Cancer Incidence near Two Facilities Utilizing Ethylene Oxide, Lake County, Ill., 1998-2017

A publication of the

Illinois Department of Public Health

Division of Epidemiological Studies

Springfield, Illinois 62761

November 19, 2021

Acknowledgements

This report would not have been possible without the diligent work of the Illinois State Cancer Registry staff, the personnel at the reporting facilities that diagnose or treat cancer patients throughout Illinois, and the staff members at other state central cancer registries with data exchange agreements.

This publication was supported by Cooperative Agreement Number NU58DP003883-05 from the U.S. Centers for Disease Control and Prevention (CDC) National Cancer Prevention and Control Program. The contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

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Abstract

Background: Following the completion of assessing cancer incidence in the area surrounding the Sterigenics facility in Willowbrook, Illinois, the Division of Epidemiologic Studies, Illinois Department of Public Health (IDPH), conducted an assessment of cancer incidence in the population surrounding two ethylene oxide (EtO) emitters, Medline and Vantage, in Lake County, Illinois. EtO is a known carcinogen.

Methods and Data: Cancer cases were obtained from the Illinois State Cancer Registry (ISCR) for diagnosis years 1998-2017. The study area was created based on 13 census tracts around the Medline and Vantage facilities and an air sampling/exposure model. Cases were geocoded into the study areas using a combination of GIS software and manual review. Two groups of cancers were examined. The first group included lymphohematopoietic cancers (non-Hodgkin lymphoma, Hodgkin lymphoma, myeloma, and lymphocytic leukemia) and female breast cancer. This is a group of cancers of high concern due to their documented association 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 populations as references.

Results: Among the first group of cancers, significantly elevated multiple myeloma cases in females were observed in the study area as compared to Lake County (SIR 1.54, CI 1.10-2.09) The increase became smaller and non-significant when compared to Cook County (SIR .28, CI 0.91-1.74). Trends in SIR's did not show clear patterns over time other than an apparent decline in Hodgkin lymphoma. For the second group

of cancers, sites observed to be elevated include male lung cancer, and female colorectal and stomach cancers. Also, female Hodgkin lymphoma was found to be significantly lower than expected, and bladder and melanoma cancers were observed to be lower in both males and females. Pediatric cancers were not observed to be elevated or depressed.

Discussion: This assessment found mixed results. For both groups of cancers, some cancers were elevated while others were depressed. Many apparent differences and inconsistences existed between genders, reference populations, and among cancer sites. This assessment has a number of limitations, including lack of information on other risk factors, imprecise exposure measures and population estimates, and the small numbers in the study area. Additional study of residential EtO exposure involving more sites and larger populations is recommended.

Background

In August 2018, the U. S. Environmental Protection Agency (U.S. EPA) released the 2014 National Air Toxics Assessment (NATA), which identifies areas of the country that may have an increased cancer risk based on emissions estimates for toxic compounds and screening level air quality modeling. The NATA identified the Waukegan-Gurnee area, in Lake County, Illinois, as potentially having elevated cancer risk, with ethylene oxide (EtO) identified as the predominant pollutant driving the elevated estimate (EPA 2018). This area contains a Medline Industries Inc. facility utilized for commercial sterilization, and a Vantage Specialties Inc. facility used for chemical manufacturing. These two facilities are separated by approximately 3 miles and are known emitters of EtO.

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 1940s. 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).

Following the Illinois Department of Public Health's (IDPH) investigation and release of a report about cancer incidence surrounding the Sterigenics facility in Willowbrook, DuPage County, concerned community residents reached out to the IDPH with questions about residential EtO exposure in the areas surrounding the Medline and Vantage facilities in Lake County. In response to the concern, IDPH has produced the following analysis to assess cancer incidence in the area surrounding the Vantage and Medline facilities.

Data Sources and Methods

The Illinois Environmental Protection Agency (IEPA) provided IDPH with modeled five-year average EtO exposure estimates for the area surrounding the Medline and Vantage facilities, which was used to define the cancer investigation's study area. It was observed to include 13 census tracts (Table 1, Map 1). Consideration was initially given to constructing two separate study areas for each facility. Given the proximity of the two facilities to one another (straight line distance of approximately 3.3 miles) and the presence of shared census tracts (8615.10 and 8626.03), it was decided to examine the two emitters under a single study area.

Cancer cases were identified through the Illinois State Cancer Registry (ISCR). All cancer cases from 1998 through 2017 were included in this assessment. This timeframe was selected because it represents the most recent and most complete years

of data in the registry that cover the operational period of the two facilities. It 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.

The cancer data were assigned to areas using geocoding. Geocoding is a process through which cancer cases are assigned to specific geographic locations. ISCR assigns a cancer patient's residential address, at the time of diagnosis, as the patient's geographic location. The geocoding process in this study was carried out in multiple steps using a series of computer programs (i.e., ArcGIS®, Accurint™, Google® Earth, and Google® Maps), and 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 1998-2017 were selected from six ZIP codes surrounding both the Vantage and Medline facilities (60087, 60083, 60031, 60085, 60064, and 60044) and prepared for additional examination. One hundred percent of cancer cases in the registry have a valid ZIP code, so this information was used to begin the process of assigning cases to census tracts. Of the 12,372 cases examined, 284 cases (2%) were not assigned a census tract after the first step in geocoding. All 284 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. Eighteen cases were found to be residents of other states and were excluded, 14 cases contained so little address information that a census tract could not be assigned, and 252 cases were eventually assigned a census tract. At the end of the process, a total of 32 (0.26%) cases were excluded. With this process finished, the selection of cancer cases for the specific census tracts was performed. A

majority of the geocoded cases fell outside of the 13 census tracts (N= 7,942). At the end of the process, a total of 4,430 cases were identified for the study area.

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). Out-of-state diagnoses among residents of the study area accounted for 3.3% of the total number of cases reported, between 1998 and 2017, and were included in the study. While identification of cancer cases in Illinois is dependent upon reporting by diagnostic and therapeutic facilities as mandated by state law, 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. To benchmark the performance of population-based cancer registries for data completeness, timeliness and quality, the North American Association of Central Cancer Registries (NAACCR) has developed a certification process to review registry data for completeness, accuracy, and timeliness of reporting. As of May 2020, ISCR data met the highest performance criteria for Gold Certification for cancer diagnosis years 1996 through 2017. The statewide completeness of case reporting from all reporting sources, assessed using the NAACCR standard, is estimated to be 100% complete for all years between 1995 and 2017. The criteria for Silver and Gold certification can be found on the NAACCR website at https://www.naaccr.org/certification-criteria/.

All cancer cases from the study area 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). For both observed and expected cases, two groups of cancer sites were considered 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 cancer group of concern was selected because of its documented associations with EtO exposure in scientific 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. This group included oral cavity, esophagus, stomach, colon and rectum, liver, pancreas, lung and bronchus, bone, melanoma, breast, cervix, uterus, ovary, prostate, testis, bladder, kidney, brain, nervous system, leukemia, thyroid, and all other cancers. This second group of tumor sites was examined to capture any other possible cancer increases and to help 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. 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/). The pediatric 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 routinely used reference groups (Cook County, five suburban 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 2 million. The two comparable populations for the study area of interest were deemed to be Lake County (referred to in this report as the Lake County referent) and Cook County (referred to in this report as the Cook County referent). Table 2 presents race, gender, ethnicity, and age distributions for the two reference populations and the study area.

Age- and sex-specific population counts for census tracts in Illinois for each year between 1998 and 2017 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 interpolate and extrapolate counts from the 2000 and 2010 census to other years. These estimates were then aggregated to form age- and sex-specific population figures for both 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 higher or lower than the expected cases, respectively. 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 true. The SIR, CI's, and resulting statistical significance are affected by the strength of the exposure, 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 20-year time period in question (1998-2017), SIR's from four five-year time periods, 1998-2002, 2003-2007, and 2008-2012, 2013-2017 were separately calculated for trends in adult EtO related cancer sites.

This by time-period analysis was 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 in the study area (Table 3). Significantly elevated myeloma cases in females were observed in the study area when compared to Lake County (Table 3). The observed cases of female myeloma were 54% higher in the study area than in Lake County (SIR 1.54, CI 1.10-2.09). This increase, however, became smaller (28%) and not statistically significant (SIR 1.28, CI 0.91-1.74) when the reference area was Cook County. Hodgkin lymphoma among females was significantly lower when compared to both reference counties (SIR 0.33, CI 0.11-0.78; SIR 0.35, CI 0.11-0.83). Significantly depressed SIR's were observed in invasive female breast cancer when compared to Lake County (SIR 0.91, CI 0.85-0.98), almost 10% lower than expected, but this depression on female breast cancer was not seen when the study area was compared to Cook County (SIR 0.99, CI 0.92-1.07).

Lymphohematopoietic and Female Breast Cancer Trends

Figure 1 displays the temporal trends in SIR's for lymphohematopoietic and female breast cancer for the study area, by four five-year time periods; 1998-2002, 2003-2007, 2008-2012 and 2013-2017. Since results were similar between the two reference populations, only results relative to the Cook County reference group are shown. No consistent trends in SIR were observed for any cancer site in men or women except for Hodgkin lymphoma where the SIR displayed a consistent and

decreasing trend in females over the time period examined. In addition, the case count also declined reaching zero cases in the last time period 2013-2017. When period and site-specific SIR's were examined for changes, the SIR in the first five-year interval for male lymphocytic leukemia was significantly elevated, but this elevation was not observed in subsequent time periods.

Other Cancer Sites

Males in the study area had a statistically significant increase in lung cancer when compared to Lake County (Table 4). Melanoma in males, however, was shown to be significantly lower in the study area as well as bladder cancers when compared to the Lake County reference group. When compared to Cook County the difference observed in melanoma was non-significant while bladder cancers were significantly lower. Females in the study area displayed significantly higher SIR's in stomach and colorectal cancers when compared to Lake County averages but not when compared to Cook County averages (Table 4). Two sites displayed significantly lower SIR's in females of the study area when compared to the Lake County average. However, melanoma and bladder cancer SIR's were in expected ranges when compared to the Cook County referent (Table 4).

Pediatric Cancers

An examination of childhood cancers, utilizing SIR's, did not reveal any pediatric cancer sites that were significantly different from either the Lake County or Cook County averages (Table 5). It should be noted that all individual pediatric sites had SIR's that were based on fewer than 10 observed cases in the study area and several sites recorded no cases.

Discussion

This cancer assessment used a single study area, two reference groups, and examined not only lymphohematopoietic and breast cancers, the cancers of concern due to their documented associations with EtO, 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 reference populations, and between cancer sites.

With respect to the EtO related cancer sites, we observed a single site being elevated above expected in female multiple myeloma when Lake County was used as the referent. This elevation, however, was accompanied by reductions in female breast cancer and Hodgkin lymphoma. This inconsistent pattern raised questions about the positive myeloma finding. Further, most of the changes became non-significant or disappeared when Cook County was used as the referent suggesting influence of the choice of reference group. Common risk factors for multiple myeloma include being greater than 65 years of age, female, Black, having a family history of the disease, and obesity. The Behavioral Risk Factor Surveillance System (BRFSS) estimated that between 2015 and 2019, 31.2% of Lake County residents were obese. This percentage was quite similar to that of Illinois as a whole with 31.6% of Illinois residents estimated to be obese (BRFSS 2019). With regard to racial composition, African American race and Hispanic ethnicity, were observed to be more prominent in the study area when compared to the Lake County referent group (Table 2). The change in the myeloma finding with the Cook County referent group, which provided a

closer approximation of the racial/ethnic makeup of the study area, suggested the confounding impact of the racial composition.

The time period analysis did not yield evidence of increasing trends overtime of lymphoid cancer sites. Outside of Hodgkin lymphoma, which displayed a decreasing trend over time, a clear time trend in SIR's was absent for lymphohematopoietic cancers and breast cancer. Pediatric cancer sites were not observed to be elevated. However, one cannot ignore the small case counts observed for these cancers. Small case counts can impact the sensitivity of the SIR to detect significant differences between the study area and referent populations.

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 inconsistent across the two reference populations. A brief review of each of the statistically significant site-specific findings and risk factors is below.

- Lung cancer incidence was observed to be significantly higher than expected in men of the study area when compared to the Lake County referent. Lung cancer is strongly associated with tobacco use (ACS 2021). Lake County has smoking rates similar to that of the state at roughly 9% of people currently smoking in 2019 (IDPH-BRFSS 2019). Other risk factors for lung cancer include exposure to radon gas, asbestos, prior radiation therapy to the lungs, air pollution, and a personal or family history of lung cancer (ACS 2021).
- Stomach cancer was observed to be significantly higher in females when compared to the Lake County. Risk factors for stomach cancer include being male; older age; minority race-ethnicity; *Helicobacter pylori* infection; being overweight or obese; diet high in processed, grilled, or charcoaled meats; three or more alcoholic drinks per day; tobacco use; previous stomach surgeries; some types of stomach polyps; pernicious anemia; Menetrier disease; hereditary syndromes; family history of stomach cancer; common variable immune deficiency (CVID); Epstein-Barr virus infection; type A blood; and occupational exposures in the metal, coal, and rubber industries (ACS 2021).
- Colorectal cancer was observed to be significantly elevated in females in the study area. Colorectal cancer is associated with older age, personal or family history of polyps or colorectal cancer, inflammatory bowel disease, inherited syndromes (e.g., Lynch syndrome), race (African American), ethnicity (Ashkenazi Jewish), Type 2 diabetes, being overweight or obese, sedentary lifestyle, diet high in red and processed meats, smoking, and moderate to heavy alcohol use (ACS 2021).

- The Illinois Department of Public Health had previously conducted a cancer incidence study in the population living close to the Sterigenics facility in Willowbrook, Illinois in DuPage County. The findings of that assessment are compared to those of this assessment (Table 6). Despite similar methodologies and data sources used, the two assessments did not offer clear convergence of evidence in specific cancer elevations. This could be related to several reasons, including possible differences in exposure, small sample size, population heterogeneity, and methodological limitations of this cancer assessment studies (see below).

The present assessment has several important limitations that need to be considered. First, with more than 200 age, sex, cancer site, 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 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 1 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 the study area, 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. Living in a study area at the time of diagnosis was a crude proxy for exposure to EtO. This is 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. Therefore, any observed increase, in and of itself, is insufficient to draw conclusions regarding the potential impact of EtO exposure. The air sampling and modeling of EtO exposure in the area did provide critical information for the study areas to be appropriately defined, and a recent study by Szwiec et. al. (2020) showed that people residing around the emission sources in question did display higher levels of EtO biomarkers in blood samples.

Finally, small numbers could lead to unstable SIR's and decreased statistical power to detect true differences. The total cancer cases (study area N=4,430) 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 several cancer sites that included cancers that have a recognized association with EtO (multiple myeloma), and other common cancer sites that have no such association with EtO, in adults surrounding the study area in Lake County, Illinois, over the years 1998 through 2017. For lymphohematopoietic and breast cancers, a cancer group of concern due to their documented EtO associations, the study found increase in multiple myeloma in females but no other sites. However, the simultaneous presence of other cancer sites displaying significant decreases raised valid questions about the overall finding regarding lymphohematopoietic and breast cancers, as a group. For other common cancer sites, the study found increased lung cancer for males, and increased cancers of the stomach and colon and rectum in females, but again, other cancers, such as bladder, showed decreases, and these differences were also reflected between genders. Several important limitations in methodology and data could be identified. Continuous tracking of the area's cancer incidence, with a particular focus on EtO related sites, and conducting more studies elsewhere with larger populations are recommended.

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Figures and Tables

Table 1: 2010 Census Tracts Comprising Lake County, Illinois Study Area

Study Area	
8615.04	8615.06
8626.04	8615.08
8626.05	8615.09
8615.10	8619.02
8626.03	8619.01
8628.00	8615.07
8632.01	

Source: U.S. Census Bureau

Map 1:Study Area and Modeled EtO Exposure

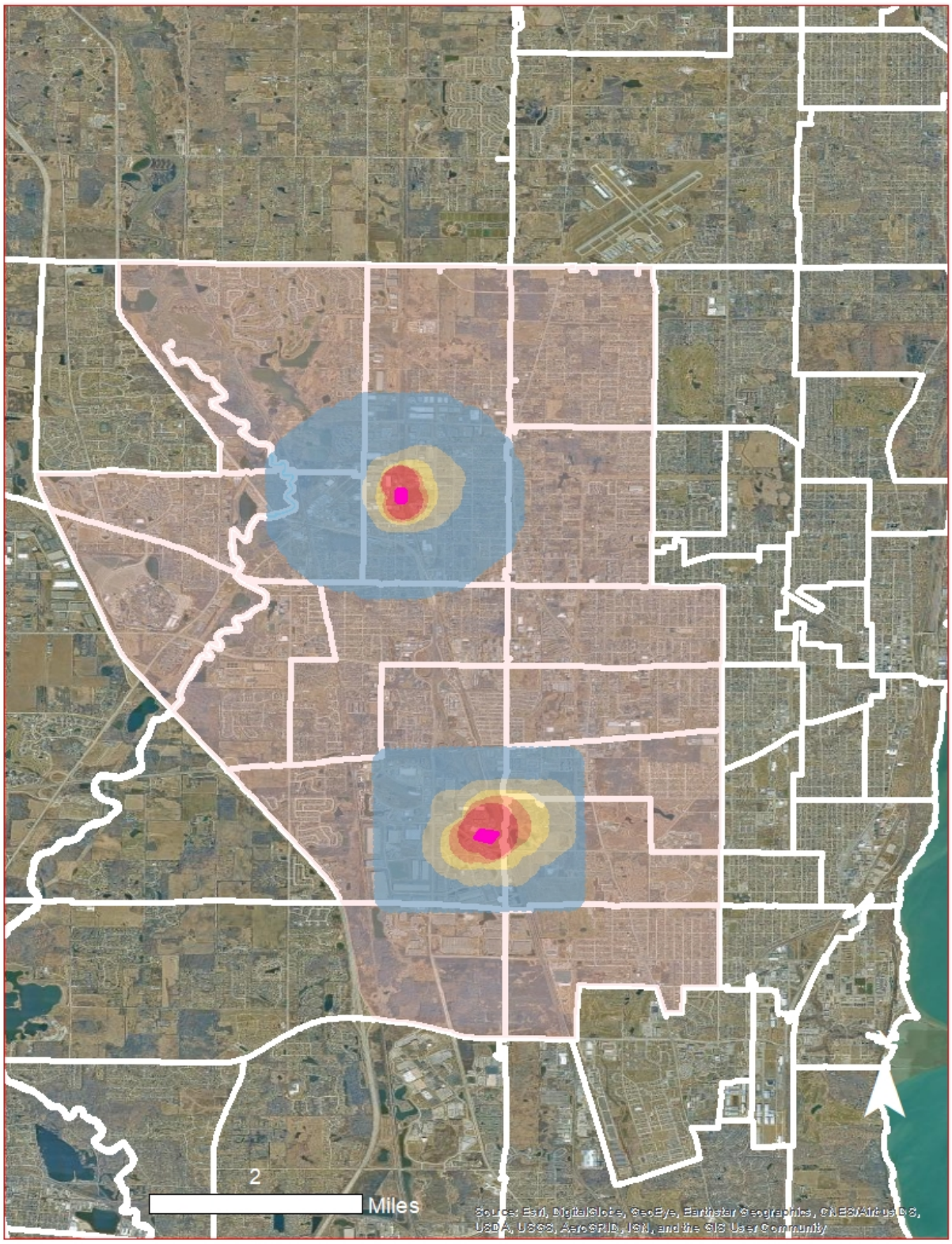

Table 2: Demographic Comparison of Referent Groups and Study Area, 2010 Census

	Study Area	Lake County Referent	Cook County Referent
Total Population	60,190	703,462	5,194,675
% White	51.4%	75.1%	55.4%
% Black	18.1%	7.0%	24.8%
% Hispanic	39.6%	19.9%	24.0%
% >50	24.5%	29.8%	30.0%
Males	48.9%	49.9%	48.4%

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

Table 3: Standardized Incidence Ratios for Lymphohematopoietic and Female Breast Cancers by Gender, Study Area, and Referent Groups, 1998-2017

	Lake County Referent					Cook County Referent				
STUDY AREA	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**
Males										
Non-Hodgkin Lymphoma	105	107.25	0.98	0.80	1.19	105	98.01	1.07	0.88	1.30
Hodgkin Lymphoma	15	16.50	0.91	0.51	1.50	15	18.11	0.83	0.46	1.37
Myeloma	30	26.64	1.13	0.76	1.61	30	33.78	0.89	0.60	1.27
Lymphocytic Leukemia	38	42.00	0.90	0.64	1.24	38	34.03	1.12	0.46	1.37
Females										
Invasive Breast	**683**	**747.73**	**0.91**	**0.85**	**0.98**	683	687.32	0.99	0.92	1.07
Non-Hodgkin Lymphoma	91	93.50	0.97	0.80	1.20	91	81.95	1.11	0.89	1.36
Hodgkin Lymphoma	**5**	**14.96**	**0.33**	**0.11**	**0.78**	**5**	**14.11**	**0.35**	**0.11**	**0.83**
Myeloma	**40**	**26.00**	**1.54**	**1.10**	**2.09**	40	31.27	1.28	0.91	1.74
Lymphocytic Leukemia	24	25.60	0.94	0.60	1.40	24	23.29	1.03	0.66	1.53

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

Source: Illinois State Cancer Registry, data as of November 2019

Table 4: Standardized Incidence Ratios for Other Common Cancer Sites by Gender and Referent Group, 1998-2017

	Lake County Referent					Cook County Referent				
STUDY AREA	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**
Males										
Oral cavity	72	70.09	1.03	0.80	1.29	72	80.28	0.90	0.70	1.13
Esophagus	28	33.38	0.84	0.56	1.21	28	36.05	0.78	0.52	1.12
Stomach	42	37.03	1.13	0.82	1.53	42	52.27	0.80	0.58	1.09
Colorectal	216	203.77	1.06	0.92	1.21	216	244.01	0.89	0.77	1.01
Liver	37	30.19	1.23	0.86	1.69	37	49.20	0.75	0.53	1.04
Pancreas	59	60.88	0.97	0.74	1.25	59	61.42	0.96	0.73	1.24
Lung	**306**	**246.03**	**1.24**	**1.11**	**1.39**	306	313.05	0.98	0.87	1.09
Bone	5	5.92	0.84	0.27	1.97	5	5.49	0.91	0.29	2.12
Melanoma	**63**	**111.77**	**0.56**	**0.43**	**0.72**	63	67.54	0.93	0.72	1.19
Invasive Breast	2	5.86	0.34	0.04	1.23	2	5.86	0.34	0.04	1.23
Testis	25	33.73	0.74	0.48	1.09	25	30.15	0.83	0.54	1.22
Prostate	579	557.01	1.04	0.96	1.13	579	624.76	0.93	0.85	1.01
Bladder	**76**	**153.59**	**0.49**	**0.39**	**0.62**	**76**	**127.99**	**0.59**	**0.47**	**0.74**
Kidney	109	97.00	1.12	0.92	1.36	109	93.01	1.17	0.96	1.41
Nervous system	26	36.74	0.71	0.46	1.04	26	33.71	0.77	0.50	1.13
Leukemia	79	80.32	0.98	0.78	1.23	79	71.19	1.11	0.88	1.38
All other sites	216	212.26	1.02	0.89	1.16	216	230.13	0.94	0.82	1.07

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

Source: Illinois State Cancer Registry, data as of November 2019

Table 4 (cont.): Standardized Incidence Ratios for Other Common Cancer Site by Gender and Referent Group, Study Area, 1998-2017

	Lake County Referent					Cook County Referent				
	Obs.	Exp.	SIR	95% LCI	95% UCI	Obs.	Exp.	SIR	95% LCI	95% UCI
Females										
Oral Cavity	36	34.30	1.05	0.73	1.45	36	33.98	1.06	0.74	1.47
Esophagus	9	10.21	0.88	0.40	1.67	9	11.75	0.77	0.35	1.45
Stomach	**43**	**26.35**	**1.63**	**1.18**	**2.20**	43	34.13	1.26	0.91	1.70
Colorectal	**251**	**193.01**	**1.30**	**1.14**	**1.47**	251	225.10	1.12	0.98	1.26
Liver	17	11.86	1.43	0.83	2.29	17	17.92	0.95	0.55	1.52
Pancreas	63	58.01	1.09	0.83	1.39	63	61.98	1.02	0.78	1.30
Lung	301	276.02	1.09	0.97	1.22	301	273.78	1.10	0.98	1.23
Bone	5	3.74	1.34	0.43	3.12	5	4.45	1.12	0.36	2.62
Melanoma	**65**	**96.97**	**0.67**	**0.52**	**0.85**	65	52.82	1.23	0.95	1.57
Cervix	42	36.81	1.14	0.82	1.54	42	56.87	0.74	0.53	1.00
Uterus	139	150.71	0.92	0.78	1.09	139	152.07	0.91	0.77	1.08
Ovary	65	66.70	0.97	0.75	1.24	65	69.05	0.94	0.73	1.20
Bladder	**37**	**56.49**	**0.65**	**0.46**	**0.90**	37	47.78	0.77	0.55	1.07
Kidney	56	51.48	1.09	0.82	1.41	56	57.07	0.98	0.74	1.27
Nervous system	36	33.78	1.07	0.75	1.48	36	27.79	1.30	0.91	1.79
Leukemia	64	60.37	1.06	0.82	1.35	64	55.20	1.16	0.89	1.48
All other sites	292	285.02	1.02	0.91	1.15	292	274.11	1.07	0.95	1.19

Note: SIR's in bold indicate significance at the p<=0.05 level
Source: Illinois State Cancer Registry, data as of November 2019

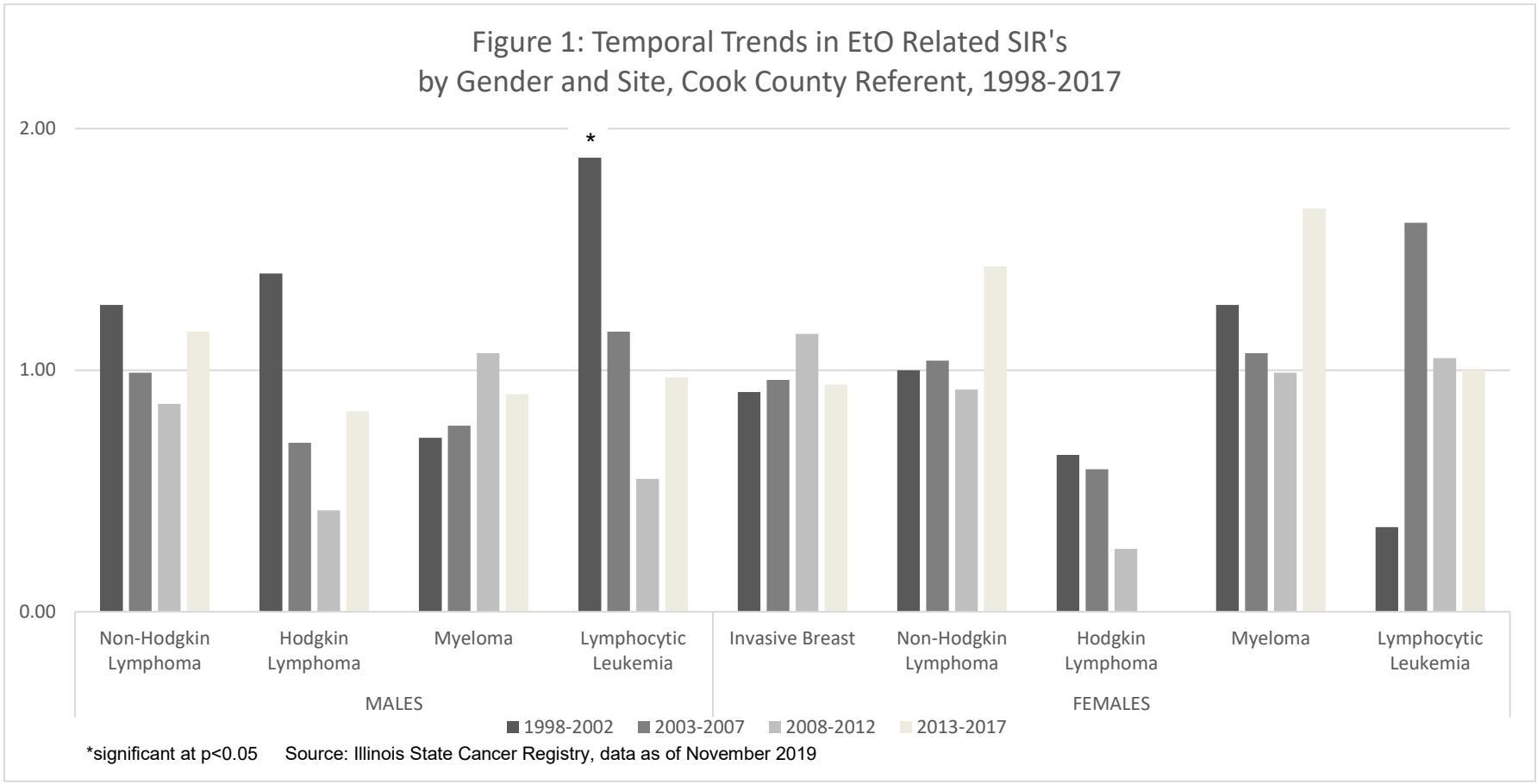
Figure 1: Temporal Trends in EtO Related SIR's
by Gender and Site, Cook County Referent, 1998-2017
2.00
1.00
0.00
*
Non-Hodgkin Lymphoma
Hodgkin Lymphoma
Myeloma
Lymphocytic Leukemia
Invasive Breast
Non-Hodgkin Lymphoma
Hodgkin Lymphoma
Myeloma
Lymphocytic Leukemia
MALES
FEMALES
1998-2002
2003-2007
2008-2012
2013-2017
*significant at p<0.05
Source: Illinois State Cancer Registry, data as of November 2019

Table 5: Pediatric Cancer Standardized Incidence Ratios for the Study Area by Gender, Referent Group, <20 years old, 1998-2017

	Lake County Referent					Cook County Referent				
STUDY AREA	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**	**Obs.**	**Exp.**	**SIR**	**95% LCI**	**95% UCI**
Males										
Leukemias	7	10.62	0.66	0.26	1.36	7	9.62	0.73	0.29	1.50
Lymphomas	6	4.59	1.31	0.48	2.85	6	5.14	1.17	0.43	2.54
Central nervous system	2	4.33	0.46	0.05	1.67	2	5.24	0.38	0.04	1.38
Neuroblastomas	4	2.55	1.57	0.42	4.02	4	1.74	2.30	0.62	5.89
Retinoblastoma	0	0.11				0	0.76			
Renal tumors	2	1.36	1.47	0.16	5.30	2	1.15	1.75	0.20	6.30
Hepatic tumors	0	0.21				0	0.38			
Bone	2	1.71	1.17	0.13	4.22	2	1.70	1.18	0.13	4.26
Soft tissue	2	2.21	0.91	0.10	3.27	2	2.46	0.81	0.09	2.93
Germ cell tumors	3	3.51	0.86	0.17	2.50	3	2.55	1.18	0.24	3.44
Other malignant melanomas	0	2.51				0	1.73			
Other unspecified	0	0.00				0	0.08			
Not classified	0	0.00				0	0.00			
Females										
Leukemias	9	6.26	1.44	0.66	2.73	9	8.13	1.11	0.51	2.10
Lymphomas	1	3.94	0.25	0.00	1.41	1	3.34	0.30	0.00	1.67
Central nervous system	9	5.64	1.60	0.73	3.03	9	5.15	1.75	0.80	3.32
Neuroblastomas	2	1.24	1.61	0.18	5.81	2	1.43	1.40	0.16	5.04
Retinoblastoma	2	0.44	4.59	0.52	16.58	2	0.79	2.53	0.28	9.13
Renal tumors	1	1.94	0.51	0.01	2.86	1	1.33	0.75	0.01	4.18
Hepatic tumors	0	0.11				0	0.42			
Bone	0	1.24				0	1.36			
Soft tissue	5	2.01	2.49	0.80	5.81	5	2.12	2.36	0.76	5.51
Germ Cell tumors	1	1.43	0.70	0.01	3.90	1	1.78	0.56	0.01	3.12
Other malignant melanomas	3	6.69	0.45	0.09	1.31	3	4.15	0.72	0.15	2.11
Other unspecified	7	6.69	1.05	0.42	2.16	7	4.15	1.69	0.68	3.48
Not classified	0	0.00				0	0.02			

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

Source: Illinois State Cancer Registry, data as of November 2019

Site/Histology Recode Based on International Classification of Childhood Cancer, third Edition (ICCC-3) Based on ICD-O-3 / WHO 2008

Table 6: Comparison of Findings from Willowbrook and Lake County Investigations

Gender	Willowbrook*		Lake County	
	DuPage County Ref.	Collar Counties Ref.**	Lake County Ref.	Cook County Ref.
	Lymphohematopoietic and Breast Cancers			
Male	-	-	-	-
Female	**Hodgkin Lymphoma**	**Hodgkin Lymphoma** **Breast**	**Myeloma** *Breast* *Hodgkin Lymphoma*	*Hodgkin Lymphoma*
	Pediatric Cancers			
Male	-	-	-	-
Female	**Lymphoma**	**Lymphoma**	-	-
	Other Cancer Sites			
Male	**Prostate**	**Prostate**	**Lung** *Melanoma* *Bladder*	*Bladder*
Female	**Pancreas** **Ovary** **Bladder** *Leukemia*	**Pancreas** **Ovary** **Bladder** *Leukemia*	**Stomach** **Colorectal** *Melanoma* *Bladder*	-

*Study area 1 from the IDPH incidence investigation

**Collar Counties include Lake, McHenry, DuPage, Kane, and Will.

(http://dph.illinois.gov/sites/default/files/publications/sterigenicswillowbrookcancer-investigation-final_0.pdf)

NOTE: Sites indicated in bold type were significantly higher incidence (p<=.05)

Sites indicated in italics are significantly lower incidence (p<=.05)

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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