may be a function of wall-to-wall analytical units that properly accommodate disease patterns. Clusters may also occur because of the presence of factors that are not measurable or are highly variable (Wakefield et al. 2000). Clusters may also be reported due to improper application of statistical analytical methods (Tango 1999).

Another method available to public health practitioners is an actual cancer cluster investigation. Cancer cluster investigations focus on characterizing the size and extent of a population with known cancer excess and determining potential causal factors. The cancer cluster methodology involves linking many causal variables, usually collected by medical record review and individual surveys or interviews, followed by complex statistical analysis to identify the few variables that seem to explain the risk (Kingsley et al. 2007). Cluster investigations rarely result in important discoveries of causality (Goodman et al. 2012; Kingsley et al. 2007).

Public Statement of Concern: The Environmental Epidemiology Program (EEP), within the Utah Department of Health (UDOH), receives concerns from the public about perceived excess (or a cluster) of cancer. During the past ten years, the EEP has received a number of concerns about excess brain cancer in neighborhoods in south Salt Lake County and north Utah County. In December 2009, the Utah County Health Department requested the EEP investigate a reported cluster of cancer including brain cancer concerns in Orem, Utah County, Utah. That investigation did not result in the finding of excess cancer rates for Orem. Since that investigation, three additional requests involving brain cancer were investigated by EEP. Those investigations focused on Herriman in Salt Lake County (two investigations), and Highland in Utah County. None of these investigations determined that these communities were experiencing a higher burden than expected. On the last investigation, the EEP conducted a limited spatiotemporal scan of Salt Lake, Utah and Tooele counties to determine if there may be an underlying cluster that was larger in size. That analysis was inconclusive – neither confirming nor ruling out the existence of a cluster. At that time, the EEP started preparations to conduct a robust statewide spatiotemporal scan for brain cancer.

Study Objectives: This report presents a statistical review of the spatial and temporal distribution of primary invasive neuromas and gliomas (two types of brain cancer) in Utah from 1973 through 2010 using a spatiotemporal scan methodology. The purpose of this review was to identify regions of Utah with a historical or ongoing excess incidence of brain cancers. Identified regions were characterized with respect to the cancer cluster.

Authority and Funding: This study was conducted as part of the UDOH Executive Director's responsibility to investigate public health concerns within Utah. The Executive Director delegates responsibility for cancer investigations to the EEP. Cancer, population, and geographic data for this investigation are collected, maintained and made available by the Utah Environmental Public Health Tracking Network (UEPHTN). The UEPHTN also funds the SAS® and ArcGIS® analytical software application licenses that were used to conduct this investigation. The UEPHTN is funded by a grant from the Centers for Disease Control and Prevention (CDC) (UEPHTN 2012). Personnel time used to conduct this investigation was charged against state-funded Environmental Health Administrative funds. No federal funds were directly used to conduct this investigation.

DATA AND METHODS

Study Design: This investigation is a retrospective statistical review of cancer using spatiotemporal scanning methodology to identify spatial clusters in the data. Statistical reviews

are not cancer cluster investigations, and lack the power to link cancer incidence to putative risk factors (Jekel et al. 1996; Kingsley et al. 2007; Mann 2003). A statistical review is a tool used by the EEP to evaluate the health status of a population, identify public health needs, and assess public health activities. A good study design includes determining the underlying spatiotemporal epidemiologic theory, selecting appropriate scales of analysis, selecting an appropriate analytical methodology, defining risk and exposure, and determining how to manage locational and attribution uncertainty (Meliker and Sloan 2011). An individual in the population either is or is not, a cancer case. Thus, the appropriate analytical model applies binomial statistics. Since cancer incidence is relatively rare, the Poisson distribution (a special case of the binomial distribution) is appropriate. The smallest consistently available scale for the case and population data for this investigation is the census tract geographic unit in the spatial dimensions and year of diagnosis in the temporal dimension. This investigation will use the spatiotemporal scan statistic to look for current and historic clusters. Identified clusters will be further evaluated for homogeneity, statistical significance, and burden to the population. The spatiotemporal scan method creates many different aggregations of contiguous spatial and temporal analytical units. This study uses the census tract as the spatial unit and the year as the temporal unit. The scan method then compares the incidence of cancer inside each aggregation to the incidence of cancer outside the aggregation to identify spatiotemporal areas of excess cancer. The study's null hypothesis is that the incidence of cancer is randomly dispersed in both the geographic and temporal dimensions. Age is an important risk factor for cancer and age will be controlled for. Risk factors for brain cancer will be discussed.

Cancer Data: Cancer incidence data on people diagnosed with primary carcinoma-in-situ (CIS, behavior type 2) and invasive cancer (behavior type 3) between 1973 and 2010 were obtained from the Utah Cancer Registry (UCR). The EEP receives cancer data for all reported CIS and invasive cancers on an annual basis (UCR 2013). Although in 2004, criteria was established for the reporting of benign brain tumors (behavior type 1), reporting is incomplete, because of the difficulty in detecting, characterizing, and diagnosing some benign tumors. Some brain cancers may not be primary to the brain meaning that are the result of metastatic movement of a primary cancer of another organ of the body. Metastatic cancers (behavior type 4) are difficult to interpret in cancer cluster investigations. The UCR does not report benign tumors (behavior type 1) or cancers resulting from metastasis of a primary cancer (behavior type 4) to the EEP. Benign brain tumors and brain tumors resulting from metastasis will not be considered in this investigation.

The UCR completes a rigorous data review for completion and data quality before data are released to the EEP. The most recent years of data are not made available to the EEP until they have been finalized. The UCR data includes diagnostic information, patient demographics, and residential addresses of the cases, as well as information about the behavior of the cancer (UCR 2013).

Individuals with multiple primary invasive cancers have multiple records in the data set in sequential order. These cancers are distinguished by unique cancer registry tracking numbers and a cancer sequence number. The sequence number allows discrimination between the first cancer diagnosis and subsequent diagnoses (UCR 2013). Diagnostic coding of cancers includes the International Classification of Disease Oncology, 3rd Edition (ICD-O-3) codes for site, histology and behavior (WHO 2012). The UCR groups cancer into 42 major cancer types by site following

the guidance provided by the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) Program (NCI 2012a). These 42 UCR site codes are a convenient grouping for conducting surveillance analyses (UCR 2013). Brain cancers are identified using the UCR site code "31." This code is for all cancer incidences that were diagnosed within the brain and may include cancers of non-brain tissue (e.g., blood vessels, etc.) located within the brain. The UCR site code "31" excludes other central nervous system (i.e., the spinal cord, etc.) cancers that are not specifically located within the brain. Other central nervous system cancers are coded by the UCR site code "32." From 1973 to 2010, there were 3,892 cases of brain cancer (UCR site code = 31) reported to the UCR.

Brain cell cancers include cancers of the neuron cells called neuromas and cancers of glial cells (the supporting cells) called gliomas. Gliomas are further categorized by type and the development state of the glial cells in which the gliomas arise. Brain cell cancers can be distinguished from cancers in the brain originating from non-brain tissue cells using the histology codes. For this investigation, only neuromas and gliomas of the brain were considered. The following histology codes were used to distinguish neuromas and gliomas from other brain cancers.

Histology Range	Cancer Classification	Type of Glioma	Case Count
8000 – 9379	Cancers not specifically classified by cell type or of a cell type that is not a neuron or glial cell		175
9380 – 9389	Glioma	Glioma, not further specified	341
9390 – 9399	Glioma	Ependymoma	109
9400 – 9429	Glioma	Astrocytoma	1,179
9430 – 9439	Glioma	Astroblastoma	29
9440 – 9449	Glioma	Glioblastoma	1,513
9450 – 9459	Glioma	Oligodendroglioma	327
9460 – 9469	Glioma	Oligodendroblastoma	2
9470 – 9479	Glioma	Medulloblastoma	192
9500 – 9509	Neuroma		25

Between 1973 and 2010, 3,717 cases of brain cancer involving brain cells (25 cases of neuroma and 3692 cases of glioma) were reported to the UCR. Throughout the remainder of this report, brain cancer will refer only to cases classified as either a neuroma or a glioma as described above. For 3,454 (93%) of the cases, brain cancer was their first cancer experience. The other 263 (7%) cases had experienced a previous cancer.

The residential address information provided by the UCR includes the street address, city and ZIP code (UCR 2013). The EEP geocodes each registry record's residential address data to obtain an x- and y-coordinate for that address. The address locator data was obtained from the Utah State Geographic Information Database (SGID) maintained by the Utah Automated Geographic Reference Center (AGRC) (AGRC 2013). Most addresses are automatically geocoded using this address locator dataset. Addresses not found due to land reutilization, street name changes, address realignment, or are newer than the address locator file, were researched

using historic street maps and references or using online street maps, integrated aerial photographs, and other references to locate the address and manually geocode it. A few (75 cases or 2%) case addresses (e.g., a postal box addresses, etc.) could not be geocoded. These cases were located in the most populated census tract for the smallest known geographical area (the ZIP code or municipal boundary) indicated by the address. Using the geocoded x- and y-coordinates, the EEP was able to geo-reference cancer case data to their respective U.S. 2000 census geographic areas.

Population Data: The 2000 U.S. census divides Utah into 496 census tracts (USCB 2004) with a median population of 4,430 (range 0 to 11,159) persons per census tract in the year 2000. These small area geographies range in size between 0.1 to 6,107 square miles and have a population density ranging from less than one person per square mile in the sparsely populated areas of Utah to more than 28,000 persons per square mile in the urbanized Wasatch Front. Commercially available U.S. census population data for Utah for the 1970, 1980, 1990, 2000 and 2010 censuses (Geolytics 2002a, 2002b, 2002c; Geolytics 2012a, 2012b) were used to estimate annual five-year age-group population counts for each census tract for each intercensal year between 1970 and 2010. These estimates were made by applying annual population growth rates derived from the previous and subsequent decennial data. This method follows national population estimation guidelines (USCB 2012a).

Census Tract Data: Geographic Information System data for the 2000 U.S. Census Bureau (USCB) geographies in the form of shape files for Utah census counties, Utah census tracts, Utah census block groups and Utah census blocks were obtained from the SGID (AGRC 2013). The 2000 U.S. Census data applies a “wall-to-wall” geographic coverage. This means that there are no areas within the state boundaries that are not accounted for within a census level geography. In Utah, some census geographies will include a mix of residential neighborhoods, commercial/industrial areas and uninhabited areas. The data for each census geography includes a geographic centroid (the center point of the area geography). The scan statistical methodology uses the centroid point to represent the “average” location of the population and diseases cases for each geographic analytical unit. This study used a Cartesian projection of the data using the North American 1983 Universal Transverse Mercator (UTM) datum for zone 12N. A Cartesian projection results in the centroid x- and y-coordinates being expressed in meters. For this investigation, a population-weighted centroid was preferable for representing the geographic location of the study population and cases. The population-weighted centroid was determined using census blocks. The U.S. census enumerates population at all geographic levels, but provides age and sex stratification only at the census block group level and larger. A population-weighted centroid was calculated by importing census tract and census block GIS data attribute tables containing fields for the census tract level standard federal identifier (STFID) and the geographic x- and y- coordinates into SAS® for Windows version 9.2 (SAS 2002) as follows:

$$Coord_T = \frac{\sum(Coord_B\ Pop_B)}{\sum Pop_B}$$

Where: *Coord* is the x- or y-coordinate
T is the target census tract
B is the source census block contained within the target census tract

Pop_B is the census block total population

On average, the population-weighted centroid differed from the geographic centroid by 3,212 (range 0 to 64,121) meters.

The STFID is a unique label applied to census geographic units. The STFID was used as the key to link census geography to population data and cancer case data.

Data Linkage: Census tract case and population data were tabulated by census tract using the STFID, and by year, and five-year age group using SAS® for Windows version 9.2 (SAS 2002). Coordinate data, case data and population data referenced by the STFID were exported to a database file that is compatible for import into SaTScan.

SaTScan: The SaTScan™ version 9.1.1 computer application applies spatiotemporal scanning methodology (Kulldorff and IMS. 2011). SaTScan implements a class of statistics known as "scan statistics." Scan statistics were originally developed to scan through the spatial and temporal dimensions of interest, looking for anomalies in incidence of events of interest (Wakefield et al. 2000). Cases and the underlying population are represented by a three-dimensional space-time point. This study uses the census tract centroid as the geographic component coordinates. The scan statistical method creates many cylindrical windows, where the base represents geography and the height represents time. These cylindrical windows are centered on each census tract and unit of time. Each cylinder is expanded incrementally to include multiple contiguous census tracts and units of time. The incidence of cancer represented inside the cylinder is compared to the incidence of cancer outside the cylinder to identify areas and time periods of statistically excessive cancer incidence. Many thousands of overlapping cylinders are evaluated and ranked for the likelihood of a cancer cluster. For this evaluation both circular shaped and elliptical shaped geography bases were used. The elliptical-based scan included all orientations and shapes of ellipses (Jones and Kulldorff 2012; Kulldorff 1997; Kulldorff and Nagarwalla 1995; Kulldorff et al. 2006).

The SaTScan application features a number of models that can be used. For this study, the discrete Poisson model for space-time cluster detection was used (Kulldorff 1997, Wagner et al. 2013). The model parameters used an elliptic spatial window shape with medium non-compactness penalty. In most cases, the choice of the penalty does not dramatically change the findings (Goujon-Bellac et al. 2011). The maximum cluster size for the spatial component was limited to 25% of the population at risk and 90% of the study period (1973-2010) (Hsu et al. 2004; Van Meter et al. 2008). The incidence rate was adjusted using an automatically calculated log-linear trend because some areas of Utah have experienced growth. Spatial nonparametric adjustments were allowed to control for the large variation in census tract size (ranging from 0.12 to 6,107 square miles) and population density (ranging from 0 to 28,469 persons per square mile) (Kulldorff 2010). Only areas with higher-than-expected rates were considered during the scan. No geographic overlapping of clusters was allowed. Scans were run with other model parameters, with or without adjustment, with little difference in the findings. A more liberal p-value of less than or equal to 0.10 was used instead of the typical 0.05 threshold, to determine statistical significance. This decision was allowed because of the small case count ("the rarity") for the clusters (Dietz et al. 2011; Hsu et al. 2004; Wagner et al. 2013; Wheeler 2007). Cluster data was output as a data file that was joined to the attribution table of a geographic (shapefile)

data file of Utah census tracts for symbolization and visualization. Relative risk is one of the measures SaTScan generates to quantify the disease burden for a likely cluster. SaTScan only reports cluster areas that have a statistically elevated relative level. Ninety-five percent confidence limits (95% CI) are a standard way of determining statistical significance of the relative risk and are presented for convenience (Frumkin and Kantrowitz 1987).

FINDINGS

State-wide Descriptive Assessment: The number of brain cancer diagnoses has increased from 35 cases in 1973 to 161 cases in 2010. This increase is highly correlated ($R^2 = 0.97$) with Utah's statewide population growth. The Utah population has increased from approximately 1.18 million persons in 1973 to 2.76 million in 2010. The rate of brain cancer has increased from 4.19 cases per 100,000 person-years for the period 1973-1980 to 5.64 cases per 100,000 person-years for the period 2006-2010. See Figure 2 in the appendices for a graphic representation of the temporal trend of the rates of diagnoses of brain cancer.

The rate of cancer appears to have increased more dramatically from the period between 1973 and 1986 and then increasing more slowly over the last 24 years. However, the data is not sufficient to statistically determine the validity of this observation. This observation is in agreement with the NCI's State Cancer Profile for Utah for brain and other nervous system cancers. The NCI categorizes Utah's brain cancer incidence rate as stable and similar to the national rate (NCI 2013a).

Statewide, the distribution of brain cancers in sex and age groups is typical of what has been observed nationally. Of the 3,717 cases, 1,669 (44.9%) cases are female, and 2,048 (55.1%) are male. The unadjusted total study period (38-year) rate of cancer incidence among females is 4.62 cases per 100,000 female person-years. The rate among males is 5.70 cases per 100,000 male person-years. See Figure 3 for a graphic representation of the age distribution.

The age distribution of brain cancers in Utah is similar to the national pattern (Preston-Martin et al. 2006). Young children ages 0 to 4 years have an incidence rate of 3.55 cases per 100,000 child-years. The rate for each five-year age group steadily declines until the 20-24 year old age group, which has an incidence rate of 1.95 cases per 100,000 person-years. From the 25-29 year age group, the rate for each five-year age group steadily increases until the 65-69 year old age group, which has an incidence rate of 17.47 cases per 100,000 person-years. From that age group, the incidence declines.

Utah's population from 1973 to 2010 was spatially represented using 496 census tract geographic areas. Brain cancer cases were assigned to one of these geographies. The average number of cases per census tract is 7.5 cases (range = 0 to 25; standard deviation = 4.6) for the 38-year study period. The spatial distribution of cases was not well correlated ($R^2 = 0.71$) with the census tracts' cumulative population. The unadjusted 38-year study period incidence rate average is 5.09 cases (range = 0 to 16.84; median = 4.84; standard deviation = 2.54) per 100,000 person years. Thirteen census tracts had no cases of brain cancer diagnosed between 1973 and 2010. Six census tracts (five in Salt Lake County and one in Washington County) had study period incidence rates greater than 12.7 (the average plus three standard deviations). These six

census tracts were found among the clusters detected by the spatial-temporal scan of the state. Figure 4 presents the distribution of the census tract 38-year unadjusted cancer incidence rates.

SaTScan Results: SaTScan is a tool that scans through the data using all possible permutation of contiguous geography and time up to the maximum limits set by the user to identify likely spatiotemporal clusters. The tool quantifies the burden of these likely clusters with a relative risk measure and the significance of the clusters with a probability or p-value (Kulldorff and IMS. 2011).

Eight historical cancer clusters were identified by scanning the data. No current cancer clusters were found. The geographic location, temporal details, magnitude, relative risk and burden of the eight clusters are presented in Figure 5. Figures 6a through 6d present a closer view of the clusters with an underlying topographical map so that the clusters can be related to impacted communities. The clusters are an aggregation of census tracts represented to the SaTScan tool as a population-weighted centroid point. The SaTScan tool is not capable of considering the geography of the census tracts other than as a centroid point. The maps present the aggregated census tract area for each possible cluster. Census tracts are politically-derived boundaries designed to segregate populations based on political habits and not necessarily on health risk. In addition, all of the state's geography is represented in a census tract, thus some census tracts must, of necessity include uninhabited areas (e.g., mountain ranges, salt flats, etc.) These characteristics of census tracts should be considered when interpreting the SaTScan output. For example, Cluster 1 includes areas in both southwest Box Elder and Cache counties. The communities included in the cluster are geographically distinct from each other. However, SaTScan cannot incorporate the natural geographic barriers (e.g., mountain ranges).

Characteristics of each cluster are provided. The impacted population is presented in the person-years units. To understand this unit, a cluster in a community of 1,000 persons lasting 10 years would be generated 10,000 person-years (1,000 persons x 10 years = 10,000 person-years). Relative risk is a ratio of the risk (incidence rate) of cancer in the cluster area population over the state's risk. If the cluster area's level of risk equals the state's level of risk, the relative risk ratio will equal one. The value 1.0 is interpreted as no increased burden of disease. Values greater than one are interpreted as higher than expected burden of disease. Conversely, values lower than one are interpreted as lower than expected. SaTScan only reports likely clusters when the relative risk ratio is statistically elevated, however, for convenience of interpretation, the 95% confidence intervals are included. Confidence interval ranges that almost include 1.0 inside the range (for example, an interval range of 1.1 – 3.9) are less meaningful than those that do not (for example, an interval range of 1.9 – 2.4). All eight possible cluster areas had meaningfully increased relative risk values.

SaTScan generates an estimate of the likelihood of the cluster being a real spatiotemporal cluster and not just an artifact of the variability in the data. The likelihood is presented as a measure (probability) of randomness (or p-value). High p-values indicate a high degree of probability that the pattern is a result of the random variability in the data and not a real cluster. Low p-values indicate a higher likelihood of a real cluster. For this investigation a p-value less than or equal to 0.10 was used to identify the significance of clustering (Dietz et al. 2011; Hsu et al. 2004; Wagner et al. 2013; Wheeler 2007). None of the eight clusters were found to be real

spatiotemporal clusters. Because of these findings, it is impossible to conclusively state that the populations represented within the cluster boundaries are experiencing more cancer than would be expected. The elevated ratios could be random variation around a static expected value. Because of the rarity of brain cancers, SaTScan cannot completely characterize the cluster locations.

DISCUSSION

Cancer: Risk factors that contribute to the development of cancer include both inherent and external factors. Inherent factors include a variety of genetic susceptibilities. External factors include life choices and behaviors (e.g., tobacco use, alcohol use, poor diet, obesity, lack of physical activity, excessive sunlight exposure, and sexual behavior), medical conditions and medications, oncogenic pathogens, and chemical or radiological environmental exposures. Cancer may be the result of several factors interacting together with a triggering event (NCI 2012b).

Brain Cancer: Most cases of brain cancer are due to unknown etiology. While its cause is not known, it is generally accepted that brain cancer may be due to an alteration in the person's genetic structure which could be inherited or caused by environmental factors (Fang et al. 2004). Only about 5% of primary brain cancers are thought to be associated only with inherited factors or chromosomal deletions such as Li-Fraumeni, neurofibromatosis (types 1 and 2), tuberous sclerosis, nevoid basal cell carcinoma syndrome, familial polyposis, and von Hippel-Lindau disease (Bondy et al. 1994; Fang et al. 2004). High doses of ionizing radiation, including occupational exposures or the use of ionizing radiation for medical treatment, account for another 5% of the total cases. The remaining 90% are thought to be attributed to a combination of environmental factors, life-style factors or behavioral risks that either directly promotes cancer or induces other genetic or epigenetic causes of brain cancer (ABTA 2012; Blumenthal and Cannon-Albright 2008; de Vocht et al. 2013; Gu et al. 2009; Scheurer et al. 2010; Schwartzbaum et al. 2006).

The following table summarizes the known or investigated risk factors for brain cancer:

Risk Factor	Level of Association	References
Genetic conditions and chromosomal deletions • Li-Fraumeni syndrome • Von Hippel-Lindau disease • Turcot's syndrome • Neurofibromatosis type 1 • Neurofibromatosis type 2 • Tuberous sclerosis • Fanconi anemia • Nevoid basal cell carcinoma syndrome	Strongly conclusive	ABTA 2013; Biegel 1999; Blumenthal and Cannon-Albright 2008; Bondy et al 2008; El-Zein et al. 2002; Fang et al. 2004; Gu et al. 2009; James et al. 2002; Kyritsis et al. 2010; Malmer et al. 2003; Malmer et al. 2007; Offit et al 2003; Olivier et al. 2003; Preston-Martin et al. 2006; Scheurer et al. 2010; Schwartzbaum et al. 2006; Wrensch et al. 2002

Risk Factor	Level of Association	References
Diabetes in women	Inconclusive	Tong et al. 2012
Occupational exposures • Organic lead and other heavy metals • Synthetic rubber industries • Petroleum industries • Nitrates, nitrites, nitrosamines • Vinyl chloride and polyvinyl chloride • Electronic components and computer industries • Engine mechanics • Metal machinists • Radiation related industries	Inconclusive	ABTA 2013; Bondy et al. 2008; Brown et al. 2012; Clapp et al 2008; El-Zein et al. 2002; Keilhorn et al 2000; Preston-Martin et al. 2006; Savitz and Chen 1990; Wrensch et al. 2002
Pesticides (occupation and domestic)	Suggestive but weak evidence	Bassil et al. 2007; Brown et al. 2012; Clapp et al. 2008; Gomes et al. 2011; Preston-Martin et al. 2006; Roberts et al, 2012; Wrensch et al. 2002; Zahm and Ward 1998
Xenoestrogenes (chemicals that behave like hormones)	Suggestive but weak evidence	Fucic et al 2012; Wrensch et al. 2002
Hair dyes and cosmetics	Inconclusive	Clapp et al. 2008; Preston-Martin et al. 2006; Wrensch et al. 2002
Head and brain trauma	Inconclusive	ABTA 2012; Preston-Martin et al. 2006; Wrensch et al. 2002
History of epilepsy or epileptic seizures	Suggestive but weak evidence	ABTA 2012; Preston-Martin et al. 2006; Wrensch et al. 2002
Tobacco and/or alcohol use	Inconclusive	ABTA 2012; Preston-Martin et al. 2006; Wrensch et al. 2002
Maternal tobacco use before and during pregnancy	Inconclusive	ABTA 2012; Milne et al. 2013
Viral infections (e.g., simian virus 40, herpes viruses, cytomegalovirus, retroviruses, influenza) or infection by Toxoplasma gondii (a parasite)	Suggestive but weak evidence	ABTA 2012; Bondy et al. 2008; El-Zein et al. 2002; Preston-Martin et al. 2006; Schwartzbaum et al. 2006; Wrensch et al. 2002
Allergies	Protective	Bondy et al 2008; Preston-Martin et al. 2006; Schwartzbaum et al. 2006
Prior exposure (immunity) to varicella-zoster virus (causes chicken pox or shingles)	Protective	Bondy et al 2008; Schwartzbaum et al. 2006

Risk Factor	Level of Association	References
Strong ionizing radiation (i.e., x-ray, gamma-ray)	Strongly conclusive	ABTA 2012; Bondy et al. 2008; Chandana et al. 2008; El-Zein et al. 2002; Preston-Martin et al. 2006; Schwartzbaum et al. 2006; Wrensch et al. 2002
Low-frequency electromagnetic (non-ionizing) radiation	Inconclusive	ABTA 2012; Bondy et al. 2008; El-Zein et al. 2002; Preston-Martin et al. 2006; Wrensch et al. 2002
Radio and cell phone use	Inconclusive	ABTA 2012; Aydin et al. 2011; Bondy et al. 2008; Clapp et al. 2008; de Vocht et al. 2013; El-Zein et al. 2002; Gomes 2011; Hardell et al. 2008, Khurana et al 2009; Kundi 2009, Levis 2011, Little et al 2012; Preston-Martin et al. 2006; Repacholi et al. 2012; Wrensch et al. 2002
Diet including excessive consumption of N-nitroso-compound	Suggestive but weak evidence	ABTA 2012; El-Zein et al. 2002; Preston-Martin et al. 2006
A healthy diet	Protective	Kyritsis et al. 2011; Wrensch et al. 2002; Wrensch et al. 2002

Performance of the SaTScan application: SaTScan is widely used and well accepted as a tool for discovering spatiotemporal clusters of cancer (Aamodt et al. 2006; Almeida et al. 2011; Chen et al. 2008; Cromley and McLafferty 2012; Oliveira et al 2011; Robertson and Nelson 2010; Van Meter et al. 2008). The discrete Poisson model performs well over a wide range of disease burden levels and geographic or temporal scales and is the preferred model (Cromley and McLafferty 2012; Neill 2009). Because the tool is easy to use and the results are easy to interpret, SaTScan is particularly popular for use by state and local public health agencies with responsibility to do cancer surveillance and cluster assessment. However, the SaTScan tool and its application in this study are not without limitations.

- SaTScan uses simple circular or elliptical shaped geographic filters to identify study areas that might be clusters. These study areas consist of aggregations of small area geographies, which are in turn represented to the application by centroid points. SaTScan is unable to consider the true geography of the small areas or the aggregations of those small areas. Rather it only considers the location of the centroid points. Because of this limitation, SaTScan responds best when the small area geographies used to represent populations are somewhat uniform in size and simple in shape. SaTScan is most able to detect circular or elliptical shaped clusters and may not be able to detect highly irregular

(e.g., “S” or “U”) shaped clusters (Aamodt et al. 2006; Goujon-Bellec et al. 2011; Oliviera et al. 2011; Wheeler 2007). This study used the 496 census tract geographic units from the U.S. 2000 census to represent the distribution of the population. The area of these census tracts range from 0.1 square miles to 6,107 square miles in size (average = 171 square miles; standard deviation = 637 square miles).

- Because of the use of simple circular or elliptical filters to identify clusters, consideration of the potential shape of clusters in the study area is an important concern (Cromley and McLafferty 2012; Wheeler 2007). For this study, both circular and elliptical filters were used and the outcomes compared to each other. The results for each filter type corresponded well, meaning they each found the same cluster areas and included for the most part the same census tracts.

- Related to the above limitations is the tendency of SaTScan to merge several small strong irregular shaped clusters that do not fit well in a circular or elliptical filter into one larger less significant cluster that fits better into the circular or elliptical filter (Oliveira et al. 2011; Van Meter et al. 2008).

- Similarly, because the clusters are detected by capturing census tract population-weighted centroids inside a scanning filter, but, are visualized and thus interpreted, by the census tract boundaries, which are wall-to-wall and may include unpopulated areas, the visualization of the cluster does not exactly reflect the true location and shape of the cluster (Read et al. 2011).

- Another concern on using census tract geographies is one of sensitivity to scaling parameters and the “modifiable areal unit problem (MAUP).” SaTScan is sensitive to the boundary effects described by MAUP (Chen et al. 2008; Ozonoff et al. 2007). There are two kinds of issues. Both are examples of the zonation problem associated with MAUP. One is that ability to aggregate neighboring census tracts bounded in this study by the state boundary (Parenteau and Sawada 2011). Census tract boundaries that include the state boundary are limited to including only those neighboring census tracts that are in the direction toward the inside of the state or are also along the boundary. In Utah 28 (5.6%) of the 496 census tracts are on the state boundary, but these census tracts represent 54% of the total state land area. The other issue is described by the number of neighboring census (Parenteau and Sawada 2011). On average each census tract has six (range = 1 to 17, standard deviation = 2.2) neighbors. Five census tracts have only one neighbor.

- At the census tract level, the statistical sensitivity of the SaTScan (the ability to detect a cluster location) decays quickly when the relative risk is below 2.5 or when the expected case count is small. The expected case count can be small when either the population in the suspected cluster area is small or when attempting to find clusters of a rare type of disease. The population can be small because the suspected cluster area is small or the population density is low. However, the SaTScan tool has good specificity (ability to distinguish between true clusters and random variation) at all levels of risk (Aamodt et al. 2006; Cromley and McLafferty 2012; Goujon-Bellec et al. 2011; Jackson et al. 2009).

- When performing spatial-temporal statistical analysis to detect disease clusters, how the local geographies are conceptualized is one of the weakest theoretical aspects of these kinds of studies. For this investigation, the 2000 U.S. census tract geographies were used. The EEP has not yet obtained the required data to make good estimates of the intercensal population sizes for the 2010 census. The EEP was not able to determine which census block groups the cancer cases belonged in for a high enough percentage of cases to consider using the census block group geographies. Census tracts are designed with the intent of election consistency and without consideration of health concerns, health status or health risks. Many census tracts include large areas within the tract that are not residential (either commercial/industrial or uninhabited) (Parenteau and Sawada 2011). The spatial scan statistic factors in uneven geographical population densities and conditions as part of the analysis for hot spots (Hsu et al. 2004). Although only a small number (2%) of the cancer cases could not be accurately geocoded, those cases may result in a geographic selection bias (Dietz et al. 2011).

- With respect to the population estimates used by the EEP, the case count reflects more accurately the true population growth trends in a region than a straight line interpolation between the decennial census tabulations. The true population growth trend is not linear. As a result, there will be periods of time where the true population sizes are significantly different from the estimated population sizes. This may be occurring in the western Salt Lake/Utah county area.

Methodology Limitations: The public often wants public health investigations to determine if cancer risk can be linked to a putative environmental concern. The methods (the indirect standardized incidence ratio and the spatiotemporal scanning for clusters) used in this investigation do not have the capability to definitively link the findings of elevated cancer risk to any inherent or external risk factors including environmental exposures. These kinds of cancer statistical reviews are based on annual incidence data reported to the UCR. The incidence of cancer per year is dependent on diagnosis of clinically-manifested cancer. There are a number of limitations that impede this linkage. There is seldom any knowledge about the frequency, duration, or intensity of cancer victims to putative environmental concern. Cancer can have a variable length latency period between the time of exposure to the actual manifestation and diagnosis of cancer. Cancer can be present for some time before an individual seeks medical assistance that leads to diagnosis. There is seldom sufficient information available to statistically control for the many non-environmental factors that contribute to cancer risk, or exposure to other potential environmental risks that are not the putative environmental concern. For small populations, the incidence of cancer has a tendency to manifest arbitrary clusters. This tendency is a common phenomenon encountered when investigating the rate of rare diseases in a small population. Often, a few types of cancer may be statistically elevated for disparate periods, but that conclusion may change if the analytical periods are changed. Overcoming these limitations usually requires a comprehensive assessment of individual risk supported by a clear and consistent trend of elevated rates for a population.

This investigation used data from the UCR and U.S. Census. In Utah, the diagnosis of cancer for all site categories is reportable to the UCR. When a Utah resident seeks diagnosis, a report is generated. The UCR follows-up on the report to confirm information and collect additional

factors about the case. This process occurs when cases are diagnosed in Utah, but may not occur if a case is diagnosed outside of Utah. The UCR may contain records of incidence of cancer in people who recently moved to the study area prior to their diagnosis. The UCR may lack records on individuals who lived most of their life in the study area but moved elsewhere before seeking diagnosis and treatment. These situations create ascertainment biases. For the purposes of diagnosis, the EEP assumes that the ascertainment bias is non-systematic, meaning that the "move-in" and "move-out" situations balance each other. It is highly unlikely that this assumption is true in all cases and can be a significant limitation when the study population is small.

The EEP uses U.S. census data purchased from a commercial vendor of the data. The vendor has re-tabulated 1980, 1990, and 2010 data for the 2000 census block groups in Utah. Re-tabulation involves population-distribution weighting based on census blocks that may not be consistent through time. The EEP estimates intercensal population counts using linear regression between the known census tabulations. This methodology does not account for short-term population growth dynamics such as the zoning and development of a new subdivision, which can occur in just a few years.

A limitation of these kinds of investigations is that inferences leading to public health meaning are based on the snapshots of reality generated by data analysis (Meliker and Sloan 2011). An investigation that uses population-based summary data rather than individual-level data is called an ecologic study by epidemiologists. This investigation is an ecologic study. An interpretation error commonly associated with ecologic investigations is to apply population-level risk findings to the individual. This kind of interpretation error is called an "ecologic fallacy." For example, this study found the risk of lung cancer to be 2.72 times higher for the study population. This risk metric should not be applied to individuals. An individual may have no risk or a risk several times higher than the population risk based on the individual's genetic makeup, behaviors, exposure history, and susceptibility or resiliency to cancer (Greenland 2001; Greenland and Robins 1994; Izquierdo and Schoenbach 2000; Morgenstern 1982, 1995; Rockhill 2005).

CONCLUSIONS AND RECOMMENDATIONS

The findings of this study are the spatiotemporal locations of eight possible clusters of primary invasive brain cancer. No current cancer clusters were found to exist. However, the EEP does not have access to cancer data up to the present time. The eight cancer clusters could not be definitively distinguished as true clusters. Rather, they could be patterns of random excess that appear as clusters. This investigation does not include benign brain tumor cases. A comprehensive literature review of known risk factors for brain cancer revealed that brain cancer in Utah is rising, but did not reveal any significant environmental risk other than exposure to strong ionizing radiation to the head level. Other risks have been studied and the available evidence was found to be generally inconclusive.

People who are afflicted with brain cancer are best served by their health care team. Concerned citizens who think they may have brain cancer should be referred to their health care provider.

This report can be used to help formulate a response to concerned citizens who perceive increased brain cancer rates in their communities.

AUTHORSHIP, REVIEW AND CITATION

This report was prepared by:

Sam LeFevre
Environmental Epidemiology Program
Bureau of Epidemiology
Utah Department of Health

Mail: PO Box 142104, Salt Lake City, Utah 84114-2104
Street: 288 North 1460 West, Salt Lake City, Utah 84116
Phone: (801) 538-6191
Fax: (801) 538-6564
Email: slefevre@utah.gov

Certifying Reviewers:

Allyn K Nakashima, MD
State Epidemiologist
Utah Department of Health

Jennifer Brown, JD
Director, Bureau of Epidemiology
Utah Department of Health

Recommended Citation:

Environmental Epidemiology Program. *Utah Statewide Investigation of Brain Cancer for Spatiotemporal Clustering Patterns Between 1973 to 2010*. October 15, 2013. Salt Lake City, UT: Utah Department of Health.

CERTIFICATION

This report titled "Utah Statewide Investigation of Brain Cancer for Spatiotemporal Clustering Patterns Between 1973 to 2010" was prepared by the Environmental Epidemiology Program, Utah Department of Health. This report covers an investigation of cancer incidence using standard and approved methodology and procedures existing at the time the investigation herein reported was begun. Editorial and technical review was completed by UDOH certifying reviewers and program partners.

Approved by:

Allyn K Nakashima, MD
State Epidemiologist
Utah Department of Health

Jennifer Brown, JD
Director, Bureau of Epidemiology
Utah Department of Health

Wu Xu, PhD
Director, Center for Health Data
Utah Department of Health

REFERENCES

Web links for citations of government or organizational websites may wrap onto multiple lines.

Aamodt G, Samuelsen SO, Skrondal A. 2006. A simulation study of three methods for detecting disease clusters. *International Journal of Health Geographics* 5:15.

ABTA (American Brain Tumor Association. 2012. About brain tumors: a primer for patients and caregivers. Chicago, IL: www.abta.org.

ACS (American Cancer Society). 2009. Lifetime risk of developing or dying from cancer web site. Available: http://www.cancer.org/Cancer/CancerBasics/lifetime-probability-of-developing-or-dying-from-cancer [accessed November 26, 2012].

AGRC (Automated Geographic Reference Center). 2013. Utah's state geographic information database: 2000 demographic data files. Available http://gis.utah.gov [accessed January 3, 2013].

Almeida ACL, Duarte AR, Duczmal LH, Oliveira FLP, Takahashi RHC. 2011. Data-driven inference for the spatial scan statistic. *International Journal of Health Geographics* 10:47.

Aydin D, Feychting M, Schuz J, Tynes T, Andersen TV, Schmidt LS, Poulsen AH, Johansen C, Prochazka M, Lannering B, Klaeboe L, Eggen T, Jenni D, Grotzer M, Von der Weid N, Kuehni CE, Roosli M. 2011. Mobile phone use and brain tumors in children and adolescents: a multicenter case-control study. *Journal of the National Cancer Institute* 103:1265-1276.

Bassil KL, Vakil C, Sanborn M, Cole DC, Kaur JS, Kerr KJ. 2007. Cancer health effects of pesticides. *Canadian Family Physician* 53:1704-1711.

Baumann N, Pham-Dinh D, 2001. Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiological Reviews* 81:871-927.

Bell BS, Hoskins RE, Pickle LW, Wartenberg D. 2006. Current practices in spatial analysis of cancer data: mapping health statistics to inform policymakers and the public. *International Journal of Health Geographics* 5:49.

Berger MS, Leibel SA, Bruner JM, Finaly JL, Levin VA. 2002. Primary cerebral tumors. In: Cancer in the nervous system, 2nd ed. (Levin VA ed.). New York, NY: Oxford University Press.

Biegel JA. 1999. Cytogenetics and molecular genetics of childhood brain tumors. *Neuro-Oncology* 1:139-151.

Blumenthal DT, Cannon-Albright LA. 2008. Familiality in brain tumors. *Neurology* 71:1015-1020.

Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, Kruchko C, McCarthy BJ, Rajaraman P, Schwartzbaum JA, Sadetzki S, Schlehofer B, Tihan T, Wiemels JL, Wrensch M, Buffler PA. 2008. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium (BTEC). *Cancer* 113:S1953-S1968.

Bondy M, Wiencke J, Wrensch M, Kyritsis AP. 1994. Genetics of primary brain tumors: a review. *Journal of Neuro-Oncolology* 18:69–81.

Bradl M, Lassmann H. 2010. Oligodendrocytes: biology and pathology. *Acta Neuropathologica* 119(1):37-53.

Brown T, Young C, Ruston L, British Occupational Cancer Burden Study Group. 2012. Occupation cancer in Britain, remaining cancer sites: brain, bone, soft tissue sarcoma and thyroid. *British Journal of Cancer* 107:S85-S91.

CDC (Centers for Disease Control and Prevention). 2012. Leading causes of death. Available: http://www.cdc.gov/nchs/fastats/lcod.htm [accessed November 26, 2012].

Chandana SR, Movva S, Arora M Singh T. 2008. Primary brain tumors in adults. *American Family Physician* 77:1423-1430.

Chedotal A, Richards LJ. Wiring the brain: the biology of neuronal guidance. *Cold Spring Harbor Perspectives in Biology* 2:a001917.

Chen J, Roth RE, Naito AT, Lengerich EJ MacEachren AM. 2008. Geovisual analytics to enhance spatial scan statistic interpretation: an analysis of U.S. cervical cancer mortality. *International Journal of Health Geographics* 7:57.

Clapp RW, Jacobs MM, Loechler EL. 2008. Environmental and occupational causes of cancer new evidence, 2005-2007. *Reviews in Environmental Health* 23:1-37.

Cromley EK, McLafferty SL. 2012. 5 Analyzing spatial clustering of health events. In: GIS and public health, 2nd ed. (Cromley EK, McLafferty SL, eds.). New York, NY: The Guilford Press.

Del Bigio MR. 2010. Ependymal cells: biology and pathology. *Acta Neuropathologica* 119:55-73.

DeVocht F, Hannam K, Buchan I. 2013. Environmental risk factors for cancers of the brain and nervous system. The use of ecological data to generate hypotheses. *Occupational and Environmental Medicine* 70:349-356.

Dicker RC. 2002. A brief review of the basic principles of epidemiology. In: Field Epidemiology, 2nd Ed. (Greg MB, ed.). New York, NY: Oxford University Press.

Dietz NA, Sherman R, MacKinnon J, Fleming L, Arheart KL, Wohler B, Lee DJ. 2011. Toward the identification of communities with increased tobacco-associated cancer burden: application of spatial modeling techniques. *Journal of Carcinogenesis* 10:22.

Edvardsson T. 2008. Consequences of brain tumours from the perspective of the patients and of their next of kin. *Studies from the Swedish Institute for Disability Research* 25:1-84.

El-Zein R, Minn AY, Wrensch M, Bondy ML. 2002. Epidemiology of brain tumors. In: Cancer in the nervous system, 2nd ed. (Levin VA ed.). New York, NY: Oxford University Press.

Fang Z, Kulldorff M, Gregorio DI. 2004. Brain cancer mortality in the United States, 1986 to 1995: A geographic analysis. *Journal of Neuro-Oncology* 6:179-187.

Forman A. 2002. Altered mental status. In: Cancer in the nervous system, 2nd ed. (Levin VA ed.). New York, NY: Oxford University Press.

Frackowiak RSJ, Ashburner JT, Penny WD, Zeki S, Friston KJ, Frith CD, Dolan RJ, Price CJ. 2004. Human brain function, 2nd ed. San Diego, CA: Academic Press.

Frumkin H, Kantrowitz W. 1987. Cancer clusters in the workplace: an approach to investigation. *Journal of Occupational Medicine* 29:949-952.

Fucic A, Gamulin M, Ferencic Z, Katic J, von Kraus MK, Bartonova A, Merlo DF. 2012. Environmental exposure to xenoestrogens and oestrogen related cancers: reproductive system, breast, lung, kidney, pancreas, and brain. *Environmental Health* 11:S8.

Geolytics, Inc. 2002a. Census CD 1970, Release 2.0 on digital optical disk (CD). Information: http://www.GeoLytics.com [accessed November 26, 2012].

Geolytics, Inc. 2002b. Census CD 1990 long form in 2000 boundaries, Release 1.0 on digital optical disk (CD). Information: http://www.GeoLytics.com [accessed November 26, 2012].

Geolytics, Inc. 2002c. Census CD 2000 short form blocks for region 4 AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA and WY, release 1.0 on digital optical disk (CD). Information: http://www.GeoLytics.com [accessed November 26, 2012].

Geolytics, Inc. 2012a. Census CD 1980 long form in 2000 boundaries, Release 1.0 on digital optical disk (CD). Information: http://www.GeoLytics.com [accessed November 26, 2012].

Geolytics, Inc. 2012b. Summary file 1 2010 in 2000 boundaries on digital optical disk (CD). Information: http://www.GeoLytics.com [accessed November 26, 2012].

Gomes J, Al Zayadi A, Guzman A. 2011. Occupational and environmental risk factors of adult primary brain cancers: a systemic review. *International Journal of Occupational and Environmental Medicine* 2:82-111.

Goodman M, Naiman JS, Goodman D, LaKind JS. 2012. Cancer clusters in the USA: what do the last twenty years of state and federal investigation tell us. *Critical Reviews in Toxicology* 42:474-490.

Goujon-Bellec S, Demoury C, Guyot-Goubin A, Hemon D, Clavel J. 2011. Detection of clusters of a rare disease over a large territory: performance of cluster detection methods. *International Journal of Health Geographics* 10:53.

Greenland S. 2001. Ecologic versus individual-level sources of bias in ecologic estimates of contextual health effects. *International Journal of Epidemiology* 30:1343-1350.

Greenland S, Robins J. 1994. Ecologic studies – biases, misconceptions, and counter examples. *American Journal of Epidemiology* 139(8):747-760.

Gu J, Liu Y, Kyritsis A, Bondy ML. 2009. Molecular epidemiology of primary brain tumors. *Neurotherapeutics* 6:427-435.

Hardell L, Carlberg M, Soderqvist F, Mild KH. 2008. Meta-analysis of long-term mobile phone use and the association with brain tumours. *International Journal of Oncology* 32:1097-1103.

Higginson J, Muir CS, Munoz N. 1992. 51. Brain and central nervous system. In: Human cancer: epidemiology and environmental causes. (Higginson J, Muir CS, Munoz N. eds.). London, UK: Cambridge University Press. Pp.435-441.

Hinrichsen VL, Klassen AC, Song C, Kulldorff M. 2009. Evaluation of the performance of tests for spatial randomness on prostate cancer data. *International Journal of Health Geographics* 8:41.

Howard BM, Mo Z, Filipovic R, Moore AR, Antic SD, Zecevic N. 2008. Radial glia cells in the developing human brain. *Neuroscientists*. 14:459-473.

Hsu CE, Jacobson H, Mas FS. 2004. Evaluating the disparity of female breast cancer mortality among racial groups - a spatiotemporal analysis. *International Journal of Health Geographics* 3:4.

Izquierdo JN, Schoenbach VJ. 2000. The potential and limitations of data from population-based state cancer registries. *American Journal of Public Health* 90:695-698.

James CD, Smith JS, Jenkins RB. 2002. Genetic and molecular basis of primary central nervous system tumors. In. Cancer in the nervous system, 2nd ed. (Levin VA, ed.) New York, NY: Oxford University Press.

Jekel JF, Elmore JG, Katz DL. 1996. Epidemiology, biostatistics and preventive medicine. Philadelphia, PA: WB Saunders Co.

Jackson MC, Huang L, Luo J, Jachey M, Feuer E. 2009. Comparison of tests for spatial heterogeneity on data with global clustering patterns and outliers. *International Journal of Health Geographics* 8:55.

Jones SG, Kulldorff M. 2012. Influence of spatial resolution on space-time disease cluster detection. *PLOS One* 7:e48036.
Keilhorn J, Melber C, Wahnschaffe U, Aitio A, Mangelsdorf I. 2000. Vinyl chloride: still a cause for concern. *Environmental Health Perspectives* 108:579-588.

Kettenmann H, Hanisch U-K, Noda M, Verkhratsky A. 2011. Physiology of microglia. *Physiological Reviews* 91:461-553.

Khurana VG, Teo C, Kundi M, Hardell L, Carlberg M. 2009. Cell phones and brain tumors: a review including the long-term epidemiologic data. *Surgical Neurology* 72:205-214.

Kingsley BS, Schmeichel KL, Rubin CH. 2007. An update on cancer cluster activities at the Centers for Disease Control and Prevention. *Environmental Health Perspectives* 115:167-171.

Kofler J, Wiley CA. 2011. Microglia: key innate immune cells of the brain. *Toxicologic Pathology* 39:103-114.

Kulldorff M. 1997. A spatial scan statistic. *Communications in Statistics: Theory and Methods*. 26:1481-1496.

Kulldorff M. 2010. SaTScan™ user guide for version 9.0 (also supplied with version 9.1). Information Management Services, Inc., Silver Spring, MD. For more information visit http://www.satscan.org.

Kulldorff M, Huang L, Pickle L, Duczmal L. 2006. An elliptical spatial scan statistics. *Statistics in Medicine* 25:3929-3943.

Kulldorff M, IMS (Information Management Services, Inc.). 2011. SaTScan™ software for spatial and space time scan statistics, for MS Windows, version 9.1.1. Information Management Services, Inc., Silver Spring, MD. For more information visit http://www.satscan.org.

Kulldorff M, Nagarwalla N. 1995. Spatial disease clusters: detection and inference. *Statistics in Medicine* 14:799-810.

Kundi M. 2009. The controversy about a possible relationship between mobile phone use and cancer. *Environmental Health Perspectives* 117:316.324.

Kyritis AP, Bondy ML, Levin VA. 2011. Modulation of glioma risk and progression by dietary nutrients and anti-inflammatory agents. *Nutrition and Cancer* 63:174-184.

Kyritsis AP, Bondy ML, Rao JS, Sioka C. 2010. Inherited predisposition to glioma. *Neuro-Oncology* 12:104-113.

Lawson AB, Kulldorff M. 1999. 7 A review of cluster detection methodology. In: Disease mapping and risk assessment for public health (Lawson A, Biggeri A, Bohning D, Lesaffre E, Viel J-F, Bertollini R, eds.). Chichester, West Sussex: John Wiley & Sons, Inc.

Levis AG, Minicuci N, Ricci P, Gennaro V, Garbisa S. 2011. Mobile phones and head tumors - the discrepancies in cause-effect relationships in the epidemiological studies - how do they arise? *Environmental Health* 10:59.

Little MP, Rajaraman P, Curtis RE, Devesa SS, Inskip DP, Check DP, Linet MS. 2012. Mobile phone use and glioma risk: comparison of epidemiological study results with incidence trends in the United States. *British Medical Journal* 344:1147.

Malmer B, Adatto P, Armstrong G, Barnholtz-Sloan J, Bernstein JL, Claus E, Davis F, Houlston R, Il'yasova D, Jenkins R, Johansen C, Lai R, Lau C, McCarthy B, Nielsen H, Olson SH, Sadetzki S, Shete S, Wiklund F, Wrensch M, Yang P, Bondy M. 2007. GLIOGENE - an international consortium to understand familial glioma. *Cancer Epidemiology, Biomarkers and Prevention* 16:1730-1734.

Malmer B, Henriksson R, Gronberg H. 2003. Familial brain tumors - genetics or environment? A nationwide cohort study of cancer risk in spouses and first-degree relatives of brain tumor patients. *International Journal of Cancer* 106:260-263.

Mann CJ. 2003. Observation research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal* 20:54-60.

Meliker JR, Sloan CD. 2011. Spatio-temporal epidemiology: principles and opportunities. *Spatial and Spatio-temporal Epidemiology* 2:1-9.

Meyers CA, Kayl AE. 2002. Neurocognitive function. In: Cancer in the nervous system, 2nd ed. (Levin VA ed.). New York, NY: Oxford University Press.

Milne E, Greenop KR, Scott RJ, Ashton LJ, Cohn RJ, de Klerk NH, Armstrong BK. 2013. Parental smoking and risk of childhood brain tumors. *International Journal of Cancer* 133:253-260.

Montgomery DL. 1994. Acrocytes: form, functions, and roles in disease. *Veterinary Pathology* 31(2):145-167.

Morgenstern H. 1982. Uses of ecologic analysis in epidemiologic research. *American Journal of Public Health* 72:1336-1344.

Morgenstern H. 1995. Ecologic studies in epidemiology: concepts, principles, and methods. *Annual Reviews of Public Health* 16:16-81.

Morrone M. 2011. From cancer to diarrhea: the moving target of public concern about environmental health risks. *Environmental Health Insights* 5:87-96.

NCI (National Cancer Institute). 2011a. SEER Cancer Statistics Review 1975-2008. Lifetime Risk (Percent) of Being Diagnosed with Cancer by Site and Race/Ethnicity: Males, 17 SEER Areas, 2006-2008 (Table 1.15) and Females, 17 SEER Areas, 2006-2008 (Table 1.16). Available: http://seer.cancer.gov/csr/1975_2008/results_merged/topic_lifetime_risk_diagnosis.pdf [accessed November 26, 2012].

NCI (National Cancer Institute). 2011b. SEER Cancer Statistics Review 1975-2008. Lifetime Risk (Percent) of Dying from Cancer by Site and Race/Ethnicity: Males, Total US, 2006-2008 (Table 1.18) and Females, Total US, 2006-2008 (Table 1.19). 2011b. Available: http://seer.cancer.gov/csr/1975_2008/results_merged/topic_lifetime_risk_death.pdf [accessed November 26, 2012].

NCI (National Cancer Institute). 2012a. Surveillance, Epidemiology and End Results (SEER) Program. Available: http://seer.cancer.gov [accessed November 26, 2012].

NCI (National Cancer Institute). 2012b. What you need to know about cancer. Available: http://www.cancer.gov/cancertopics/wyntk/cancer [accessed November 26, 2012].

NCI (National Cancer Institute). 2013a. Utah state cancer profile for brain & ONS cancers. Query for Area = “Utah” and Cancer = “Brain & ONS”. Available: http://statecancerprofiles.cancer.gov/cgi-bin/quickprofiles/profile.pl?49&076 [accessed June 11, 2013].

NCI (National Cancer Institute). 2013b. SEER Stat Fact Sheets: Brain and Other Nervous System Cancer. Available: http://seer.cancer.gov/statfacts/html/brain.html [accessed June 11, 2013].

Ndubaku U, de Bellard ME. 2008. Glial cells: old cells with new twists. *Acta Histochemica* 110(3):182-195.

Neill DB. 2009. An empirical comparison of spatial scan statistics for outbreak detection. *International Journal of Health Geographics* 8:20.

Neumann H, Kotter MR, Franklin RJM. 2009. *Brain* 132:288-295.

NINDS (National Institute of Neurological Disorders and Strokes). 2013. The life and death of a neuron. NIH Publication No. 11-3340d. Bethesda, MD: Office of Communications and Public Liasison, National Institute of Neurological Disorders and Stroke.

Nowakowski RS. 2006. Stable neuron numbers from cradle to grave. *PNAS*. 193(33):12219-12220.

Offit K, Levran O, Mullaney B, Mah K, Nafa K, Batish SD, Diotti R, Schneider H, Deffenbaugh A, Scholl T, Proud VK, Robson M, Norton L, Ellis N, Hanenberg H, Auerbach AD. 2003. Shared genetic susceptibility to breast cancer, brain tumors and Fanconi anemia. *Journal of the National Cancer Institute* 95:1548-1551.

Oliveira FLP, Duczmal LH, Cancado ALF, Tavares R. 2011. Nonparametric intensity bounds for the delineation of spatial clusters. *International Journal of Health Geographics* 10:1.

Olivier M, Goldgar DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P, Eeles RA. 2003. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, an TP53 genotype. *Cancer Research* 63:6643-6650.

Ozonoff A, Jeffery C, Manjourides J, Forseberg White L. Pagano M. 2007. Effect of spatial resolution on cluster detection: a simulation study. *International Journal of Health Geographics* 6:52.

Parenteau M-P, Sawada MC. 2011. The modifiable areal unit problem (MAUP) in the relationship between exposure to NO2 and respiratory health. *International Journal of Health Geographics* 10:58.

Preston-Martin S, Munir R, Chakrabarti I. 2006. 62. Nervous system. In: Cancer epidemiology and prevention, 3rd ed. (Schottenfeld D, Fraumeni JF Jr, eds). New York, NY: Oxford University Press. pp 1173-1195.

Raine CS. 1999. Chapter 1. Neurocellular anatomy. In: Basic neurochemistry: molecular, cellular and medical aspects, 6th Ed. (Siegle GJ, Agranoff BW, Albers RW, et al. eds.). Philadelphia, PA: Lippencott-Raven Press.

Read S, Bath P, Willett P, Maheswaran R. 2011. Measuring the spatial accuracy of the spatial scan statistic. *Spatial and Spatio-temporal Epidemiology* 2:69-78.

Repacholi MH, Lerchl A, Röösli M, Sienkiewicz Z, Auvinen A, Breckenkamp J, d'Inzeo G, Elliott P, Frei P, Heinrich S, Lagroye I, Lahkola A, McCormick DL, Thomas S, Vecchia P. 2012. Systematic review of wireless phone use and brain cancer and other head tumors. *Bioelectromagnetics* 33:187-206.

Roberts JR, Karr CJ, Council on Environmental Health. 2012. Pesticide exposure in children. *Pediatrics* 130:1765-1788.

Robertson C, Nelson TA. 2010. Review of software for space-time disease surveillance. *International Journal of Health Geographics* 9:16.

Rockhill B. 2005. Theorizing about causes at the individual level while estimating effects at the population level: implications for prevention. *Epidemiology* 16:124-129.

SAS. 2002. SAS® statistical analytical software for MS Windows desktop version 9.2. SAS Institute, Inc., Cary, NC.

Savitz DA, Chen J. 1990. Parental occupation and childhood cancer: review of epidemiologic studies. *Environmental Health Perspectives* 88:325-337.

Scheurer ME, Etzel CJ, Barnholtz-Sloan J, Wiklund F, Tavelin B, Wrensch MR, Melin BS, Bondy ML. 2010. Familial aggregation of glioma: a pooled analysis. *American Journal of Epidemiology* 172:1099-1107.

Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. 2006. Epidemiology and molecular pathology of glioma. *Neurology* 2:494-503.

Seth P, Koul N. 2008. Astrocyte, the star avatar: redefined. *Journal of Bioscience* 33(3):405-421.

Sild M, Ruthazer ES. 2011. Radial glia: progenitor, pathway, and partner. *Neuroscientist* 17(3):288-302.

Stanbury M, Anderson H, Blackmore C, Fagliano J, Heumann M, Kass D, McGeehin M. 2012. Functions of environmental epidemiology and surveillance in state health departments. *Journal of Public Health Management and Practice* 18:453-460.

Stiles J, Jernigan TL. 2010. The basics of brain development. *Neurophychology Review* 20:327-348.

Sofroniew MV, Vinters HV. 2010. Astrocytes: biology and pathology. *Acta Neuropathologica* 119:7-35.

Tango T. 1999. 8 Comparison of general tests for spatial clustering. In: Disease mapping and risk assessment for public health (Lawson A, Biggeri A, Bohning D, Lesaffre E, Viel J-F, Bertollini R, eds.). Chichester, West Sussex: John Wiley & Sons, Inc.

Thacker SB. 2000. Historical development. In: Principles and practice of public health surveillance, 2nd Ed. (Teutsch SM, Churchill RE, eds.). New York, NY: Oxford University Press.

Thacker SB, Qualters JR, Lee LM. 2012. Public health surveillance in the United States: evolution and challenges. *Morbidity and Mortality Weekly Report – Surveillance Supplement* 61:3-9

Tong JJ, Tao H, Hui OT, Jian C. 2012. Diabetes mellitus and risk of brain tumors: a meta-analysis. *Experimental and Therapeutic Medicine* 4:877-882.

USCB (U.S. Census Bureau). 2004. Appendix A. Geographic terms and concepts in summary file 3: 2000 census population and housing, technical documentation. SF3/14 RV. Available: http://www.census.gov/prod/cen2000/doc/sf3.pdf [accessed November 26, 2012].

USCB (U.S. Census Bureau). 2012a. Method for intercensal population estimates: 2000 to 2010. Available: http://www.census.gov/popest/methodology/2000-2010_Intercensal_Estimates_Methodology.pdf [accessed November 26, 2012].

UCR (Utah Cancer Registry). 2013. 2013 cancer dataset for the Utah Environmental Public Health Tracking Network: containing public use data records for primary in-situ Utah resident cancers from 1973 to 2010. Electronic data transfer. Information: http://ucr.utah.edu [accessed November 26, 2012].

UEPHTN (Utah Environmental Public Health Tracking Network). 2012. Utah environmental public health tracking network. Information: http://health.utah.gov/enviroepi [accessed November 26, 2012].

Valentine AD, Passic SD, Massie MJ. 2002. Psychiatric and psychosocial issues. In: Cancer in the nervous system, 2nd ed. (Levin VA ed.). New York, NY: Oxford University Press.

Van Meter KC, Christiansen LE, Hertz-Picciotto I, Azari R, Carpenter TE. 2008. A procedure to characterize geographic distributions of rare disorders in cohorts. *International Journal of Health Geographics* 7:26.

Vassilopoulou-Sellin R. 2002. Neuroendocrine function. In: Cancer in the nervous system, 2nd ed. (Levin VA ed.). New York, NY: Oxford University Press.

Wagner SE, Bauer SE, Bayakly AR, Vena JE. 2013. Prostate cancer incidence and tumor severity in Georgia: descriptive epidemiology, racial disparity, and geographic trends. *Cancer Causes and Control*. 24:153-166.

Wakefield JC, Kelsall JE, Morris SE. 2000. 8 Clustering, cluster detection, and spatial variation in risk. In: Spatial epidemiology: methods and application (Elliott P, Wakefield JC, Best N, Briggs D, eds.). New York, NY: Oxford University Press, Inc.

Wheeler DC. 2007. A comparison of spatial clustering and cluster detection techniques for childhood leukemia incidence in Ohio, 1996 – 2003. *International Journal of Health Geographics* 6:13.

WHO (World Health Organization). 2012. International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) website. Available: http://www.who.int/classifications/icd/adaptations/oncology/en/ [accessed November 26, 2012].

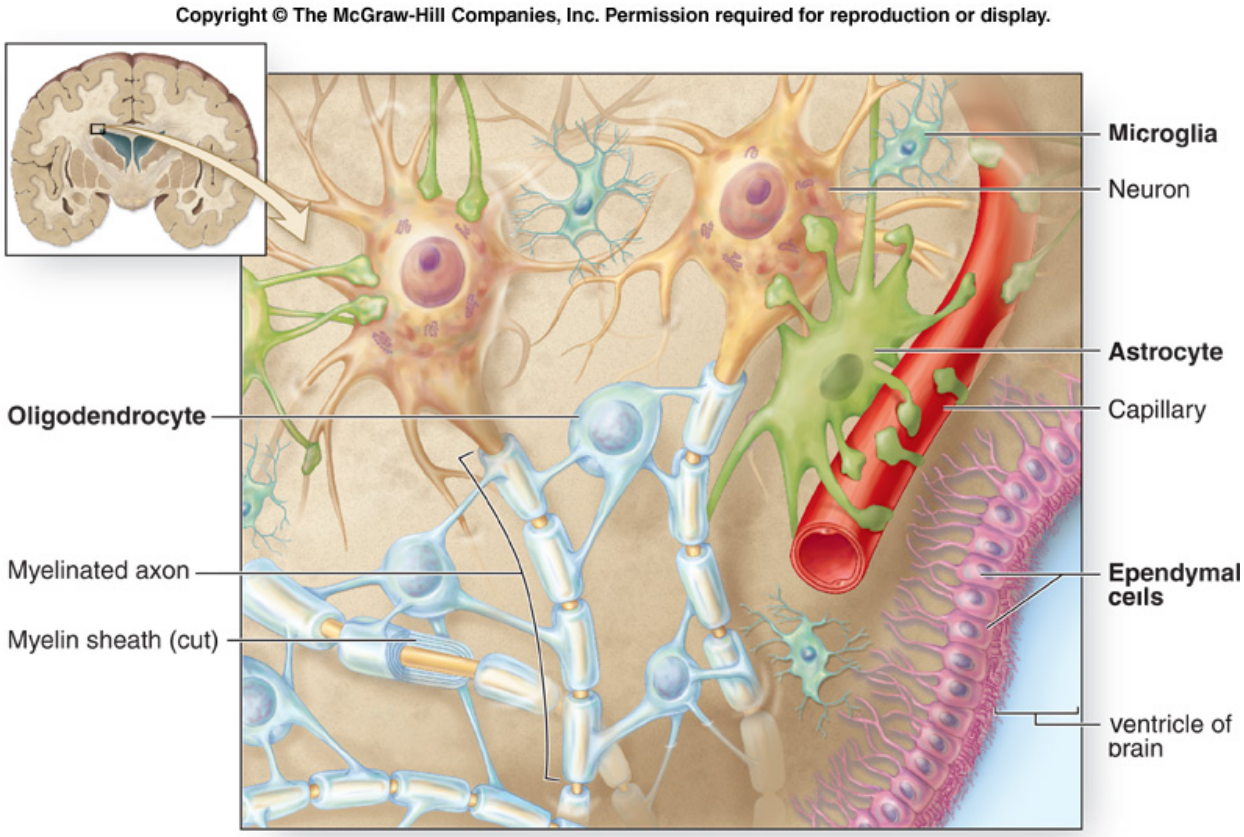
Wilkins KL, Woodgate RL. 2008. Preventing second cancers in cancer survivors. *Oncology Nursing Forum* 35:E12-E22.

Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. 2002. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neuro-Oncology* 4:278-288.

Zahm SH, Ward MH. 1998. Pesticides and childhood cancer. *Environmental Health Perspectives* 106:S893-S908.

FIGURES

Figure 1. Cellular organization of the human brain, showing the relationships and connectivity of neural and glial cells.



Graphic obtained online from http://www.flickr.com/photos/29693317@N00/4964163348/. Permission requested.

Figure 2. Periodic unadjusted (crude) incidence rate of neuroma and glioma brain cancers per 100,000 person-years diagnosed among Utah residences from 1973 through 2010. This figure shows the state-wide temporal trend for diagnosis of brain cancers.

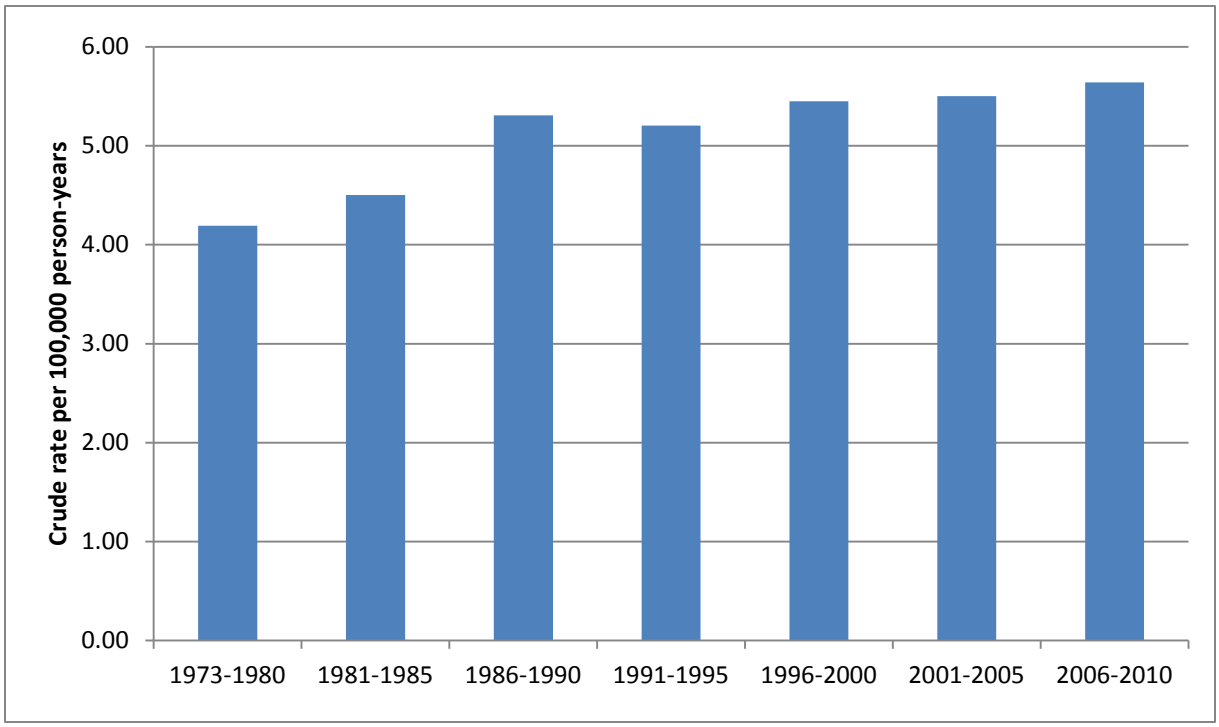


Figure 3. Age-specific incidence rates of neuromas and gliomas diagnosed among Utah residents from 1973 through 2010.

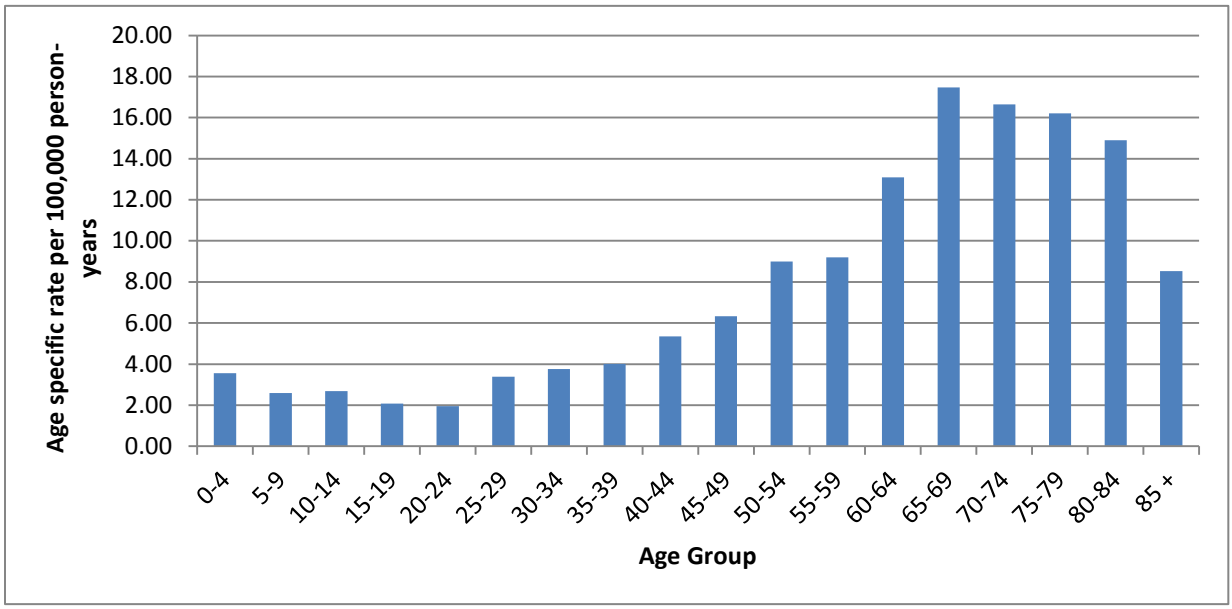


Figure 4. Distribution of the census tract 38-year unadjusted incidence rates per 100,000 person years for Utah from 1973-2010.

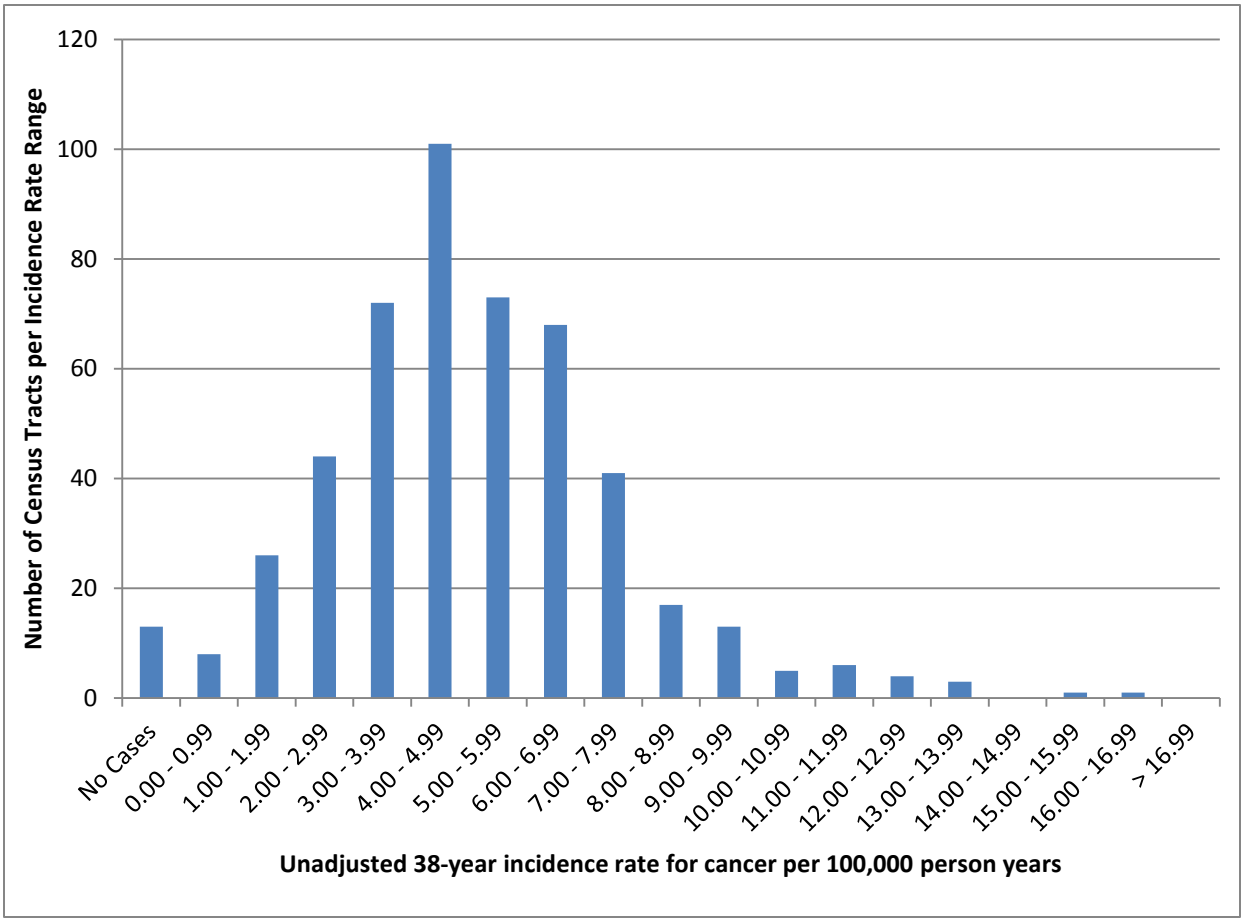
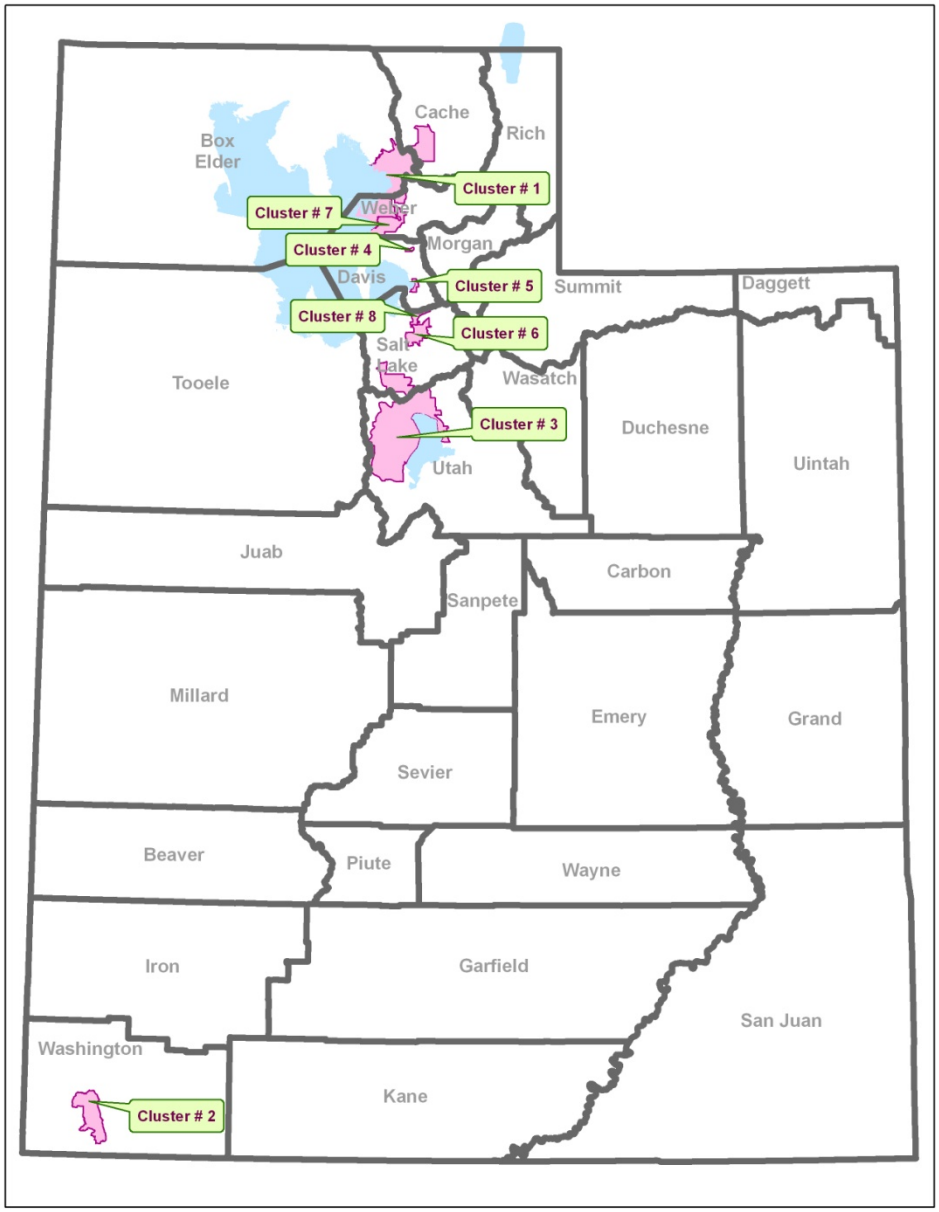


Figure 5. Map and table of Utah presenting the location and statistical details of eight possible (statistically non-significant) brain cancer clusters identified by SaTScan testing in Utah from 1973 to 2010.



Cluster	Time Period	Years	Cases	Population (person-years)	Relative Risk (95% CI)	p-Value
1	1994 – 2002	9	51	41,735	2.3 (1.7-3.0)	0.260
2	2003 – 2009	7	37	16,961	2.6 (1.8-3.5)	0.495
3	1999 – 2008	10	115	94,042	1.6 (1.3-2.0)	0.578
4	1988 – 1999	12	14	4,469	5.0 (2.7-8.4)	0.635
5	1985 – 1994	10	10	4,069	6.6 (3.2-12.2)	0.875
6	1990 – 1998	9	114	143,609	1.6 (1.3-1.9)	0.885
7	1977 – 1982	6	21	29,971	3.2 (2.0-4.9)	0.995
8	1987 – 1989	3	14	19.245	4.4 (2.4-7.3)	0.995

Figure 6a. Geographic details of possible cluster numbers 1, 4 and 7 in Cache, Weber and Davis counties in Utah.

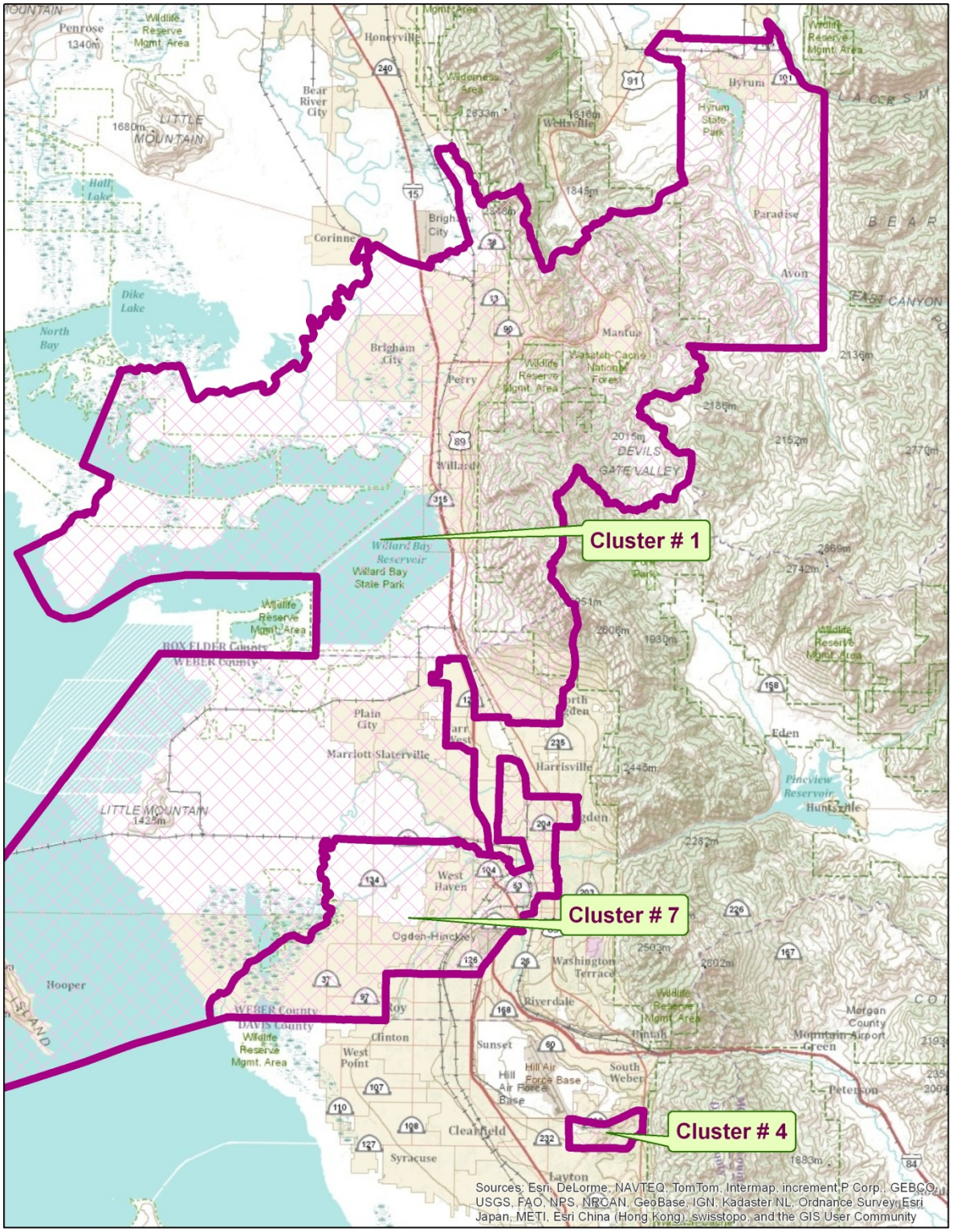


Figure 6b. Geographic details of possible cluster numbers 5, 6 and 8 in Davis and Salt Lake counties in Utah.

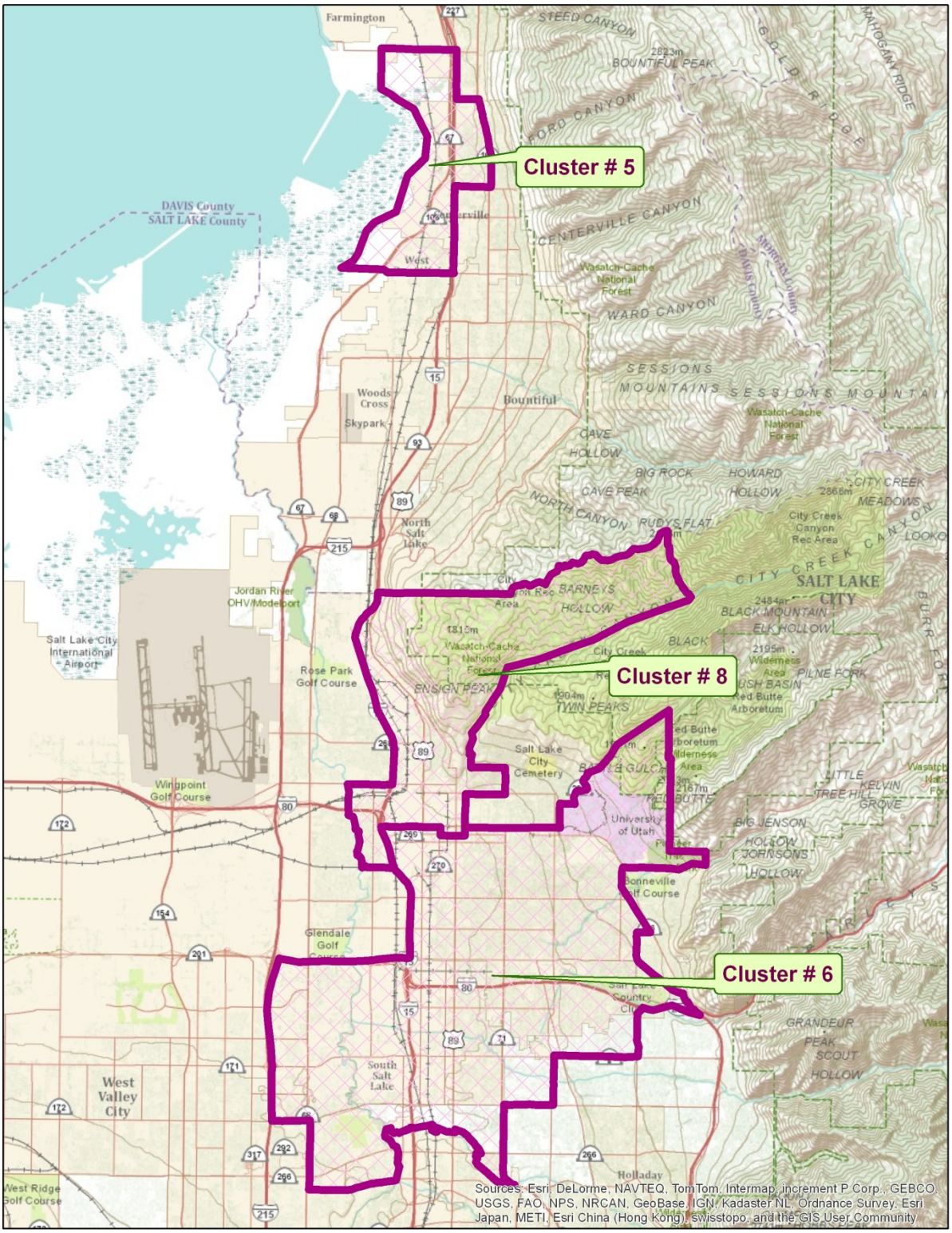


Figure 6c. Geographic details of possible cluster number 3 in Salt Lake and Utah counties in Utah.

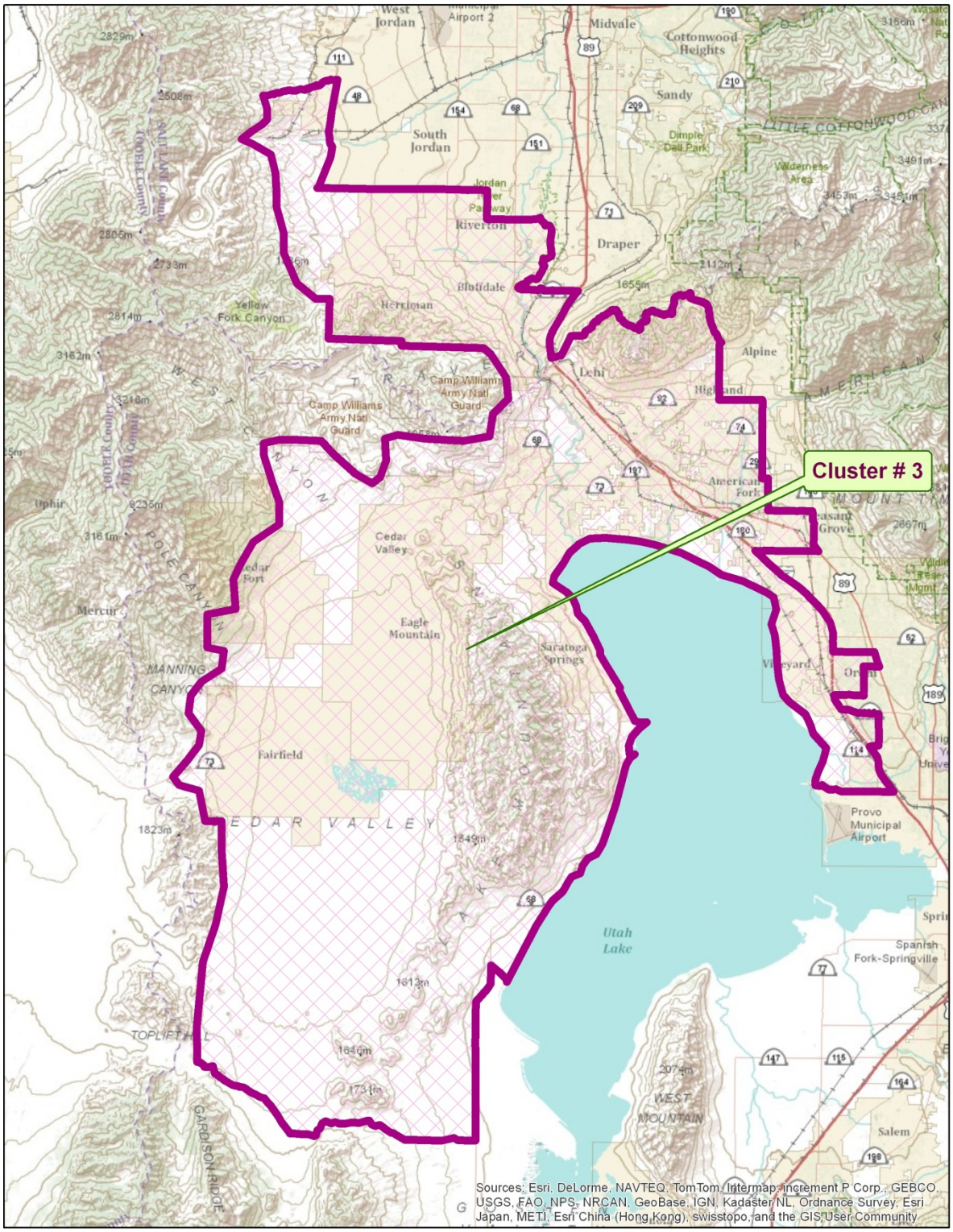
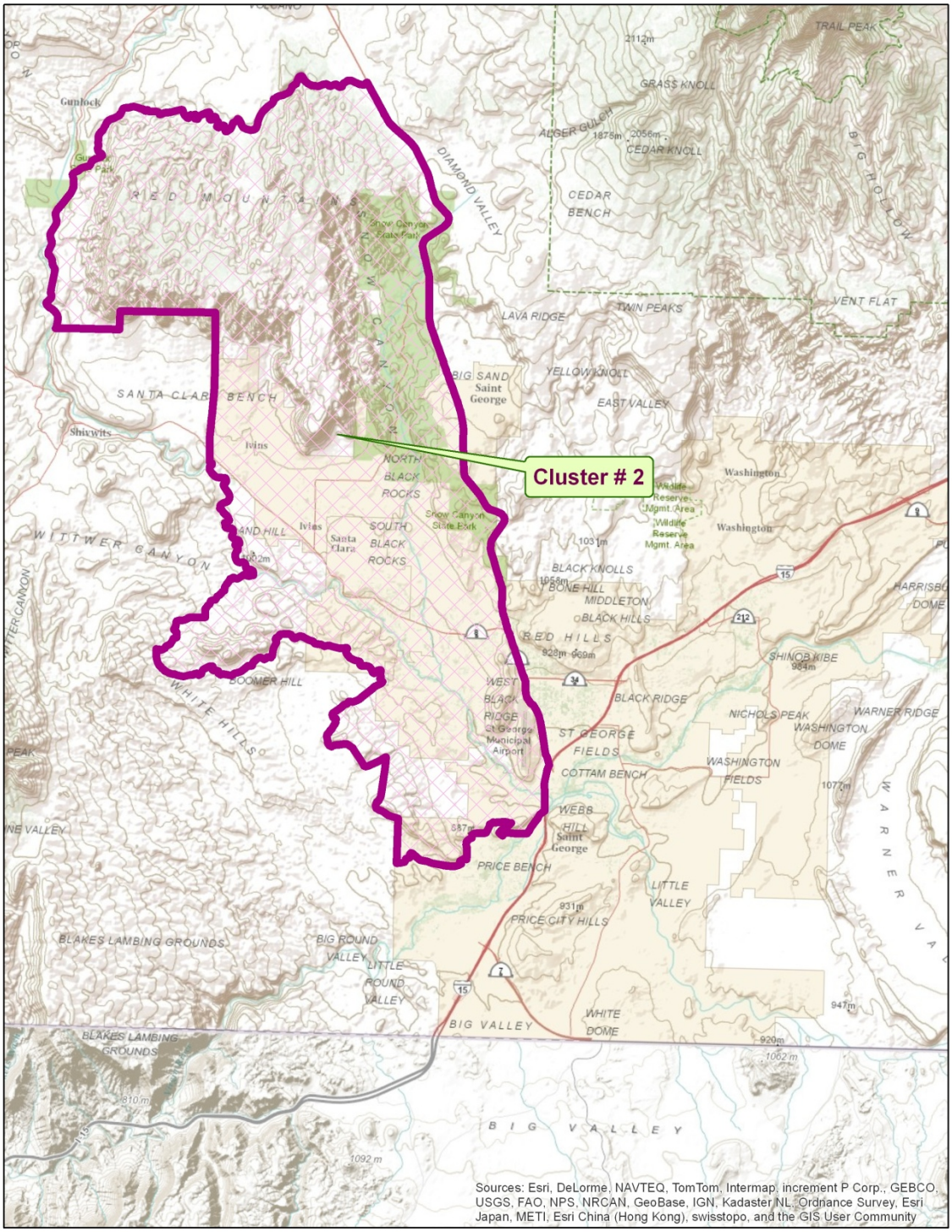


Figure 6d. Geographic details of possible cluster number 2 in Washington County in Utah.



DEFINITIONS

ACS — American Cancer Society. The ACS, first established in 1913, is a nationwide voluntary health organization dedicated to eliminating cancer. The society, headquartered in Atlanta, Georgia, has over 900 offices throughout the United States. ACS funding is used for patient support services, research, prevention, detection and treatment and society operations. For more information see: http://www.cancer.org.

AGRC — Automated Geographic Reference Center. An agency within the Utah Department of Information Technology, responsible for maintaining a repository of geographic information system (GIS) data files and GIS functionality. For more information see: http://gis.utah.gov/.

ArcGIS — A complete desktop GIS software application for producing maps and conducting spatial analysis. This application is developed and distributed by ESRI. EEP uses version 10.0. For more information see: http://www.esri.com/software/arcgis.

CDC — Centers for Disease Control and Prevention. The CDC is a federal agency under the U.S. Department of Health and Human Services responsible for protection and promoting public health at the national level. For more information see: http://www.cdc.gov/.

CI — Confidence Interval. Because there is some error in estimating a population parameter, and that error increases as the population size decreases, the confidence interval is used to indicate the reliability of the parameter estimate. The way a 95% confidence interval is interpreted along with the estimated parameter is that the measured value of the parameter is the reported value and one can be assured with 95% confidence (or 1 in 20 chances of being wrong) that the real parameter values is within the reported confidence interval.

CIS — Carcinoma in-situ is an early form of cancer that is defined by the absence of invasion of tumor cells into the surrounding tissue. Instead, the lesion is flat or follows the existing architecture of the organ. In this state CIS, seldom cause clinical systems sufficient to prompt the person with CIS to seek medical assistance and are generally undetected. CIS can progress to invasive tumors and are therefore considered a precursor or incipient form of cancer.

CNS — Central Nervous System includes the brain and the spinal cord. The rest of the nervous system (the ganglia outside of the spinal cord and the nerve fibers found through the body) are called the peripheral nervous system.

EEP — Environmental Epidemiology Program. A program within the Bureau of Epidemiology, Division of Disease Control and Prevention, UDOH. The EEP was established in 1996 and is responsible for investigating diseases related to the environment. The program has two sections. One section conducts surveillance

and data management activities including managing the UEPHTN. The other section conducts health hazards risk assessment, including cancer investigations. The program is staffed by personnel with experience and expertise in environmental epidemiology, environmental sciences, toxicology, statistics, public health informatics and geomatics, and health education. For more information see: http://health.utah.gov/enviroepi/.

ESRI — ESRI is a leading developer and supplier of GIS software and geographically referenced data. ESRI is headquartered in Redlands, California. The EEP uses the ArcGIS software application developed by ESRI. For more information see: http://www.esri.com.

GeoLytics — GeoLytics is a commercial vendor of census and demographic data calibrated to the 2000 census boundaries. The EEP purchased 1970, 1980, 1990, 2000 and 2010 census data from GeoLytics to be the basis for estimating intercensal population counts for each of the 1,481 census block group boundaries in Utah. Population counts are aggregated into 5-year age groups for each sex. For more information see: http://www.geolytics.com.

GIS — Geographic Information Systems. A GIS includes computer software and geographically referenced data. The EEP uses ArcGIS as the computer software, and obtains data from ESRI or AGRC.

ICD-O-3 — International Classification of Disease - Oncology, 3rd Edition. The ICD-O-3 is one of a number of internationally established coding standards for coding site (topography) and histology (morphology) of neoplasms (cancers). For more information see: http://www.who.int/classifications/icd/adaptations/oncology/en/.

MAUP — Modifiable Areal Unit Problem is a source of statistical bias that can affect the results of statistical hypothesis testing. There are two concerns associated with MAUP. One is a scale problem associated with the number and size of arbitrary geographic units. The other is the zonation effect which is associated with the , arrangement and the establishment of boundaries of the geographic units.

NAACCR — North American Association of Central Cancer Registries. NAACCR was established in 1987 as a collaborative professional organization for cancer registries, governmental agencies and professional associations that work with cancer registries. All central cancer registries in the United States and Canada are members. The purpose of NAACCR is to promote standards and enhance the quality of cancer registry data. The NAACCR also promotes training, epidemiologic research, public health activities and patient care improvement policies related to cancer. For more information see: http://www.naaccr.org.

NCI — National Cancer Institute. The NCI is one of the National Institutes of Health and part of the U.S. Department of Health and Human Services. The NCI was established under the National Cancer Act of 1937 and is primarily responsible

for conducting surveillance and research about cancer incidence, diagnosis, prevention, treatment, and rehabilitation. The SEER program is operated by the NCI. For more information see: http://www.cancer.gov/.

ONS — Other nervous system. All of the peripheral nervous system nerve fibers, ganglia, and the spinal cord (which is part of the central nervous system, but not part of the brain). The classification of cancers of the nervous system separates brain cancers from the other nervous system cancers.

p-Value — Probability value. A measure of probability of randomness. The range of the p-Value is between 0 and 1. This measure associated with a parameter is interpreted as the probability that the particular parameter's value could occur randomly. Thus a significant parameter value is one that has little random probability or a small p-Value. Typically a p-Value less than 0.05 is considered significant.

R^2 — Correlation Coefficient. The R^2 is a measure of the degree of agreement between two or more parameters. The R^2 value range is between negative one (-1) and positive one (+1). An R^2 value close to zero (0) means that considered parameters are uncorrelated. Their relationships are completely random. R^2 values close to negative one (-1) are inversely correlated meaning that as one parameter increases the other parameters decrease. R^2 values close to positive one (+1) are correlated meaning that the parameters increase or decrease together. The R2 is significant when it is large (close to either negative or positive one).

RR — Relative Risk. The RR is a statistical measure used by epidemiology to quantify the risk of an event such as developing a disease is related to the presence of a causal factor (e.g., exposure or spatial-temporal location). Relative is a ratio of the risk (or probability of the event occurring) among a target population compared to a comparison population. If the risks of the two populations are equal then RR will equal 1.0. If the risk in the target population is greater then the comparison population than RR will be greater than 1.0 and the degree of increase is reflective of the magnitude of the increased risk in the target population. Thus an RR of 2.0 indicates that the target population has twice the risk compared to the comparison population. An RR less than 1.0 indicates that the target population has less risk than the comparison population. The ability of a risk estimate to quantify the true risk increases as the population increases. Thus it is common practice to report the estimated relative risk along with a 95% confidence interval.

SAS — SAS® (originally from "Statistical Analysis System") is a globally-recognized system of integrated computer software products provided by SAS Institute Inc. The SAS system includes a large variety of data manipulation and statistical analysis processes. The EEP uses the desktop version 9.2. For more information see: http://www.sas.com.

SaTScan — SaTScan™ (from "Space and Time Scan") is an internationally recognized computer application that applies various space, time, or space-time scanning

	techniques to data that contains geographic and temporal locating variables. This tool is designed to aggregate data, test for disease and determine the likelihood of a cluster. For more information see: http://www.satscan.org/.
SEER	Surveillance, Epidemiology and End Results Program. The SEER program is an agency within the NCI. The SEER program works with state cancer registries to develop and disseminate incidence and mortality statistics about cancer in the United States. The SEER program also establishes standards for the analysis of cancer data and interpretation of cancer statistics. For more information see: http://seer.cancer.gov/.
SGID	Utah State Geographic Information Database. The SGID is a state central data warehouse of digital mapping information established by Utah Code 63F-1-507. The SGID contains a variety of state and state agency data used for epidemiologic investigations. For more information see: http://gis.utah.gov/data/.
STFID	Standard Federal Identifier. The STFID is a unique code for each census unit that can be used as a primary link key for tabular linking of GIS-enabled data. The code consists of a chained sequence of state (2 numerals), county (3 numerals), census tract (6 numerals), census block group (1 numeral) and census block (4 numerals) identifiers. The state and county identifiers are the state and county federal information processing standards (FIPS) codes. The state of Utah is 49, thus for all Utah STFID, the first two numerals are 49.
UCR	Utah Cancer Registry. The UCR is operated under authority from the UDOH by the University of Utah. The UCR was established in 1966 to be a statewide population-based cancer registry. Utah administrative rule requires the reporting of cancer diagnoses to the UCR. The UCR collaborates with the NCI, SEER and the North American Association of Central Cancer Registries to implement data standards for cancer data. The UCR provides cancer to the EEP through the UEPHTN. For more information, see: http://ucr.utah.edu/.
UDOH	Utah Department of Health. The UDOH is one of the executive agencies within Utah state government. The UDOH strives to improve health in Utah through promoting healthy lifestyles, evidence-based interventions, creating healthy and safe communities and eliminating health disparities. The EEP is a program within the UDOH. For more information, see: http://health.utah.gov/.
UEPHTN	Utah Environmental Public Health Tracking Network. The UEPHTN is a data warehouse that contains health outcomes, environmental and supporting data. Data from the UCR and population data derived from the USCB is warehoused in the UEPHTN. For more information see: http://epht.health.utah.gov.
USCB	U.S. Census Bureau. Officially the “Bureau of the Census,” the USCB is an agency authorized by Federal law, within the U.S. Department of Commerce that is charged with preparing and conducting regular surveys and censuses of the U.S.

population. In addition to the decennial population survey, the USCB conducts a number of other surveys and has recently implemented the ACS. For more information, see: http://www.census.gov/.

UTM — Universal Transverse Mercator. The UTM is a geographic coordinate system that uses a series of zones and the Cartesian x- and y-coordinates to represent the location of a point on the Earth. The value is of the UTM system is that the final component of the UTM x- and y-coordinates are given in meters as an offset from the zonal reference point. Thus it is easy to accurately measure the distance between two points within the same zone.