CANCER INCIDENCE STUDY

Utah Statewide Investigation of Thyroid Cancer for Spatio-temporal Clustering Patterns Between 1980 to 2012

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# TABLE OF CONTENTS

ACKNOWLEDGMENT
EXECUTIVE SUMMARY
INTRODUCTION
DATA AND METHODS
FINDINGS
DISCUSSION
CONCLUSIONS AND RECOMMENDATIONS
AUTHORSHIP, REVIEW AND CITATION
CERTIFICATION
REFERENCES
FIGURES AND TABLES
DEFINITIONS
RESOURCES
ACKNOWLEDGMENT

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EXECUTIVE SUMMARY

Cancer is a dominating environmental public health concern (CDC 2012). 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 thyroid cancer incidence in Utah.

This report presents a statistical review of the spatial and temporal distribution of invasive thyroid cancer in Utah from 1980 to 2012 using a spatio-temporal scan methodology. The purpose of this review was to identify regions of Utah with a historical or ongoing excess occurrence of thyroid cancers. Identified regions were characterized with respect to the cancer cluster. Two clusters of thyroid cancer were identified by the scanning tool. One cluster involving most of Cache Valley is recent, starting in 1994 and lasting through 2011. The second cluster was found in the northern part of Utah County starting in 2008 and continuing through the end of the study period. Details of these two clusters are presented along with a discussion of known risk factors for thyroid cancer.

The rate of thyroid cancer in Utah is rising and is similar to the current national rate. A comprehensive literature review of known risk factors for thyroid cancer did not reveal any significant environmental risk other than exposure to strong ionizing radiation. 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 thyroid cancer rates in their communities.
INTRODUCTION

The Thyroid: The thyroid is a small gland, approximately 30 grams in weight that sits low on the front of the neck just below the larynx. Figure 1 presents a graphical presentation of the location of the thyroid in the neck. The thyroid has two 5-6 centimeter long side lobes that wrap around the trachea and are bridged in the middle by a portion called the isthmus. Two small glands called parathyroid glands are imbedded in each lobe (for a total of four parathyroid glands). In many people, a residual third lobe called the pyramidal lobe extends upward from the isthmus along the front of the trachea. Thyroid tissue includes many capillary vessels, giving it a reddish brown color. Nerves for the voice box pass through the thyroid tissue (Bursuk 2012; Whitehead 2001).

Cellular Structure: Figure 2 presents the cellular anatomy of thyroid tissue. Thyroid tissue is composed of thyroid epithelial cells called follicular cells, arranged in many tiny spherical sacs called thyroid follicles. The follicles are filled with a protein material called colloid. Colloid is a precursor material used in the production of thyroid hormones. The thyroid follicular cells forming the follicle sacks produce the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Nested between layers of thyroid epithelial cells from adjoining follicles is a third type of cell called parafollicular or C cells. Parafollicular cells produce a hormone called calcitonin (Bursuk 2012; Davis 1972; Whitehead 2001). The gland also contains blood capillary cells, stromal cells, and is contained within a layer of connective epithelial cells (ACS 2014; NCI 2012a).

Thyroid Hormones: The follicular cells metabolize iodine and tyrosine (an amino acid) stored in the colloid material of the follicles to produce the T3 and T4 hormones. T3 is more active than T4 in its regulatory functions. Some T4 is further metabolized into T3 outside of the thyroid (e.g., in the liver or kidney) in order to regulate the activity level of these hormones (Bursuk 2012; Davis 1972; Silverthorn 2013a). T3 and T4 interact with many different tissue targets to affect lipid and carbohydrate metabolism, growth, development, cardiovascular performance, mental state, and reproductive health (Bowen 2010, Davis 1972; Silverthorn 2013b). The parafollicular cells (C cells) produce calcitonin, which, in conjunction with a hormone from the parathyroid glands, is used to regulate blood calcium and phosphate levels, calcium absorption and reabsorption, and helps mediate mental well-being, bone development and health, and other conditions involving calcium (Copp et al. 1962; Pondel 2000).

Thyroid Cancer: Thyroid cancer is relatively uncommon compared with other cancer types, but is the most common malignancy of the endocrine system (Brown et al. 2012; Higginson et al. 1992; Lebastchi & Callender 2014; Omur & Baran 2014; Ron & Schneider 2006). Four types of thyroid cancer account for most of the cases of thyroid cancer. Three are well-differentiated and include (ACS 2014; Brown et al. 2012; Gimm 2001; Higginson et al. 1992; Lebastchi & Callender 2014; Li et al. 2013; Monson 2002; NCI 2012a; O'Neill & Shaha 2013; Patel & Shaha 2006; Ron & Schneider 2006):

- Papillary carcinoma, which originates in the follicular cells and accounts for about 80% of the cases;
- Follicular carcinoma, which also originates in the follicular cells and accounts for about 10% of the cases;
- Medullary thyroid carcinoma, which arises from the parafollicular cells and accounts for about 2% of the cases.

There are variants of differentiated thyroid cancer, such as mixed papillary-follicular carcinoma and Hurthle cell carcinoma (a variant of follicular carcinoma).

- The fourth, anaplastic carcinoma, is poorly differentiated and the most aggressive. Anaplastic carcinoma accounts for about 1-2% of all thyroid cases (ACS 2014; Brown et al. 2012; Gimm 2001; Higginson et al. 1992; Lebastchi & Callender 2014; NCI 2012a; O’Neill & Shaha 2013; Patel & Shaha 2006; Ron & Schneider 2006).

In addition to these thyroid cell specific cancers, the thyroid may be the site of nonthyroid cell cancers such as lymphoma (arising from white blood cells) and sarcoma (arising from the supporting tissue) (ACS 2014).

The incidence of thyroid cancer has been increasing steadily since 1990 (Chen et al. 2009; Davis & Welch 2006; Lebastchi & Callender 2014; Leux & Guenel 2010; Sipos & Mazzaferri 2010). Between 1975 and 1990, the national incidence rate of cancer rose slightly from 4.8 cases to 5.5 cases per 100,000 people. By 2012, the rate had increased to 14.9 cases per 100,000 people (NCI 2015a). Part, but not all, of this observed increase is due to better diagnostic tools and increased detection of cancer early in its development (Davis & Welch 2006; Lebastchi & Callender 2014).

The annual thyroid cancer incidence rate (18.3 cases per 100,000 people) for Utah is higher than the incidence rate for the rest of the U.S. (Albright et al. 2012; NCI 2015b). In 2010, the Utah incidence rate was exceeded only by five states: Massachusetts, New Jersey, New York, Pennsylvania, and Rhode Island (NCI 2015b).

**Known Risk Factors for Thyroid Cancer:** In addition to the known risk factors discussed below, differences in screening and detection practices may contribute to variations in thyroid cancer incidence across geographies and over time.

*Sex:* Thyroid cancer is more common in women than men (Higginson et al. 1992; Lebastchi & Callender 2014; Nagataki & Nystrom 2002; Navarro Silvera et al. 2005; Peterson et al. 2012; Rahbari et al. 2010; Ron & Schneider 2006; Sipos & Mazzaferri 2010). Nationally, about 0.55% of men and 1.61% of women will experience thyroid cancer sometime during life. About 0.05 to 0.07% of people will die of thyroid cancer (ACS 2009; NCI 2011a, 2011b).

*Radiation:* Ionizing radiation > 10 milliSieverts (mSv) for an acute exposure or > 50 mSv for a protracted exposure has been demonstrated to significantly increase the risk for thyroid cancer (Brenner et al. 2003; Brown et al. 2012; Higginson et al. 1992; Kleinerman 2006; Nagataki & Nystrom 2002; Papadopoulou & Efthimiou 2009; Reiners 2009; Richardson 2009; Ron 1998, 2007; Ron et al. 1995, 2012; Ron & Schneider 2006; Schonfeld et al. 2011; Wakefield 2004; Williams et al. 2004). X-rays and gamma-rays are examples of ionizing radiation. There is no evidence that naturally-occurring radiation (cosmic radiation or soil radiation) increases the risk for thyroid cancer (Reiners 2009; Ron & Schneider 2006). Naturally-occurring radiation is very weak. Nonionizing radiation sources (e.g., radio waves or microwaves) are not associated with
increased risk of thyroid cancer (Ron & Schneider 2006; Wakefield 2004). The risk of developing thyroid cancer from ionizing radiation exposure is especially evident in those exposed during childhood (Brown et al. 2012; Cardis et al. 2005; Dal Maso et al. 2009; Nagataki & Nystrom 2002; Papadopoulou & Efthimiou 2009; Reiners 2009; Ron et al. 1995, 2012; Ron & Schneider 2006). The testing of nuclear weapons technology as well as a number nuclear power plant events released radioactive iodine (\(^{131}\text{I}\)) into the environment. Exposure to \(^{131}\text{I}\) during childhood is a particularly well-documented risk factor for adult thyroid cancer (Brenner et al. 2011; Cardis et al. 2005; Robbins & Schneider 1998, 2000; Ron 1998, 2007; Ron et al. 1995, 2012). Investigations into childhood exposure to \(^{131}\text{I}\) in Utah will be discussed below. The fetus of a pregnant woman exposed to high doses of ionizing radiation may also be at increased risk for later development of thyroid cancer (Constantinides & Palazzo 2013). The average latency period between a tumor-inducing radiation exposure event and the clinical manifestation resulting in the diagnosis of thyroid cancer is 30 years (Kikuchi et al. 2004; Ron et al. 1995, 2012).

**Previous cancer experience:** A history of surviving leukemia increases the risk in adults for development of therapy-induced cancers, including thyroid (Nielsen et al. 2011; Ron & Schneider 2006; Schonfeld et al. 2011). This may be due in part to the chemo- and radio-therapy used to treat the leukemia. Excessive routine low level exposures to radiation (i.e., medical and dental X-rays) have been found to slightly increase the risk (1 to 13% per 10 exposure events) for thyroid cancer (Memon et al. 2010; Neta et al. 2013). Patients who undergo multiple imaging examinations that require higher exposure levels (e.g., computed tomography scans) to the head and neck may have an increased risk for developing thyroid cancer (Schonfeld et al. 2011).

**Obesity:** Obesity and weight gain increase the risk for a number of different cancer categories including thyroid cancer (De Pergola & Silvestris 2013; Mijovic et al. 2011; Peterson et al. 2012; Wolin 2010). This risk increase is thought to be the result of hormonal and/or metabolic abnormalities that are prevalent in obesity as well as hormonal and/or metabolic stresses caused by obesity (DePergola & Silvestris 2013).

**Diet:** Up to 50% of the risk for thyroid cancer has been attributed to a poor diet and insufficient iodine. A poor diet is one that lacks adequate consumption of fresh vegetables and fruit and is rich in starchy foods (Dal Maso et al. 2009; Fioretti et al. 1999; Ron & Schneider 2006). There has been some suggestion that cruciferous vegetables (e.g., cabbage, broccoli, cauliflower, turnips, etc.) increase the risk for goiter, which in turn increases the risk for thyroid cancer. However, there is no consistent association with the consumption of these vegetables and the development of thyroid cancer (Peterson et al. 2012).

**Thyroid disease:** A history of benign thyroid disease is another leading risk factor for development of thyroid cancer. Thyroid disease includes hypothyroidism, hyperthyroidism, and thyromegaly (goiter) (Botrugno et al. 2011; Cerci et al. 2007; Constantinides & Palazzo 2013; D'Avanzo et al. 1995; Dal Maso et al. 2009; Donnellan et al. 2009; Gandolfi et al. 2004; Gul et al. 2009; Lee et al. 2004; Pazaitou-Panayiotou et al. 2012; Ron & Schneider 2006). The causes of benign thyroid disease include iodine deficiency, congenital defects, autoimmune diseases (e.g., Grave's disease or Hashimoto’s disease), acute or chronic thyroiditis, pituitary gland dysfunction, exposure to goitrogenic substances, exposure to a thyroid toxicant, exposure to endocrine
disruptors, and adverse reactions to some drugs (Dal Maso et al. 2009; Guarino et al. 2010; Pazaitou-Panayiotou et al. 2012; Soto & Sonnenschein 2010).

**Genetic predisposition:** Familial history is a strong risk indicator for thyroid cancer and may account for 3 to 7 percent of the risk (Albright et al. 2012; Gimm 2001; Higginson et al. 1992; Khan et al. 2010; Lebastchi & Callender 2014; Lodish & Stratakis 2008; Malchoff & Malchoff 2006; Nagataki & Nystrom 2002; NCI 2012a; Omur & Baran 2014; O'Neill & Shaha 2013; Patel & Singh 2006; Richards 2010; Ron & Schneider 2006; Xing 2005). Familial risk is associated with at least 11 different gene mutations (Gimm 2001; Guarino et al. 2010; Lebastchi & Callender 2014; Omur & Baran 2014). These mutations often manifest other adverse health conditions as well, such as Cowden's Disease (Gimm 2001; Lebastchi & Callender 2014; Malchoff & Malchoff 2006; Richards 2010).

**Occupational exposures:** Occupational exposure to ionizing radiation in an industrial or health care setting has been consistently shown to increase risk for thyroid cancer. Suggestive, but inconsistent, associations have been found for occupational exposures to pesticides or other agricultural chemicals (Aschebrook-Kilfoy et al. 2014; Leux & Guenel 2010; Ron & Schneider 2006).

**Life choices often associated with cancer risk:** Tobacco use, alcohol consumption and coffee consumption have not been shown to increase the risk for thyroid cancer (Belpomme et al. 2007; Dal Maso et al. 2009; Irigaray et al. 2007; Navarro Silvera et al. 2005; Ron & Schneider 2006).

**Previous Studies of Thyroid Cancer Risk in Utah:** The United States started conducting test detonations of nuclear weapons in July 1945. The first test took place at the Alamogordo Bombing Range (now known as the White Sands Missile Range) in New Mexico. Within the United States, nuclear testing was conducted at ten different tests sites in Alabama, Alaska, Colorado, and Nevada (Beck & Bennett 2002; DOE 2000).

The Nevada Test Site (now the Nevada National Security Site), located in Nye County, Nevada, was used to conduct nuclear detonation tests from 1951 to 1992. One thousand twenty-one (1,021) detonations occurred at the site, including 100 detonations that were above ground. The above ground detonations all occurred between 1951 and 1958 (Beck & Bennett 2002; DOE 2000; Fehner & Gosling 2000; NCI 1997).

$^{131}$I is a short-lived (half-life = 8 days) daughter product that is produced during the fission of the uranium. Exposure to iodine results in its accumulation in the follicles of the thyroid. Decay of radioactive iodine results in the production of a beta particle (an electron) and gamma radiation. Beta radiation has sufficient energy to penetrate and damage cellular genetic material, resulting in mutations. In most cases, the damage is fatal for the cell. Sometimes, the resulting mutation damages cellular regulatory mechanisms without killing the cell, allowing the cell to become cancerous (Beck et al. 1990; NCI 1997). Figure 3 presents a map of the geometric mean exposure levels in radiation dose units (rads) for the Utah population resulting from nuclear fallout containing $^{131}$I that originated from Nevada Test Site nuclear detonation tests. Because of the short half-life of $^{131}$I, the concern for exposure derived from nuclear detonations is focused on individuals who lived in these locations at the time of, or shortly after, the test events.
Several investigations of school-aged children born in Utah, Nevada and Arizona, between 1947 and 1958 found a statistically significant increased risk (relative risk [RR] as high as 7.5) for the development of thyroid cancer later in life (Kerber et al. 1993; Lyon et al. 2006; Rallison 1990). However, another study of the same cohort of children found no risk for children who were older than one at the time of exposure and only suggestive evidence of a risk for children who were younger than one at the time of exposure (Gilbert et al. 1998).

**Cancer Incidence Statistical Reviews:** A core function of epidemiology is to track and evaluate disease patterns. This function helps public health officials and policymakers 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 & Kulldorff 1999; Stanbury et al. 2012; Thacker 2000; Thacker et al. 2012). Cancer is a dominating environmental public health concern (CDC 2012; 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 several methods. The first is a cancer incidence statistical review, which 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. 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 spatio-temporal cluster is a cluster defined in both the geographic and temporal dimensions (Aamodt et al. 2006; Hinrichsen et al. 2009; Lawson & Kulldorff 1999; Wakefield et al. 2000; Wheeler 2007).

The discovery 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. When evaluating 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 do not properly accommodate disease patterns. For example, there are no areas within the boundaries of Utah that are not also part of a census tract geographic area. Thus some census tracts include areas of geography (e.g., the Bonneville Salt Flats, or upper elevations of Utah’s mountain ranges) where no people live. Clusters also may occur because of chance or because of the presence of factors that are not measurable or are highly variable (Wakefield et al. 2000).
Furthermore, clusters may be reported due to improper application of statistical analytical methods (Tango 1999).

Another method available to public health practitioners is a 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 a complex statistical analysis to identify the few variables that seem to explain the risk (Kingsley et al. 2007). However, 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 cases of cancer (or clusters). During the past ten years, the EEP has received a number of concerns about excess thyroid cancer in communities in Duchesne, Emery, Tooele, and Utah counties. Those investigations examined the rate of thyroid cancer compared to the rest of the state for a prior defined small area (i.e., a neighborhood or community) using a retrospective statistical review methodology (CDC 1990; Jekel et al. 1996; Mann 2003). None of the statistical reviews were able to find a statistically significant increased risk for thyroid cancer in the communities investigated.

**Study Objectives:** This report presents a statistical review of the spatial and temporal distribution of all types of primary invasive thyroid cancer in Utah from 1980 through 2012 using a spatio-temporal scan methodology. The purpose of this review was to identify statewide trends of thyroid cancer and regions of Utah with a historical or ongoing excess incidence of thyroid cancers.

**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 2015). 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 spatio-temporal 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 spatio-temporal 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 & Sloan 2011). As an individual in the population either is or is not, a cancer case, 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 scales for the case and population data for this investigation are the census tract geographic unit in the spatial dimensions and year of diagnosis in the temporal dimension. This investigation used the spatio-temporal scan statistic to look for current and historic clusters. Identified clusters were further evaluated for homogeneity, statistical significance, and burden to the population. The spatio-temporal scan method creates many different aggregations of contiguous spatial and temporal analytical units (e.g., northern Utah County from 2008 to 2012). The method then compares the incidence of cancer inside each aggregation to the incidence of cancer outside the aggregation to identify spatio-temporal 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 was controlled for.

**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 2012 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 2014). For this investigation, only invasive thyroid cancers were considered. Population data aggregated by age group and sex at the 2010 U.S. census tract geography for Utah is only available from 1980 forward. Therefore, cancer data from 1980 through 2012 were used for this investigation.

The primary site of a tumor is that body site, organ, or tissue in which the tumor originates. Metastasis is the spread of cancer cells originating in one site or tissue to another organ or tissue within the body (e.g., ovarian cancer cells spreading to the liver). Metastatic cancer cells carry with them some characteristics of tissue type where they originated often allowing the primary site of metastatic tumors to be identified (Higginson et al. 1992). Metastasis into the thyroid gland is rare, but not unheard of. Spread of malignant melanoma and carcinomas of the lung, breast, kidney, gastrointestinal tract, and head or neck area to the thyroid have been documented (Bohn et al. 2009; Lam & Lo 1998; Nakhjavani et al. 1997; Stevens et al. 2011). The UCR data categorizes a metastatic cancer according to the organ or tissue that was the site of the primary tumor, regardless of the location of metastasis. Additionally, the UCR does not report benign tumors (behavior type 0) or borderline tumors (behavior type 1) to the EEP.

The UCR completes a rigorous data review for completion and quality before data are released to the EEP. The most recent years of data are not made available to the EEP until the review has 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 2014).

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 (NCI 2012c; UCR 2014). Diagnostic coding of cancers includes the International Classification of Disease Oncology, 3rd Edition (ICD-O-3) codes for site, histology, and behavior (WHO 2012). For convenience to the UDOH, 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 2012b). These site codes are a convenient grouping for conducting surveillance analyses (UCR 2014). Thyroid cancers were identified using the site code “33” which corresponds to ICD-O-3 site code C73.9 and histology codes ranging from 8000 through 9589. This site code was used to filter the UCR data for thyroid cancer cases.

Between 1980 and 2012, 6,159 cases of thyroid cancer were reported to the UCR. The residential address information provided by the UCR includes the patient’s street address, city, and ZIP code at the time of diagnosis (UCR 2014). The EEP geocodes each registry record’s residential address data to obtain an x- and y-coordinate for that address. Most addresses are automatically geocoded using address locator data obtained from the Utah State Geographic Information Database (SGID), maintained by the Utah Automated Geographic Reference Center (AGRC) (AGRC 2013). 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. Using the geocoded x- and y-coordinates, the EEP was able to geo-reference 5,868 (95.3%) of the cancer cases to their respective U.S. 2010 census geographic tracts. A few (248 cases or 4%) case addresses could not be geocoded (e.g., a postal box addresses, etc.). These cases were geo-referenced to the most populated census tract for the smallest known geographical area (the ZIP code or municipal boundary) indicated by the address. Nine (3.6%) of these cases were located within the two clusters that were discovered. It is highly unlikely that this geo-referencing method effected the final outcome. Finally, 43 (0.7%) of the cases were patients of the Veterans Administration (VA) hospital in Salt Lake City. As the VA policy is to not report any identifying information to the state, those cases could not be assigned to an appropriate geographic census area and were excluded from the remainder of the investigation. The final count for thyroid cancers included in this statistical review was 6,116 cases.

**Population Data:** The 2010 U.S. census divides Utah into 588 census tracts (USCB 2004, 2012a) with a median population of 4,700 (range 0 to 21,591) persons per census tract in the year 2010. These small area geographies range in size between 0.2 to 6,108 square miles (average = 144 square miles, standard deviation = 608 square miles) and have a population density ranging from less than one person per square mile in the sparsely populated areas to more than 29,400 persons per square mile in the urbanized Wasatch Front. The average density was 3,443 people per square mile (standard deviation = 3,358). Commercially available U.S. census population data for Utah for the 1980, 1990, 2000 and 2010 censuses (Geolytics 2014) were used to estimate annual five-year age-group population counts in each census tract for each intercensal year between 1980 and 2012. These estimates were made by applying annual population growth rates derived from the previous and subsequent decennial data following national population estimation guidelines (USCB 2012b).
Census Tract Data: Geographic Information System data for the 2010 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 2010 U.S. Census data applies a “wall-to-wall” geographic coverage, meaning 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 disease 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, which 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 9.3 (SAS 2011) as follows:

\[ \text{Coord}_T = \frac{\sum (\text{Coord}_B \times \text{Pop}_B)}{\sum \text{Pop}_B} \]

Where:  
\( \text{Coord} \) is the x- or y-coordinate  
\( T \) is the target census tract  
\( B \) is the source census block contained within the target census tract  
\( \text{Pop}_B \) is the census block total population

On average, the population-weighted centroid differed from the geographic centroid by 472 (range 0 to 16,346) 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, by year, and five-year age group using SAS® for Windows version 9.3 (SAS 2011). 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 9.4.1 computer application applies spatio-temporal scanning methodology (Kulldorff 2010; Kulldorff & IMS 2011; SaTScan 2015). SaTScan implements a class of statistics known as “scan statistics” originally developed to scan through the spatial and temporal dimensions of interest, looking for anomalies in the 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 elevated 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 & Kulldorff 2012; Kulldorff 1997, 2010; Kulldorff & 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 (Amin & Burns 2014; Kulldorff 1997, 2010; Wagner et al. 2013). Age was added to the model as a covariate. Model parameters are decisions or limitations applied within the application to “tune” the model. Examples of model parameters include limits on the shape and size of the windows and the inclusions of various adjustments for spatial nonstationarity. For this investigation, the model used an elliptic spatial window shape with medium noncompactness 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 identified by a cluster information criterion (CLIC) statistic to be 35% of the population (Han et al. 2011). The temporal maximum cluster size was set at 90% of the study period (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 at unequal rates (Kulldorff 2010). This parameter is important because of the recent new growth in the areas where clusters were identified. No geographic overlapping of clusters was allowed. Scans were run with other model parameters (e.g., more or less compactness, population size limits, with or without stationarity adjustment, etc.) 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; Park 2010; Wagner et al. 2013; Wheeler 2007). The SaTScan application implements methodology as part of the likelihood calculation to control for the many calculations. Only areas with higher-than-expected rates were considered during the scan. Cluster data was output as a data file that was joined to the attribution table of a geographic data file (shapefile) 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.

**Cluster Homogeneity and Cluster Confirmation**: Several discrete and noncontiguous areas with slightly elevated rates that individually are not statistically powerful enough to be distinguished from the random variation may, when combined within an aggregated area, result in the delineation of a cluster area. This kind of false-cluster would be represented visually by a heterogeneous presentation of small area rates. True clusters would have a homogenous presentation of high rates compared to the surrounding small areas (Chen et al. 2008). A direct age-standardized incidence rate for the aggregated cluster period for each of the 588 census tracts within the state was calculated using the overall state rate as the standard (Anderson & Rosenberg 1998; Besag & Newell 1991; Breslow & Day 1987; Esteve et al. 1994; Jekel et al. 2007).
The census tracts within each cluster area were isolated using a spatial clipping technique and the global Moran’s I test was used to determine the level of spatial homogeneity of rates within the cluster area (Cromley & McLafferty 2012; Marshall 1991; Moore & Carpenter 1999; Moran 1950; Wakefield et al. 2001; Waller & Gotway 2004). The local Moran’s I and the local Getis-Ord G tests were used to confirm the cluster locations determined by the scan test (Anselin 1995; Cromley & McLafferty 2012; Getis & Ord 1992, 1996; Jackson et al. 2009; Jacquez & Greiling 2003; Ord & Getis 1995; Tiefelsdorf & Boots 1997; Wakefield et al. 2001; Waller & Gotway 2004).

**FINDINGS**

**Statewide Descriptive Assessment**: Between 1980 and 2012, 6,116 geocode-able cases of primary thyroid cancer were reported to the UCR. For 5,598 (92%) of those individuals, thyroid cancer was their first cancer experience. The other 518 (8%) cases had experienced a previous primary cancer of some other type. Of those 5,598 cases diagnosed with thyroid cancer as their first cancer experience, 445 (7%) patients had a subsequent primary cancer diagnosis.

The distribution of cases by age at the time of their diagnosis is shown in Figure 4. The median age of cases is 44 years (range 2 years to 97 years). Three quarters (4,711 or 77%) of cases were women. Most (5,934 or 97%) of the cases were Caucasian.

Of the cases diagnosed during the 33-year study period (1980-2012), 784 (13% cases) had died by the end of the study period (2012). Those cases died from a variety of causes, including 205 (26% of deaths) who died of thyroid cancer and 201 (25% of deaths) who died of cancer other than thyroid cancer.

The thyroid consists of several different kinds of cells and tissue structures (see Figure 2). Cancer can arise from any of those cell types, resulting in different kinds of thyroid cancer. Papillary carcinoma is the most frequently observed form of thyroid cancer followed by follicular carcinoma (ACS 2014; Brown et al. 2012; Gimm 2001; Higginson et al. 1992; Lebastchi & Callender 2014; Li et al. 2013; Monson 2002; NCI 2012a; O’Neill & Shaha 2013; Patel & Shaha 2006; Ron & Schneider 2006). The following table presents the distribution of thyroid cancer by their general classification. Each of these classes of cancer may have several subclasses.

<table>
<thead>
<tr>
<th>Cancer Classification</th>
<th>Case Count</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>3,730</td>
<td>61.0%</td>
</tr>
<tr>
<td>Follicular</td>
<td>354</td>
<td>5.8%</td>
</tr>
<tr>
<td>Mixed Papillary-Follicular</td>
<td>1,657</td>
<td>27.1%</td>
</tr>
<tr>
<td>Medullary (or mixed)</td>
<td>98</td>
<td>1.6%</td>
</tr>
<tr>
<td>Hurthle cell</td>
<td>5</td>
<td>0.1%</td>
</tr>
<tr>
<td>Insular (Poorly differentiated)</td>
<td>9</td>
<td>0.1%</td>
</tr>
<tr>
<td>Other Adenomas</td>
<td>138</td>
<td>2.3%</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>54</td>
<td>0.9%</td>
</tr>
<tr>
<td>Other or not differentiated</td>
<td>71</td>
<td>1.2%</td>
</tr>
<tr>
<td>Total</td>
<td>6,116</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
The number of primary thyroid cancer diagnoses has increased from 56 cases in 1980 to 506 cases in 2012. This increase is correlated ($R^2 = 0.89$) with Utah’s statewide population growth. This correlation was used to inform the approach for the temporal trend adjustments applied to the final model. The Utah population has increased from approximately 1.47 million people in 1980 to 2.77 million in 2010 (GOMB 2015).

According to the Utah state cancer profile provided by the NCI, the rate of thyroid cancer among Utah’s population changed around 1996. Figure 5 presents a graphic taken from the NCI cancer profile. The standardized thyroid cancer incidence rate in Utah in 1980 was 5.4 cases per 100,000 people. By 1996, the incidence rate in Utah was 7.3 cases per 100,000 people. The average rate increase is 0.1 cases per 100,000 people per year between 1980 and 1996 and appears to be fairly uniform. By 2011, the incidence rate was 19.4 cases per 100,000 people. The average annual rate increase for the period between 1996 and 2011 was 0.8 cases per 100,000 people per year (NCI 2015b).

**SaTScan Results:** SaTScan is a tool that scans through the data using all possible permutations of contiguous geography and time up to the maximum limits set by the user to identify likely spatio-temporal 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 & IMS 2011).

Two recent or current cancer clusters were identified by scanning the data. Figure 6 presents the geographic location of these two clusters. Cluster 1 includes most of Cache Valley in Cache County, Utah. Cluster 2 is located in the northern half of Utah Valley and all of Cedar Valley in Utah County, Utah. Figures 7 and 8 present a closer view of geographic location of each cluster respectively with an underlying topographical map so that the clusters can be related to the impacted communities. Table 1 presents information about the temporal details, magnitude, relative risk and burden of each cluster location. Figures 9 and 10 present a temporal annual plot of the relative risk for each cluster area respectively. These figures demonstrate the degree of annual variability. It should be noted that a possible earlier cluster (1980-1984) existed in the area of Cluster 2, but lacked sufficient statistical power and stability to be found by the scan statistic.

The population is presented in the person-years units. To understand this unit, a cluster in a community of 1,000 persons lasting 10 years represents 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 to 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 which is interpreted as no increased burden of disease. Values greater than one are interpreted as higher risk than expected burden of disease. Conversely, values lower than one are interpreted as lower risk than expected. SaTScan only reports likely clusters when the relative risk ratio is statistically elevated, however, for convenience of interpretation, the 95% confidence intervals (95% CIs) are included (Frumkin & Kantrowitz 1987). The 95% CI ranges that almost include 1.0 (for example, an interval range of 1.1 – 1.5) are less meaningful than those that do not (for example, an interval range of 2.0 – 2.5). Both possible cluster areas had meaningfully increased relative risk values.
SaTScan generates an estimate of the likelihood of the cluster being a real spatio-temporal 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). Both clusters were found to be significantly likely.

**Cluster Confirmation:** The global Moran’s I for spatial autocorrelation was used to test the heterogeneity of the risk levels among the census tracts that were contained within the cluster area. A significant Moran’s I suggests that the cluster risk is homogeneous and the identified boundaries of the cluster are likely to be accurate. A nonsignificant Moran’s I suggests that the cluster risk is heterogeneous and that the identified boundaries of the cluster are not accurate.

The local indicators of spatial autocorrelation (LISA) using two methods, the local Moran’s I tests and the Getis-Ord G test, were used to confirm the location of the cluster.

The Moran’s I for Cluster 1 was highly significant (p-value < 0.0001, Moran’s I = 0.2613, z-value = 4.4909). Both the local Moran’s I and the Getis-Ord G found Cluster 1. These findings suggest that SaTScan accurately determined the spatial location of Cluster 1 and that Cluster 1 is meaningful.

The Moran’s I for Cluster 2 was not significant (p-value = 0.5870, Moran’s I = -0.0290, z-value = -0.5432). Neither the local Moran’s I nor the Getis-Ord G test found this cluster. These findings suggest that Cluster 2 may not be accurately represented by the SaTScan results or that Cluster 2 may be a statistical artifact and not real.

**DISCUSSION**

**Cancer:** Cancer is second only to heart disease as a leading cause of death and public health concern in the U. S. (CDC 2012; Goujon-Bellec et al. 2011; Morrone 2011; Wakefield et al. 2000). 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 style 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 2012a).

**Utah Thyroid Cancer Cluster:** Two clusters were identified by the spatio-temporal scan method. One cluster, aggregating 23 census tracts and including most of Cache Valley in Cache County, Utah, is recent (1994-2011) and may be resolving. This cluster was found to have a homogenous risk distribution and its location was confirmed by spatial autocorrelation, indicating that it is most likely real and meaningful. A second cluster aggregated 68 census tracts
in northern Utah Valley (from the Provo-Orem area northward) and all of the populated area of Cedar Valley in Utah County. This cluster is current (2008-2012). The risk distribution within this cluster was found to be heterogeneous. Spatial autocorrelation methods were not able to confirm the location of this cluster, and it is likely that multiple smaller pockets of real elevated risk were aggregated by the scan method to become this cluster.

Performance of the SaTScan Application: SaTScan is widely used and well accepted as a tool for discovering spatio-temporal clusters of cancer (Aamodt et al. 2006; Almeida et al. 2011; Chen et al. 2008; Cromley & McLafferty 2012; Oliveira et al. 2011; Robertson & 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 & 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 very irregularly (e.g., “S” or “U”) shaped clusters (Aamodt et al. 2006; Goujon-Bellec et al. 2011; Oliveira et al. 2011; Wheeler 2007).

• 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 & McLafferty 2012; Wheeler 2007). For this study, elliptical filters were used.

• Related to the above limitations is the tendency of SaTScan to merge several small, strong irregularly shaped clusters that do not fit well in a circular or elliptical filter into one larger, less significant cluster that fits better (Oliveira et al. 2011; Van Meter et al. 2008). This may be the situation for Cluster 2.

• 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 (e.g., mountain ranges, salt flats, etc.). The visualization of the cluster does not exactly reflect the true location and shape of the cluster (Read et al. 2011).

• Additionally, the SaTScan tool is not capable of considering geographical features other than the census tracts represented by their centroid point. As a result, the aggregating process may result in the combining of distinct communities that may have natural barriers (i.e., lakes, mountain ranges, etc.) that tend to isolate them from each other. For
example, Cluster 2 includes areas in both northern Utah Valley on both sides of Utah Lake and communities in Cedar Valley that are separated from Utah Valley by the Lake Mountains.

- Census tracts are politically-derived boundaries designed to segregate populations based on political habits and not necessarily on health risk.

- SaTScan identifies those contiguous census tract areas with sufficient levels of elevated risk most likely to be part of the cluster. The clusters are presented as the boundary that includes all of the census tracts that were part of the cluster. This boundary is an epidemiological tool for presentation and not a definitive location of where excess risk starts or ceases to exist. A census tract may include one or more unique local neighborhoods. Local neighborhoods within a census tract in a cluster may have a normal level of risk that is lost to the averaging with other neighborhoods in the census tract or cluster. Correspondingly, neighborhoods outside of the cluster may experience an excess level that is lost in the averaging process. Thus, individuals may not experience what this report is presenting with respect to the rate of thyroid cancer in their neighborhoods.

- Another concern about 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 examples of the zonation problem associated with MAUP. One is the ability to aggregate neighboring census tracts bounded in this study by the state boundary (Parenteau & 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 tracts (Parenteau & 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 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 & 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 2010 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 & 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 more accurately reflects the true dynamic population growth in a region than the steady state growth represented by 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 spatio-temporal 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. There are a number of limitations that impede this linkage. These kinds of cancer statistical reviews are based on annual incidence data reported to the UCR, and the incidence of cancer per year is dependent on diagnosis of clinically-manifested cancer. There is seldom any knowledge about the frequency, duration, or intensity of cancer victims’ exposure to a 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 a diagnosis. There is seldom sufficient information available to statistically control for the many non-environmental factors that contribute to cancer risk, let alone exposure to other potential environmental risks that are not the putative environmental concern. Chance also plays a role in the distribution of cancer and is often the dominating causal factor in small populations or for diseases that occur rarely. 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 and 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 the state. The UCR may contain records of incidence of cancer in people who recently moved to the study area prior to their diagnosis, and conversely 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. The vendor has re-tabulated 1980, 1990, 2000, and 2010 data for the 2010 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 & 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.” 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 & Robins 1994; Izquierdo & Schoenbach 2000; Morgenstern 1982, 1995; Rockhill 2005).

CONCLUSIONS AND RECOMMENDATIONS

This study identified the spatio-temporal locations of two possible clusters of primary invasive thyroid cancer. Both clusters were recent or active at the end of the study period (2012). The cluster located in Cache Valley is likely to be real and meaningful. The cluster located in northern Utah County is most likely a statistical aggregation of several areas with slightly higher levels of risk. The rate of thyroid cancer is known to be rising in Utah and in the United States.

A comprehensive review of the literature did not reveal any significant environmental risk other than exposure to ionizing radiation such as $^{131}$I. Potential causal factors identified by literature review were presented, but not investigated as part of this investigation. Random variation (chance) is an important element in any investigation involving cluster, and can play a dominate role when the investigation involves rare diseases or small population units.

People who are afflicted with thyroid cancer are best served by their health care team. Concerned citizens who think they may have thyroid cancer or may be at risk for developing thyroid 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 thyroid cancer rates in their communities.
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CERTIFICATION

This report titled “Utah Statewide Investigation of Thyroid Cancer for Spatiotemporal Clustering Patterns Between 1980 to 2012” 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.

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REFERENCES

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


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FIGURES AND TABLES

**Figure 1.** Anatomical location and structure of the thyroid and parathyroid glands.
Figure 2. Cellular organization of the thyroid gland showing the relationships and connectivity of the follicular cells, C cells, and connective tissues.
**Figure 3.** Average dose levels of radioactive iodine-131 by Utah county resulting from nuclear weapons testing in Nevada. Values are given in radiation dose units (rad). An $^{131}$Iodine dose level of 0.5 rad increases an individual’s chances of developing thyroid cancer to 1 in 1,000.
Figure 4. Distribution of primary invasive thyroid cancer (n = 6,116) by age for cases in Utah.
Figure 5. Standardized annual incidence rate of primary thyroid cancers in Utah from 1975 to 2011. Figure was obtained from the Utah State Cancer Profile provided by the National Cancer Institute (NCI 2015b).
**Figure 6.** Location of two spatio-temporal clusters of thyroid cancer incidence among Utah residents. The cluster located in Cache County is identified as “Cluster 1.” The cluster located in Utah County is identified as “Cluster 2.”
Figure 7. A Detailed geographic view of the thyroid cancer Cluster 1 located in Cache County, Utah and existing between 1994 and 2011.
**Figure 8.** A detailed geographic view of the thyroid cancer Cluster 2 Located in northern Utah County, Utah and existing between 2008 and 2012.
Table 1. Statistical details of two clusters of thyroid cancer identified by spatio-temporal scanning of cancer data for the period 1980 through 2012. Cluster 1 is located in Cache County, Utah. Cluster 2 is located in Utah County, Utah. Total cases in state = 6,116.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cluster 1: Cache Valley in Cache County, Utah</th>
<th>Cluster 2: northern Utah Valley and Cedar Valley in Utah County, Utah</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic area</td>
<td>23 Census Tracts, 319 square miles</td>
<td>69 Census Tracts, 456 square miles (of land)</td>
</tr>
<tr>
<td>Impacted population size (person-years)</td>
<td>1,421,352</td>
<td>915,380</td>
</tr>
<tr>
<td>Number of observed cases during the time frame</td>
<td>290</td>
<td>287</td>
</tr>
<tr>
<td>Number of cases that would be expected if this area experienced a typical level of risk. The typical level is that level experienced by the State of Utah as a whole.</td>
<td>159</td>
<td>193</td>
</tr>
<tr>
<td>Relative Risk (95% Confidence Limits). This is a measure of the magnitude of increased risk.</td>
<td>1.82 (1.62 – 2.05)</td>
<td>1.49 (1.32 – 1.67)</td>
</tr>
<tr>
<td>Probability that this observation is due to a random chance. The probability of this being a real cluster is 1 – this value.</td>
<td>&lt; 0.0001</td>
<td>0.0013</td>
</tr>
<tr>
<td>Probability that the risk pattern observed inside the cluster is heterogeneous as determined by the Global Moran’s I test. The level of homogeneity is 1 – this value. A homogeneous cluster pattern is more likely than a heterogeneous pattern to be a real cluster.</td>
<td>&lt; 0.0001</td>
<td>0.5870</td>
</tr>
</tbody>
</table>
Figure 9. Plot of the Annual Relative Risk within Cluster 1 (Cache County). The cluster period is indicated when the plot changes to red. The green line (RR = 1.0) indicates a “normal” amount of risk (defined as the state risk level).
Figure 10. Plot of the Annual Relative Risk within Cluster 2 (Utah County). The cluster period is indicated when the plot changes to red. The green line (RR = 1.0) indicates a “normal” amount of risk (defined as the state risk level).
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 more than 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 value 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 symptoms 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.

CLIC  Cluster Information Criteria. This is a calculated value that integrates a goodness-of-fit of the cluster and the complexity of scan. The best model window is the one that generates the smallest CLIC value.

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.

**Gy**  
Gray is a derived unit of ionizing radiation dose in the International System of Units. The Gray unit replaced the rad unit as a measurement of exposure. A Gray is defined as one joule of energy per kilogram of tissue. See “rad” for additional information.

**I**  
131I Iodine-131. An isotope of the element iodine having an atomic weight of 131 units. Elements are identified by the number of protons contained in their atoms. Iodine has 53 protons. Isotopes of elements are identified by the number of neutrons that are contained within the atom’s nucleus. The number of protons plus the number of neutrons equals the atomic weight. Iodine has seven isotopes 127I, 124I, 125I, 127I, 129I, 131I and 135I. Natural iodine is 127I. This isotope of iodine is stable and does not decay. The other isotopes are unstable and transform into other elements such as tellurium or xenon by radioactive decay through a process that changes the number of protons contained in the atom’s nucleus. The isotope 131I is produced in the process of decay after fission of uranium or plutonium. The half-life (meaning half of the atoms will have decayed further in that amount of time) for 131I is eight days. The shorter the half-life the more dangerous the radioactivity is to human health.

**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/.
LISA  Local Indicator of Spatial Autocorrelation is a measure of how distinct adjacent small areas are to each other. When the disease rate value is used as the test criteria, a LISA is one method that can be used to identify cluster areas.

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.

mSv  MilliSieverts. The Sievert is an internationally accepted unit of health effect resulting from low level radiation exposure. It is similar to the Gray. Both equal 1 joule of energy per kilogram of material. The Gray is a physical quantity, whereas the Sievert is a biological effect quantity. It is derived from ionizing radiation dose standardized for inhalation or ingestion of a radioactive substance. A milliSievert is 1/1000 of a Sievert.

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.

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.

rad  A deprecated unit of absorbed radiation dose. It is the amount of radiation energy (100 ergs) absorbed by one gram of tissue. Modern dose measurements longer use the rad. Instead exposure is now measured using the Gray (Gy) unit. For conversion, 1 rad = 0.01 Gy = 0.01 Joules/kilogram (J/kg). A dose of 25 rad has been shown to cause clinically observable changes in the blood. A dose less than 100 rad will typically produce no immediate symptoms but can result in
longer term adverse health outcomes such as cancer. A dose of 200 to 1,000 rad in less than a day causes sufficient cellular destruction to result in acute radiation syndrome, but is usually not fatal. Whole body doses over 1,000 rad in a day are nearly always fatal.

**R²**

Correlation Coefficient. The R² is a measure of the degree of agreement between two or more parameters. The R² value range is between negative one (-1) and positive one (+1). An R² value close to zero (0) means that considered parameters are uncorrelated. Their relationships are completely random. R² values close to negative one (-1) are inversely correlated meaning that as one parameter increases the other parameters decrease. R² 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 with 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 than the comparison population then 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

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 exposure and hazards data, 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 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.

- The EEP uses the 1983 North American Datum. This refers to a geodetic network of reference points (typically a brace marker anchored in a concrete block) that were placed in 1983. This survey was conducted to update a 1927 survey using the latest satellite and remote sensing technology and has a much higher level of precision.
- The UTM system defined the Earth into 60 zones, each 6% of longitude in width. The zone boundary provides a reference point for the east-west measurement. Utah is completely in Zone 12.

VA Veterans Administration. An agency of the U.S. Department of Veterans Affairs that provides benefits to military veterans. Among the benefits managed by the VA is a system of clinics and hospitals for veterans. Because the VA is a Federal agency, it is exempt from state reporting of health data requirements to state public health agencies. For more information, see: http://www.va.gov/.
RESOURCES

Web links for websites may wrap onto multiple lines.

American Cancer Society: http://www.cancer.org/cancer/thyroidcancer/
American Society of Clinical Oncology: http://www.cancer.net/cancer-types/thyroid-cancer
Intermountain Healthcare Cancer Services: http://intermountainhealthcare.org/services/cancer/Pages/home.aspx
Mayo Clinic: http://www.mayoclinic.org/diseases-conditions/thyroid-cancer/basics/definition/con-20043551
National Cancer Institute: http://www.cancer.gov/types/thyroid
Thyroid Cancer Survivors’ Association: http://www.thyca.org/
THANC Foundation: http://www.thancfoundation.org/
Utah Cancer Action Network: http://www.ucan.cc/
Utah Cancer Control Program: http://cancerutah.org/
Utah Cancer Specialists: http://www.utahcancer.com/