Cancer Incidence Assessment near Sterigenics in Willowbrook, IL, 1995-2015

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Abstract

Background: The Division of Epidemiologic Studies, Illinois Department of Public Health (IDPH), conducted an assessment to determine if there is elevated cancer incidence in the population surrounding the Sterigenics facility in Willowbrook, Illinois. The facility, operating since 1984, has been emitting ethylene oxide (EtO), a currently known carcinogen.

Methods and Data: Cancer cases were obtained from the Illinois State Cancer Registry (ISCR) for diagnosis years 1995-2015. Two study areas were created based on census tracts and an air sampling/exposure model. Study area 1 included nine census tracts around the Sterigenics facility, and study area 2 included study area 1 and eight additional census tracts. Cases were geocoded into the study areas based on addresses using a combination of GIS software and manual scrutiny. Two groups of cancers were examined. The first group included lymphohematopoietic cancers (non-Hodgkin's lymphoma, Hodgkin's lymphoma, myeloma, and lymphocytic leukemia) and female breast cancer, a group of cancers that have been documented to be associated with EtO exposure. The second group included other common cancer sites. Trends in the lymphohematopoietic and breast cancers were examined, and pediatric cancers were studied separately. Standardized incidence ratios (SIR's) and their 95% confidence intervals (CI) were calculated with comparable county and state populations as references.

Results: Significantly elevated Hodgkin's lymphoma cases in females were observed in study area 1 as compared to county (SIR 1.86, CI 1.12-2.91) and state averages (SIR

1.89, CI 1.14-2.95). Female breast cancer was elevated in both study areas when compared to the state average (Study Area 1: SIR 1.10, CI 1.02-1.18; Study Area 2: SIR 1.07, CI 1.02-1.13). The elevation, however, became non-significant when compared to the county average. Trends in SIR's showed a monotonic increase with time in female non-Hodgkin's lymphoma, with the SIR becoming statistically significant in the most recent time period, 2009-2015 (Study Area 1: SIR 1.61, CI 1.19-2.21; Study Area 2: SIR 1.33, CI 1.07-1.63). Pediatric lymphoma was observed to be elevated over the entire study period in females of both study areas. Other adult cancer sites observed to be elevated include prostate cancer, and female pancreatic, ovarian, and bladder cancers. Also, female leukemia was found to be significantly lower than expected, and lung cancer seemed to be lower in both males and females.

Conclusions: The study's results, when taken as a whole, indicated that some cancers were elevated in populations living near the Sterigenics facility in Willowbrook, Illinois. Many apparent differences and inconsistences, however, existed between genders, across study areas, and among cancer sites. Further studies, preferably with larger populations and multiple facilities, are strongly recommended to confirm this assessment's findings.

Background

In December 2016, the U.S. Environmental Protection Agency (EPA) updated its cancer risk assessment for ethylene oxide (EtO). The new calculations, based on breathing elevated levels of EtO for many decades, resulted in a 30-fold increase in EtO's cancer potency. In response, the Agency for Toxic Substances and Disease Registry (ATSDR) evaluated the implications of the increased cancer risk associated with EtO emissions at a Sterigenics International Inc. facility in Willowbrook, Illinois (referred to in this paper as Sterigenics). The Sterigenics facility has been operating since 1984, releasing between 17,000 and 33,000 pounds of EtO annually before 1999, and about 5,000 pounds of EtO since 1999.

In July of 2018, the ATSDR released an open letter to the EPA regarding ethylene oxide (EtO) emissions at the Sterigenics facility in Willowbrook, Illinois (ATSDR, 2018). In this letter ATSDR concluded that "if modeled and measured data represent typical EtO concentrations in ambient air, an elevated cancer risk exists for residents and off-site workers in the Willowbrook community surrounding the Sterigenics facility. These elevated risks present a public health hazard to these populations." ATSDR then recommended that the Illinois Department of Public Health (IDPH) investigate whether there is elevated cancer incidence in the population surrounding the Sterigenics facility (US DHHS-ATSDR, 2018). Cancer incidence describes how many people were actually diagnosed with cancer.

EtO is a highly reactive gas used in the production of antifreeze, textiles, detergents, and other products, as well as a fumigant for sterilizing foodstuffs and a sterilizing agent for heat sensitive medical equipment. If EtO is inhaled, it is readily absorbed into the human body and easily distributed throughout the body. EtO leaves the body very rapidly (over 2-3 days) through urine and feces or by exhaling it.

The health effects of EtO exposure have been studied since the 1940's. Exposure to EtO can cause difficulty breathing, blurred vision, dizziness, nausea, headache, convulsions, blisters, and vomiting. It is also known to be mutagenic in animals and induce chromosome damage. EtO is known to be carcinogenic in mice and rats. There is evidence of an increased risk of lymphohematopoietic cancers (i.e. non-Hodgkin's lymphoma, myeloma, and lymphocytic leukemia) and of breast cancer in females among people employed in EtO manufacturing and sterilizing facilities (Steenland, Whelan et al 2004 and Steenland, Stayner et al 2003). EtO is identified as a known carcinogen by both the International Agency for Research on Cancer and the U.S. National Toxicology Program (IARC 2009 and NTP 2016).

IDPH has produced the following analysis to answer the following question: Is there evidence of increased cancer incidence in the area surrounding the Sterigenics facility that is consistent with cancers associated with EtO exposure?

Materials and Methods

The U.S. EPA provided the IDPH with modeled 5-year average EtO exposure estimates for the area surrounding the Sterigenics facility. This modeled exposure area was used to define the cancer investigation's first study area, which is comprised

of nine census tracts (Table 1, Map 1). A second, larger study area was created to approximate the zip code 60527, which includes study area 1 and eight additional census tracts (Table 1, Map 2). Zip code areas have typically been used by the Illinois State Cancer Registry (ISCR) to assess cancer incidence. The use of two different study areas helps capture any possible cancer increases in the area around the Sterigenics facility. Also, use of the two study areas assists researchers in determining if results vary between the study areas when the same set of standardizing or reference populations are used. Both study areas were defined using census tracts.

The source for cancer case data was the Illinois State Cancer Registry (ISCR). ISCR abstracts, verifies, and compiles cancer information from medical records. The verified medical information that ISCR collects is much more accurate than alternative information sources such as self reported surveys, which are highly prone to recall bias and errors. The ISCR data , as of November 2017, includes the years 1995 through 2015. This time period was selected for this assessment as it represents the most recent and most complete years of data in the registry that also correlate with the operation of the Sterigenics facility. This choice of time frame also allows for the typical cancer latency period which would be 4 to 10 years for lymphohematopoietic and 10 to 15 years for solid tumors.

Cancer registry data was reviewed to ensure cancer cases were geocoded accurately. Geocoding is a process through which cancer cases are assigned to a geographic location. ISCR, like any other cancer registry in the country, assigns a cancer patient's residential address, at the time of diagnosis, as the patient's

geographic location. The geocoding process was carried out in this study using a series of computer programs (e.g. ArcGIS®, Accurint™, Google® Earth, and Google® Maps), in combination with manual examination of address data to ensure that cancer cases were being placed in the correct census tract. First, cancer cases from 1995-2015 were selected from 10 zip codes surrounding Sterigenics (60480, 60525, 60527, 60521, 60561, 60439, 60559, 60514, 60517, 60558) and prepared for additional examination. One hundred percent of cancer cases in the registry have a valid zip code, so this variable was used to begin the process of assigning cases to census tracts. Of the 24,747 cases examined, 788 cases (3%) did not have a geocode specific enough for a census tract to be assigned. All of the 788 cases had address information reviewed and checked manually for accuracy using Accurint™, a commercial address verification tool, in addition to Google® Earth, to visually identify the residential address. Two cases were found to be residents of other states and were excluded, 33 cases did not fall into the 10 zip code catchment area, and 9 cases contained so little address information that a census tract could not be assigned. As a result, a total of 44 (0.1%) cases were excluded. With this process finished, the selection of cancer cases for the specific census tracts contained in study area 1 (N=4,534) and study area 2 (N=9,416) was completed.

Illinois residents who are diagnosed with cancer do not always get diagnosed in Illinois. In order to capture out-of-state cases, ISCR has standing agreements with other central cancer registries to identify Illinois resident cases that are identified outside the state and to share that data with ISCR. These registries include Arkansas, California, Florida, Indiana, Iowa, Kentucky, Michigan, Mississippi (through August 2004), Missouri,

North Carolina, Washington, Wisconsin, Wyoming (through February 2008), and the Mayo clinic in Minnesota (through October 2005). Completeness of out-of-state reporting depends upon the years of operation of these other central registries, the extent of their identification of out-of-state residents, and their standards of quality. Out-of-state diagnoses among residents of the two study areas accounted for less than one percent (0.5%) of the total number of cases reported, between 1995 and 2015, and were included in the study.

Identification of cancer cases in Illinois is dependent upon reporting by diagnostic and therapeutic facilities as mandated by state law. To benchmark and foster best practices for cancer reporting among population-based cancer registries, the North American Association of Central Cancer Registries (NAACCR) has developed a certification process that reviews registry data for completeness, accuracy, and timeliness of reporting. As of May 2018, ISCR data met the criteria for gold certification for cancer diagnosis years 1996 through 2015. The statewide completeness of case reporting from all reporting sources, assessed using the NAACCR Standard, is estimated to be 100 percent complete for all years between 1995 and 2015. The criteria for silver and gold certification can be found on the NAACCR web site at https://www.naaccr.org/certification-criteria/.

All cancer cases from the study areas were grouped by tumor site, sex, and age. These are referred to as the *observed* cases. Age- and sex-specific rates from comparable populations in Illinois were applied to each age group of the study population (indirect age adjustment) and to each tumor site to obtain an *expected*

number of cases for the study area (Mattson 1986). Two groups of cancer sites were examined in this study. The first group includes female breast, and lymphohematopoietic cancers. The lymphohematopoietic cancers specifically include Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, and lymphocytic leukemia. This group was selected because of their documented associations with EtO exposure in previous studies, almost all of which were conducted in an occupational setting (Steenland, Whelan et al 2004 and Steenland, Stayner et al 2003, Jinot, Fritz et al 2018). The second group includes other tumor sites that ISCR routinely examines when conducting a cancer assessment study, which are oral cavity, esophagus, stomach, colon and rectum, liver, pancreas, lung and bronchus, bone, melanoma, breast, cervix, uterus, ovary, prostate, testis, bladder, kidney, brain, and nervous system, leukemia, thyroid, and all other cancers. This second category of tumor sites was examined to capture other possible cancer increases and generate new hypotheses for future studies. The site recode scheme used in this analysis was the International Classification of Diseases for Oncology version 3 (ICD-O-3) with adjustment for hematopoietic histologies as defined by the Surveillance Epidemiology and End Results Program (SEER) of the National Cancer Institute (NCI) (https://seer.cancer.gov/siterecode/index.html).

In addition to the evaluation of adult cancers, this study also examined pediatric cancer for children ages 0 to 19 years old in both study areas. Tumors diagnosed in children are classified using the SEER site/histology recode based on the International Classification of Childhood Cancer (ICCC), Third Edition and ICD-O-3 (https://seer.cancer.gov/iccc/). Sites examined include leukemia, lymphomas, central

nervous system tumors, neuroblastoma, retinoblastoma, renal tumors, hepatic tumors, bone, soft tissue, germ cell tumors, and all other sites. The category 'all other sites' includes other malignant tumors and those that were unspecified or unclassified by ICCC definitions.

According to the longstanding ISCR practice, cancer incidence in a study area is compared to a population with a similar population density, race distribution, and a large enough size to provide stable estimates (Howe and Keller et al 1993). In addition to state and county geographies, ISCR has defined and maintained four reference groups (urban Cook County, suburban five collar counties, small urban with 13 counties, and rural with 83 counties) for Illinois based on population density, rate of growth, Beale codes, and with a total population of at least two million. The two comparable populations for the study areas of interest were deemed to be the suburban five collar counties (referred to in this report as the state average) and DuPage County (referred to in this report as the county average). The population density and other demographic characteristics of the two comparable populations matched those of the study area better than any other existing county or state level referent group. Table 2 presents race, gender, ethnicity, and age distributions for the two reference populations and the two study areas.

Age-, sex-, and race-specific population counts for census tracts in Illinois for each year between 1995 and 2015 were required in order to compute the observed and expected cases in this cancer assessment. While this level of population information is available for census years, 2000 and 2010, it was not available for intercensal years.

Because of this, intercensal population figures were interpolated/extrapolated based on the population counts from the 2000 and 2010 U.S. Census, the most reliable sources for small area population. Age- and sex-specific population counts for census tracts were created through application of a linear function to stratified counts from the 2000 and 2010 census. These were then aggregated to form age- and sex-specific population figures for both of the study areas.

The observed number of cases was compared with the expected number of cases for all age-, sex-, and site-specific categories. Standardized incidence ratios (SIR) and their 95% confidence intervals (CI) were calculated. An SIR is the ratio of observed cases to the expected number of cases, and an SIR greater than 1.0 or less than 1.0 indicates that observed cases are either higher or lower than the expected cases. The SIR is considered statistically significant when the SIR's confidence interval (CI) does not include 1.0. A statistically significant SIR means that the SIR, as judged by statistical significance, is unlikely to have occurred by chance. More technically, a statistically significant SIR indicates that there is a low probability (less than 5% chance) of getting a result as extreme or more extreme than what is observed, if there is truly no difference between the expected and observed numbers, and all assumptions related to the statistical test are also true. The SIR, CI's, and resulting statistical significance are affected by the strength of the effect, incidence of the disease, the size of the population studied, and many other factors such as quality of the data, choice of the study areas, and changes in cancer reporting, etc. (Aschengrau and Seage 2003, Last 2001). See appendix A for formulas used in the calculation of SIR's.

In addition to examining SIR's for the overall 21-year time period in question (1995-2015), SIR's from three 7-year time periods, 1995-2001, 2002-2008, and 2009-2015, were separately examined for trends in adult EtO related cancer sites. This by time-period analysis was also conducted to detect cancer changes that would otherwise be hidden when only the overall time-period was examined.

Results

Lymphohematopoietic and Female Breast Cancers

No increases in any subgroup of lymphohematopoietic cancers were observed in men of either study area 1 or study area 2 (Table 3). Significantly elevated Hodgkin's lymphoma cases in females, however, were observed in study area 1 when compared to the county and state averages (Table 3). The increase in observed cases in study area 1 was almost 90% higher than expected (SIR 1.86, CI 1.12-2.91). In study area 2, Hodgkin's lymphoma among females was no longer significantly different from either reference group. Significantly elevated SIR's were observed in invasive female breast cancer in both study area 1 and study area 2 when compared to the state average. The observed effect was small with case counts roughly 10% higher than expected in both study areas (Study Area 1: SIR 1.10, CI 1.02-1.18; Study Area 2: SIR 1.07, CI 1.02-1.13). When the study areas were compared to the county average the SIR's in female invasive breast cancer became non-significant.

Lymphohematopoietic and Female Breast Cancer Trends

Figures 1 and 2 display the temporal trends in SIR's for lymphohematopoietic and female breast cancer for study area 1 and study area 2, respectively, by three 7-year time periods; 1995-2001, 2002-2008, and 2009-2015. Since results were similar between the two reference populations, only results relative to the state reference group are shown. Non-Hodgkin's lymphoma in females displayed a consistent and increasing trend in SIR over the time period examined, and its SIR reached statistical significance in the most recent time period, 2009-2015, (SIR: 1.61, 95%CI: 1.19-2.11 for study area 1 and SIR: 1.33, 95%CI: 1.07-1.63 for study area 2). This positive trend and the significant elevation in the last and most recent time period was observed in both study areas. During the earliest time period, 1995-2001, non-Hodgkin's lymphoma among males seemed to be high, although the elevation could only be described as borderline significant (SIR: 1.30, 95%CI: 0.91-1.79 for study area 1 and SIR: 1.27, 95%CI: 1.00-1.59 for study area 2). No other cancer sites showed any clear trends over time or were significantly different from the reference population.

Other Cancer Sites

Males in both study areas had a small but statistically significant increase in prostate cancer when compared to both the state and county averages (Table 4-5). Lung cancer in males, however, was shown to be significantly lower in study area 2. In study area 1, females displayed significantly higher SIR's in the following sites when compared to both the state and county averages: pancreas, ovary, and bladder cancer (Table 4). All of these increases disappeared in study area 2 (Table 5), except for pancreatic cancer, which remained significantly elevated. Leukemia was observed to

be significantly lower in females of study area 1 when compared to both the county and state averages (Table 4). Lung cancer, which was observed to be significantly lower in males for study area 2, seemed to be lower among females, as judged by the value of SIR's and their 95% confidence interval bounds, in both study areas and relative to both county and state averages. However, the decreases only reached a statistical level of significance in study area 2 when compared to the state average (Tables 4 and 5).

Pediatric Cancers

An examination of childhood cancers, utilizing SIR's, showed a significantly higher than expected number of childhood lymphomas in females of both study area 1 and study area 2 (Table 7). Again, results shown are relative to the state reference, as the results relative to the county were similar to those relative to the state reference. No other pediatric cancer sites were observed to have higher or lower incidence relative to either reference group in either study area 1 or study area 2. It should be noted that all of the other individual pediatric sites had SIR's that were based on fewer than 10 cases.

Discussion

This cancer assessment used two study areas, two reference groups, and examined not only lymphohematopoietic and breast cancers, associated with EtO exposure in the literature, but also other cancer sites and pediatric cancers that have not been shown to be related to EtO exposure. While this was done to mainly capture and screen for as many potential cancer elevations as possible and to provide comparisons to assess the stability and robustness of this study's findings, this

approach generated many inconsistencies, which were reflected in differences between genders, between study areas, and even between reference populations.

Despite these inconsistencies, the study's results, when taken as a whole, suggest that some cancers were indeed elevated in populations living in and around the Willowbrook, Illinois area. The main evidence for this came from Hodgkin's lymphoma and, to a lesser extent, breast cancer. Breast cancer was elevated, by about 10%, when comparing the study areas to the state reference group. The elevation became non-significant when the study areas were compared to the county reference group. This change could be plausibly explained by the fact that DuPage County, the county reference group in this study, has consistently displayed higher levels of breast cancer compared to other counties in the state (IDPH-ISCR 2018). Despite the loss of statistical significance, the lower bounds of the 95% confidence intervals were still close to 1.0, suggesting that breast cancer was high even in relation to DuPage County. Some common behavioral risk factors for breast cancer include; drinking alcohol, being overweight or obese, lack of physical activity, not having children, not breastfeeding, use of birth control containing hormones, post-menopausal hormone usage, and breast implants (ACS 2019). In addition, certain genetic mutations can increase the risk of breast cancer, as well as a family or personal history of the disease, certain benign breast conditions, early menstruation, menopause after age 55, having radiation to your chest, and exposure to diethylstilbestrol (ACS 2019).

Hodgkin's lymphoma was observed to be high in females of study area 1. This cancer, which belongs to the lymphohematopoietic group of cancers, has been studied

much less than other sites in that group. Past occupational studies have identified an association between EtO exposure and three lymphohematopoietic cancers, namely non-Hodgkin's lymphoma, myeloma, and lymphocytic leukemia. Similar associations with respect to these three specific sites were not observed in this study. To our knowledge, only one past study observed an elevation of Hodgkin's lymphoma in workers who were exposed to EtO in combination with other chemicals. The sample size in that study was small and the exposure was not limited to EtO (Swaen and Slangen et al. 1996). Many studies only included Hodgkin's lymphoma when lymphohematopoietic cancers, as a group, were used as a single target cancer (US EPA 2016). Because of the lack of specific studies on Hodgkin's lymphoma, the results of this study should be treated with caution and verified in any future examination of this association. The apparent absence of this cancer in males was inconsistent with the finding in females, but it could be the result of some unmeasured difference in exposure or biology. The lack of elevation in females of study area 2 was noticeable, and a simple explanation could be that EtO exposure has been much more concentrated in study area 1 than in study area 2, which is more than twice the size of study area 1 in terms of population and geographical size. Although SIR's failed to reach a significant level in study area 2, their values were relatively large, 1.29 and 1.31, when compared to the state and the county averages, respectively. Current understanding of risk factors for Hodgkin's lymphoma describes that men are slightly more likely to develop the disease; it's most common in early adulthood (20s) and after age 55, and an increased risk exists for those who have had infectious mononucleosis

(Epstein-Barr virus), HIV, those who use immune suppressing drugs, and siblings of a young person with the disease (ACS 2019).

The time period analysis of lymphoid cancer and the examination of pediatric cancer provide further evidence. Although a clear time trend was absent for most lymphohematopoietic cancers and breast cancer, non-Hodgkin's lymphoma in females was observed to be increasing over time and was observed to be significantly elevated for the most recent time period, 2009-2015, and non-Hodgkin's lymphoma in males was borderline significant for the earliest time period, 1995-2001. These patterns were consistent across study areas. Non-Hodgkin's lymphoma has been frequently linked to EtO exposure by prior occupational studies (Steenland, Whelan et al 2004 and Steenland, Stayner et al 2003).

Pediatric lymphoma was observed to be significantly higher than expected in females of both study areas. Known risk factors for pediatric lymphoma are gender (boys), race (white), immune deficiency syndromes at birth, immune suppressing medications, infectious mononucleosis (Epstein-Barr virus), HIV/AIDS, and radiation exposure. Lymphoma has been shown to be associated with EtO exposure in adult occupational studies (Steenland, Whelan et al 2004 and Steenland, Stayner et al 2003). No previous studies have examined this association in children. In this assessment, the elevation was observed only in females, a pattern that seems to be congruent with the adult gender difference found in this study.

In addition to lymphohematopoietic and breast cancers, this study examined a number of other common cancer sites and found increases in several of them. These

results should be viewed with an abundance of caution, as none of these sites have yet been reported by previous studies as having an association with EtO exposure. Likewise, decreases observed in a few cancer sites should not be interpreted as a possible protective effect of EtO. It was observed that increases and decreases were quite consistent across the two reference populations. On the other hand, large and inconsistent changes seemed to exist between study areas, probably reflecting differences in distributions of cancer risk factors and screening practices. A brief review of each of the statistically significant site-specific findings and risk factors is below.

- Prostate cancer was observed to be high in both study areas. Current understanding of the risk of prostate cancer suggest that age, race, geography, and family history are important risk factors in the development of the disease. Screening availability and utilization may also play a role in the differences observed (ACS 2019).
- Pancreatic cancer incidence in females was high in both study areas. Risk factors for the development of pancreatic cancer include: smoking, age (>60), chronic pancreatitis, diabetes, obesity, poor diet, and genetic factors (ACS 2019).

- Females in study area 1 displayed a higher than expected incidence of bladder cancer. Risk factors for bladder cancer include smoking, exposure to aromatic amines, certain medicines and herbal supplements, arsenic in drinking water, not drinking enough fluids, race (white), gender (male), age (>55), chronic bladder irritation or infections, prior bladder or urothelial cancer, bladder birth defects, family history of bladder cancer and chemotherapy or radiation therapy (ACS 2019).
- Ovarian cancer was observed to be higher in study area 1. Ovarian cancer is in association with: age (>65), obesity, not having children or having them after age 35, fertility treatment, post-menopausal hormone therapy, family history, and hereditary genetic mutations and syndromes (ACS 2019).
- Lung cancer incidence was observed to be lower than expected in study area 2 in men and women. In study area 1, lung cancer was also low among females, but the difference was not statistically significant. Lung cancer is strongly associated with tobacco use (ACS 2019). DuPage County has some of the lowest smoking rates in the state (IDPH-BRFSS 2017).
- Females in study area 1 displayed lower than expected incidence of leukemia. This finding was surprising given that EtO exposure has been noted in prior studies to be associated with an increase in lymphocytic leukemia, a sub-set of leukemia. Factors that may increase the risk of developing leukemia include prior cancer treatment, genetic disorders, exposure to certain chemicals (benzene), smoking, and a family history of the disease (ACS 2015).

The present assessment has several significant limitations that need to be considered. First, with more than 400 age, sex, cancer site, study area, and reference group combinations being compared, it is highly likely that the process may produce some 'false significant values' by chance. In statistical terms, this is called the multiple comparison problem. The more comparisons made, the more pronounced the problem is. Clearly, simultaneously examining many cancer sites and employing more than one reference and study area would exacerbate the problem. The potential consequence is that chance occurrences cannot be ruled out in explaining differences between the observed and expected numbers. The confidence interval was set at 95%, which means that there was a one out of 20 chance that a finding could be a false positive. Although the level could be adjusted to potentially reduce false positives, the use of 95% confidence intervals in the study was appropriate as the purpose of the study was to screen as many cancer differences as possible.

Second, due to the lack of annual population data from the Census for both of the study areas, the 2000 and 2010 Census population numbers were used in interpolating and extrapolating population counts for non-census years. These imprecise denominator numbers, when used to derive sex-specific expected numbers, might have introduced errors and biases into the comparison, of which neither the direction nor the magnitude was known.

Third, many potential risk factors for cancer, including occupational exposure, smoking, diet, lifestyle, family history, and other medical conditions, are not collected by the current registry system and, as a result, their inclusion for analysis was not possible.

The Willowbrook community is close to interstate highways and motor vehicle fuel exhaust is a known source of EtO. Living in a study area at the time of diagnosis was used to represent potential exposure to EtO, but it was a very crude proxy because a cancer patient could have either left or moved into the study area right after or before their cancer diagnosis, resulting in either a case under-count or a case over-count. This lack of individual-level information on the history of residence and other risk factors for cases in the study areas and the reference population made more refined analysis and comparison impossible. The EPA air sampling and modeling of EtO exposure in the area provided critical information for the study areas to be appropriately defined, but even with this information, data on actual exposure in individuals was non-existent. There is considerable uncertainty about the length and the level of exposure to EtO that each individual in Willowbrook, and surrounding areas, may have actually experienced in the past. Any observed increase, in and of itself, is insufficient to draw conclusions regarding the potential impact of EtO exposure. Cancers are diseases of complex etiology often with a number of risk factors, and this may particularly be true for common cancers such as female breast cancer.

Finally, small numbers could lead to unstable SIR's and decreased statistical power to detect true differences. The total cancer cases (study area 1 N=4,534 and study area 2 N=9,416) seemed to be adequate for overall analyses in this assessment. However, in by-group analysis, such as with the time-period or pediatric cancer comparisons, some SIR's were based on small numbers that were often less than 10. These SIR's could have large swings in values and should not be given too much weight as a result. The direct consequence of small numbers would be the lack of

statistical power for the study to identify a difference when indeed a true difference existed. The problem could be further amplified by the presence of the study's other limitations (e.g., imprecise measures of EtO exposure and lack of measures on other risk factors), resulting in false negative findings.

In conclusion, this cancer assessment examined a number of cancer sites that included cancers that have a recognized association with EtO (lymphohematopoietic and breast cancers), and other common cancer sites that have no such association with EtO, in both adult and pediatric surrounding the Sterigenics facility in Willowbrook, Illinois, over the years 1995 through 2015. For lymphohematopoietic and breast cancers the study found increases in Hodgkin's lymphoma, and in recent years, non-Hodgkin's lymphoma. Pediatric lymphoma was also elevated during the study period. For other common cancer sites, the study found increased cancer in prostate for males, and increased cancers of the pancreas, ovary, and bladder in females. However, many apparent differences and inconsistences existed between genders, across study areas, and among cancer sites. A number of limitations in methodology and data also exist. Future studies with larger populations and preferably involving multiple EtO emissions sites are strongly recommended to confirm this assessment's findings.

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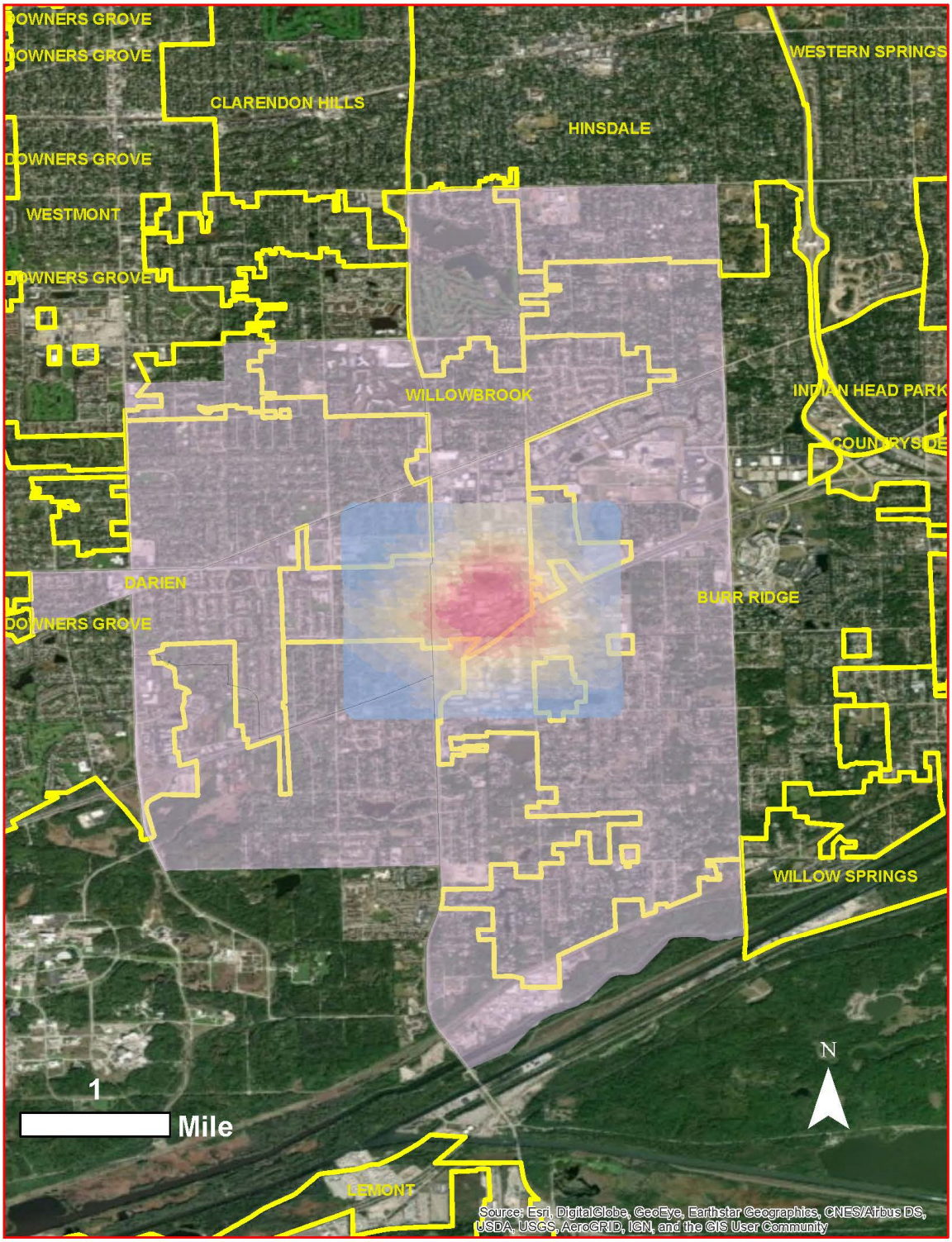
Table 1: 2010 Census Tracts Comprising Study Area 1 and Study Area 2

Study Area 1	**Study Area 2**	
8454.01	8454.01	8455.07
8454.02	8454.02	8455.08
8459.01	8459.01	8458.03
8459.02	8459.02	8458.10
8458.05	8455.02	8458.11
8458.10	8455.10	8458.05
8458.11	8455.09	8202.01
8455.07	8455.06	8201.01
8455.08	8455.05	

Source: U.S. Census Bureau

Map 1: Municipal Boundaries, Study Area 1, and EPA Modeled EtO Exposure



Map 2: Municipal Boundaries, Study Area 2, and EPA Modeled EtO Exposure

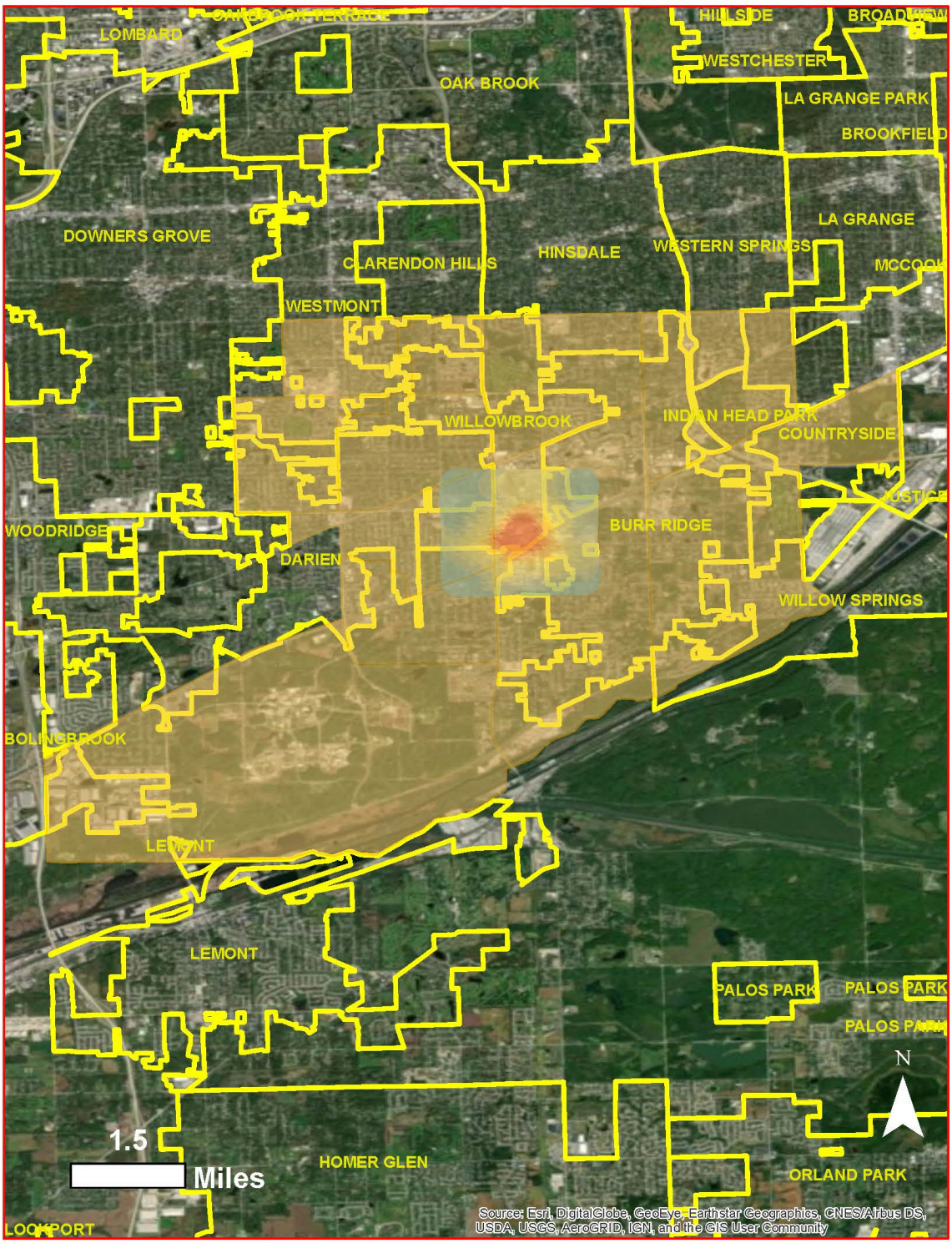


Table 2: Demographic Comparison of Referent Groups and Study Areas, 2010 Census

	Study Area 1	Study Area 2	State* Referent	County** Referent
Total Population	31,808	72,029	3,121,975	916,924
% White	81.0%	78.3%	77.5%	77.9%
% Black	3.4%	6.3%	6.4%	4.6%
% Hispanic	6.2%	7.4%	18.0%	13.3%
% >50	44.7%	41.5%	29.2%	32.1%
Males	47.6%	47.3%	49.6%	49.0%

Source: 2010 Census Summery File 1 accessed through American Fact Finder https://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml

*State referent includes Lake, McHenry, Kane, DuPage and Will counties

**County referent includes DuPage County

Table 3: Standardized Incidence Ratios for Lymphohematopoietic and Female Breast Cancers by Gender, Study Area and Referent Group*, 1995-2015

	County Referent**					State Referent*				
	Obs.	Exp.	SIR	95% LCI	95% UCI	Obs.	Exp.	SIR	95% LCI	95% UCI
STUDY AREA 1										
Males										
Non-Hodgkin's Lymphoma	108	99.63	1.08	0.89	1.31	108	99.63	1.08	0.89	1.31
Hodgkin's Lymphoma	7	11.82	0.59	0.24	1.22	7	11.62	0.60	0.24	1.24
Myeloma	28	28.69	0.98	0.65	1.41	28	28.69	0.98	0.65	1.41
Lymphocytic Leukemia	34	31.52	1.08	0.75	1.51	34	31.52	1.08	0.75	1.51
Females										
Invasive Breast	747	710.76	1.05	0.98	1.13	**747**	**680.60**	**1.10**	**1.02**	**1.18**
Non-Hodgkin's Lymphoma	95	88.87	1.07	0.86	1.31	95	89.16	1.07	0.86	1.30
Hodgkin's Lymphoma	**19**	**10.20**	**1.86**	**1.12**	**2.91**	**19**	**10.06**	**1.89**	**1.14**	**2.95**
Myeloma	23	24.72	0.93	0.59	1.40	23	25.50	0.90	0.57	1.35
Lymphocytic Leukemia	19	24.01	0.79	0.48	1.24	19	22.71	0.84	0.50	1.31
STUDY AREA 2										
Males										
Non-Hodgkin's Lymphoma	222	205.91	1.08	0.94	1.23	222	204.71	1.10	0.95	1.24
Hodgkin's Lymphoma	19	24.90	0.76	0.46	1.19	19	24.45	0.78	0.47	1.21
Myeloma	62	59.08	1.05	0.80	1.35	62	58.89	1.10	0.81	1.35
Lymphocytic Leukemia	69	65.97	1.05	0.81	1.32	69	71.19	1.00	0.75	1.23
Females										
Invasive Breast	1,548	1,507.88	1.03	0.98	1.08	**1,548**	**1,444.64**	**1.07**	**1.02**	**1.13**
Non-Hodgkin's Lymphoma	208	190.61	1.09	0.95	1.25	208	191.11	1.09	0.95	1.25
Hodgkin's Lymphoma	30	23.32	1.29	0.87	1.84	30	22.86	1.31	0.89	1.87
Myeloma	58	52.97	1.09	0.83	1.42	58	54.53	1.06	0.81	1.37
Lymphocytic Leukemia	40	52.06	0.77	0.55	1.05	40	49.24	0.81	0.58	1.11

Note: SIR's in bold indicate statistically significant differences at the $p<0.05$ level

* State Referent group includes Lake, McHenry, Kane, DuPage, and Will counties.

**County Referent is DuPage County

Source: Illinois State Cancer Registry, data as of November 2017

Table 4: Standardized Incidence Ratios for Other Common Cancer Site by Gender and Referent Group*, Study Area 1, 1995-2015

	County Referent**					State Referent*				
	Obs.	Exp.	SIR	95% LCI	95% UCI	Obs.	Exp.	SIR	95% LCI	95% UCI
Males										
Oral Cavity	65	62.57	1.04	0.80	1.32	65	64.53	1.01	0.78	1.28
Esophagus	36	35.03	1.03	0.72	1.42	36	35.90	1.00	0.70	1.39
Stomach	32	40.06	0.80	0.55	1.13	32	39.86	0.80	0.55	1.13
Colorectal	203	221.41	0.92	0.80	1.05	203	227.88	0.89	0.77	1.02
Liver	28	30.76	0.91	0.60	1.32	28	30.90	0.91	0.60	1.31
Pancreas	48	59.81	0.80	0.59	1.06	48	60.46	0.79	0.59	1.05
Lung	273	293.59	0.93	0.82	1.05	273	308.62	0.88	0.78	1.00
Bone	7	3.77	1.86	0.74	3.83	7	3.87	1.81	0.72	3.73
Melanoma	91	83.10	1.10	0.88	1.34	91	86.45	1.05	0.85	1.29
Testis	25	19.46	1.28	0.83	1.90	25	19.09	1.31	0.85	1.93
Prostate	**680**	**629.79**	**1.08**	**1.00**	**1.16**	**680**	**623.24**	**1.09**	**1.01**	**1.18**
Bladder	162	165.97	0.98	0.83	1.14	162	167.31	0.97	0.82	1.13
Kidney	98	84.10	1.17	0.95	1.42	98	88.72	1.10	0.90	1.35
Nervous System	29	33.12	0.88	0.59	1.26	29	31.13	0.93	0.62	1.34
Leukemia	68	66.37	1.02	0.80	1.30	68	70.90	0.96	0.74	1.22
All Other Sites	230	207.43	1.11	0.97	1.26	230	213.22	1.08	0.94	1.23

Note: SIR's in bold indicate significance at the $p<0.05$ level

* State Referent group includes Lake, McHenry, Kane, DuPage, and Will counties.

**County Referent is DuPage County

Source: Illinois State Cancer Registry, data as of November 2017

Table 4 (cont.): Standardized Incidence Ratios for Other Common Cancer Site by Gender and Referent Group*, Study Area 1, 1995-2015

	County Referent**					State Referent*				
	Obs.	Exp.	SIR	95% LCI	95% UCI	Obs.	Exp.	SIR	95% LCI	95% UCI
Females										
Oral Cavity	30	32.03	0.94	0.63	1.34	30	32.01	0.94	0.63	1.34
Esophagus	17	11.91	1.43	0.83	2.28	17	10.91	1.56	0.91	2.50
Stomach	23	25.44	0.90	0.57	1.36	23	25.42	0.90	0.57	1.36
Colorectal	218	215.46	1.01	0.88	1.16	218	221.25	0.99	0.86	1.13
Liver	16	13.37	1.20	0.68	1.94	16	12.79	1.25	0.71	2.03
Pancreas	**77**	**58.74**	**1.31**	**1.03**	**1.64**	**77**	**59.72**	**1.29**	**1.02**	**1.61**
Lung	262	270.36	0.97	0.86	1.09	262	295.00	0.89	0.78	1.00
Bone	1	3.37	0.30	0.00	1.65	1	2.93	0.34	0.00	1.90
Melanoma	57	59.22	0.96	0.73	1.25	57	63.35	0.90	0.68	1.17
Cervix	23	26.66	0.86	0.55	1.29	23	29.96	0.77	0.49	1.15
Uterus	147	149.82	0.98	0.83	1.15	147	145.35	1.01	0.85	1.19
Ovary	**84**	**67.01**	**1.25**	**1.00**	**1.55**	**84**	**65.16**	**1.29**	**1.03**	**1.60**
Bladder	**78**	**56.41**	**1.38**	**1.09**	**1.73**	**78**	**58.62**	**1.33**	**1.05**	**1.66**
Kidney	48	50.93	0.94	0.69	1.25	48	53.31	0.90	0.66	1.19
Nervous System	28	27.33	1.02	0.68	1.48	28	27.20	1.03	0.68	1.49
Leukemia	**38**	**54.80**	**0.69**	**0.49**	**0.95**	**38**	**53.95**	**0.70**	**0.50**	**0.97**
All Other Sites	282	265.95	1.06	0.94	1.19	282	264.54	1.07	0.95	1.20

Note: SIR's in bold indicate significance at the $p<0.05$ level

* State Referent group includes Lake, McHenry, Kane, DuPage, and Will counties.

**County Referent is DuPage County

Source: Illinois State Cancer Registry, data as of November 2017

Table 5: Standardized Incidence Ratios for Other Common Cancer Site by Gender and Referent Group*, Study Area 2, 1995-2015

	County Referent**					State Referent*				
	Obs.	**Exp.**	**SIR**	**95% LCI**	**95% UCI**	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**
Males										
Oral Cavity	120	129.04	0.93	0.77	1.11	120	133.10	0.90	0.75	1.08
Esophagus	74	71.99	1.03	0.81	1.29	74	73.75	1.00	0.79	1.26
Stomach	89	82.54	1.08	0.87	1.33	89	82.20	1.08	0.87	1.33
Colorectal	464	456.83	1.02	0.93	1.11	464	470.03	0.99	0.90	1.08
Liver	71	63.35	1.12	0.88	1.41	71	63.64	1.12	0.87	1.41
Pancreas	115	123.04	0.93	0.77	1.12	115	124.42	0.92	0.76	1.11
Lung	**551**	**603.09**	**0.91**	**0.84**	**0.99**	**551**	**633.77**	**0.87**	**0.80**	**0.95**
Bone	11	7.93	1.39	0.69	2.48	11	8.12	1.36	0.68	2.42
Melanoma	195	172.09	1.13	0.98	1.30	195	178.92	1.09	0.94	1.25
Testis	44	41.58	1.06	0.77	1.42	44	40.73	1.08	0.78	1.45
Prostate	**1,367**	**1,286.83**	**1.06**	**1.01**	**1.12**	**1,367**	**1273.57**	**1.07**	**1.02**	**1.13**
Bladder	335	341.67	0.98	0.88	1.09	335	344.51	0.97	0.87	1.08
Kidney	189	173.30	1.09	0.94	1.26	189	182.82	1.03	0.89	1.19
Nervous System	62	69.21	0.90	0.69	1.15	62	65.03	0.95	0.73	1.22
Leukemia	135	138.30	0.98	0.82	1.16	135	147.47	0.92	0.77	1.08
All Other Sites	467	429.73	1.09	0.99	1.19	467	441.46	1.06	0.96	1.16

Note: SIR's in bold indicate significance at the $p<0.05$ level

* State Referent group includes Lake, McHenry, Kane, DuPage, and Will counties.

**County Referent is DuPage County

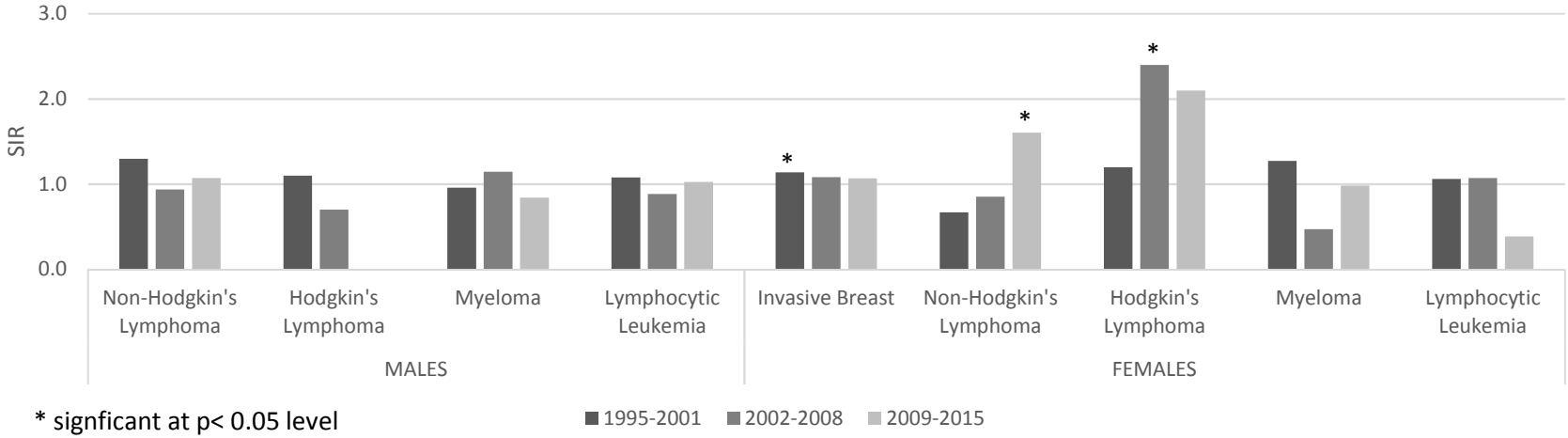
Source: Illinois State Cancer Registry, data as of November 2017

Table 5 (cont.): Standardized Incidence Ratios for Other Common Cancer Sites by Gender and Referent Group, Study Area 2, 1995-2015

	County Referent**					State Referent*				
	Obs.	**Exp.**	**SIR**	**95% LCI**	**95% UCI**	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**
Females										
Oral Cavity	68	68.29	1.00	0.77	1.26	68	68.25	1.00	0.77	1.26
Esophagus	23	25.51	0.90	0.57	1.35	23	23.32	0.99	0.62	1.48
Stomach	61	54.86	1.11	0.85	1.43	61	54.85	1.11	0.85	1.43
Colorectal	483	463.03	1.04	0.95	1.14	483	475.75	1.02	0.93	1.11
Liver	24	28.66	0.84	0.54	1.25	24	27.42	0.88	0.56	1.30
Pancreas	**151**	**126.10**	**1.20**	**1.01**	**1.40**	**151**	**128.22**	**1.18**	**1.00**	**1.38**
Lung	541	575.21	0.94	0.86	1.02	**541**	**627.67**	**0.86**	**0.79**	**0.94**
Bone	3	7.44	0.40	0.08	1.18	3	6.49	0.46	0.09	1.35
Melanoma	114	128.00	0.89	0.73	1.07	114	136.53	0.83	0.69	1.00
Cervix	52	57.62	0.90	0.67	1.18	52	64.93	0.80	0.60	1.05
Uterus	322	315.45	1.02	0.91	1.14	322	306.07	1.05	0.94	1.17
Ovary	152	142.80	1.06	0.90	1.25	152	138.92	1.09	0.93	1.28
Bladder	140	121.13	1.16	0.97	1.36	140	125.64	1.11	0.94	1.31
Kidney	98	108.51	0.90	0.73	1.10	98	113.58	0.86	0.70	1.05
Nervous System	57	58.98	0.97	0.73	1.25	57	58.72	0.97	0.74	1.26
Leukemia	101	118.75	0.85	0.69	1.03	101	116.76	0.87	0.70	1.05
All Other Sites	582	573.88	1.01	0.93	1.10	582	571.07	1.02	0.94	1.11

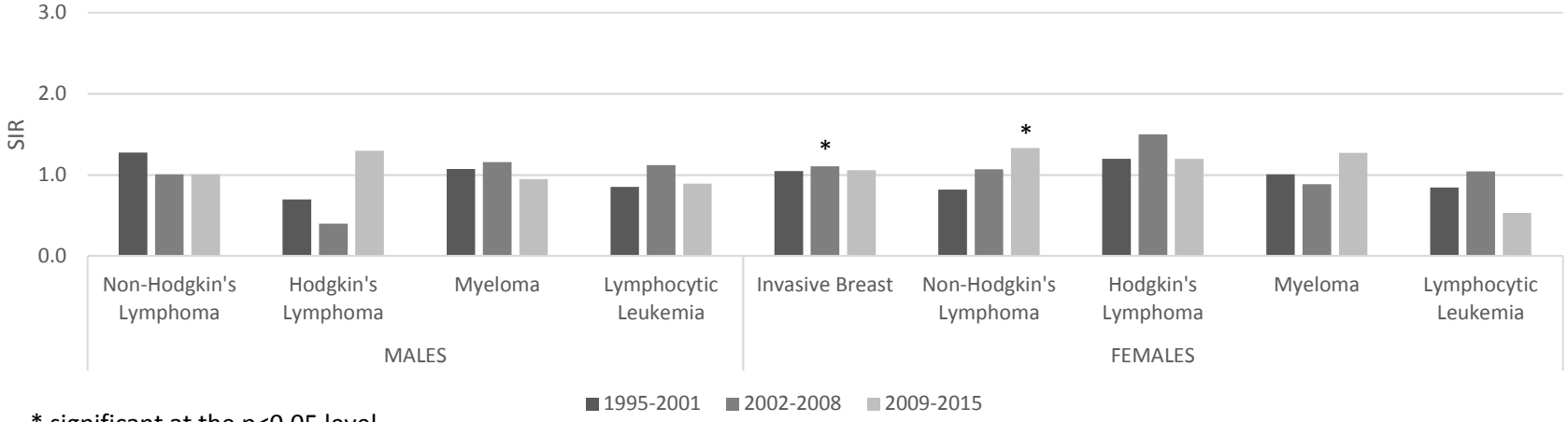
Note: SIR's in bold indicate significance at the p<0.05 level
* State Referent group includes Lake, McHenry, Kane, DuPage, and Will counties.
**County Referent is DuPage County
Source: Illinois State Cancer Registry, data as of November 2017

Figure 1: Temporal Trends in EtO Related SIR's by Gender and Site, Study Area 1, State Referent, 1995-2015



* signficant at p< 0.05 level

Figure 2: Temporal Trends in EtO Related SIR's by Gender and Site, Study Area 2, State Referent, 1995-2015



* significant at the p<0.05 level

Table 7: Pediatric Cancer Standardized Incidence Ratios for Study Area 1 and 2 by Gender, State Referent Group*, <20 years old, 1995-2015

STATE REFERENT	Study Area 1					Study Area 2				
	Obs.	Exp.	SIR	95% LCI	95% UCI	Obs.	Exp.	SIR	95% LCI	95% UCI
Males										
Leukemia	3	4.26	0.70	0.14	2.06	9	9.65	0.93	0.43	1.77
Lymphomas	5	2.69	1.86	0.60	4.34	7	5.69	1.23	0.49	2.54
Central Nervous System	1	2.48	0.40	0.01	2.24	2	5.50	0.36	0.04	1.31
Neuroblastomas	0	0.58	0.00	---	---	2	1.41	1.42	0.16	5.13
Retinoblastoma	0	0.16	0.00	---	---	0	0.41	0.00	---	---
Renal Tumors	0	0.38	0.00	---	---	0	0.91	0.00	---	---
Hepatic Tumors	0	0.17	0.00	---	---	1	0.40	2.50	0.03	13.90
Bone	2	0.93	2.14	0.24	7.73	3	1.95	1.54	0.31	4.50
Soft tissue	0	0.98	0.00	---	---	1	2.18	0.46	0.01	2.56
Germ Cell Tumors	0	1.60	0.00	---	---	1	3.33	0.30	0.00	1.67
Other malignant melanomas	1	1.09	0.92	0.01	5.10	4	2.26	1.77	0.48	4.52
Other unspecified	0	0.03	0.00	---	---	0	0.06	0.00	---	---
Not Classified	0	0.03	0.00	---	---	0	0.07	0.00	---	---
Females										
Leukemia	5	3.20	1.56	0.50	3.64	5	7.29	0.69	0.22	1.60
Lymphomas	**7**	**2.36**	**2.96**	**1.19**	**6.11**	**11**	**4.98**	**2.21**	**1.10**	**3.96**
Central Nervous System	3	2.10	1.43	0.29	4.17	4	4.67	0.86	0.23	2.19
Neuroblastomas	0	0.53	0.00	---	---	0	1.25	0.00	---	---
Retinoblastoma	0	0.18	0.00	---	---	0	0.43	0.00	---	---
Renal Tumors	0	0.65	0.00	---	---	0	1.55	0.00	---	---
Hepatic Tumors	1	0.12	8.42	0.11	46.87	1	0.28	3.59	0.05	19.95
Bone	0	0.82	0.00	---	---	0	1.72	0.00		
Soft tissue	3	0.98	3.07	0.62	8.96	3	2.11	1.42	0.29	4.15
Germ Cell Tumors	1	0.78	1.29	0.02	7.18	3	1.64	1.83	0.37	5.34
Other malignant melanomas	2	2.67	0.75	0.08	2.71	9	5.50	1.64	0.75	3.10
Other unspecified	0	0.03	0.00	---	---	0	0.06	0.00	---	---
Not Classified	0	0.01	0.00	---	---	0	0.02	0.00	---	---

Note: SIR's in bold indicate significance at the p<0.05 level

* State Referent group includes Lake, McHenry, Kane, DuPage, and Will counties.

Source: Illinois State Cancer Registry, data as of November 2017
Site/Histology Recode Based on International Classification of Childhood Cancer, third Edition (ICCC-3) Based on ICD-O-3 / WHO 2008

APPENDIX A: Standardized Incidence Ratio and Confidence Limits

Various authors discuss the standardized mortality ratio (SMR) and provide exact and approximate confidence limits for the true SMR. These results are also applicable to the standardized incidence ratio (SIR). The following sections provide a brief outline of the results and give references to more detailed discussions.

Definition of the SIR

Suppose the person-time from the study group (i.e. cohort) is allocated among *M* cells defined by the cross-classification of various adjustment variables such as gender, race, attained age group, and attained calendar year group. Let *tk* represent the person-time and *Dk* represent the observed events that the cohort subjects contribute to the *k*th cell, and let λ_k^* represent the standard rate for the *k*th cell, where *k* = 1, 2, ..., *M*. Given this notation, the SIR is defined as

$$\mathrm{SIR} = \frac{\sum_{k=1}^{M} D_k}{\sum_{k=1}^{M} t_k \lambda_k^*} = \frac{D}{E^*}$$

where the total number of events observed in the cohort is $D = \sum_{k=1}^{M} D_k$, and the total number of expected events is $E^* = \sum_{k=1}^{M} E_k^* = \sum_{k=1}^{M} t_k \lambda_k^*$ (Breslow and Day,1987; Sahai and Khurshid,1996).

Approximate Confidence Limits for the True SIR

The approximate limits for the true SIR, *Φ*, are $\mathrm{SIR}_{\hat{L}} = \frac{D}{E^*}\left(1 - \frac{1}{9D} + \frac{Z_{\alpha/2}}{3\sqrt{D}}\right)^3$ and

$$\mathrm{SIR}_{\hat{U}} = \frac{D+1}{E^*}\left(1 - \frac{1}{9(D+1)} + \frac{Z_{1-\alpha/2}}{3\sqrt{D+1}}\right)^3$$

where *Zα* is the 100*α* percentile of the standard normal distribution (Rothman and Boice, 1979, 1982;

Breslow and Day, 1987; Sahai and Khurshid, 1993, 1996). Rothman and Boice (1979, 1982) mention that these limits were first proposed by Byar (unpublished).

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