BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006713
Article Type:	Research
Date Submitted by the Author:	22-Sep-2014
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	natural gas manufacturing, community, ONCOLOGY

Historical Cancer Incidence and Mortality Assessment in an Illinois Community Proximal to a Former Manufactured Gas Plant

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Word count: 5,164 words

Abstract word count: (243 words)

Kewords: natural gas manufacturing, community, cancer incidence, epidemiology

ABSTRACT

Objectives: Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant in Champaign, IL. Thus, we compared historical rates of cancer in this area to comparison communities as well as with nationally standardized rates.

Design: Retrospective population-based community cancer assessment during 1990-2010

Setting: Champaign County, IL, and zip codes encompassing the location of the former manufactured gas plant to counties that were similar demographically.

Participants: Residents of the counties and zip codes studied between 1990-2010.

Main outcome measures: The relative risk (RR) and 95% confidence interval (CI) were used to compare cancer incidence and mortality in the areas near the gas compression site to the comparison counties. Standardized incidence ratios (SIR) were calculated to compare rates in the areas near the gas compression site to expected rates based on overall United States cancer rates.

Results: Total cancer mortality (RR = 0.91, 95% CI: 0.88-0.94) and incidence (RR = 0.95, 95% CI: 0.94-0.97) were reduced significantly in Champaign County versus the comparison counties. Similarly, a reduced rate of total cancer was observed in analyses by zip code (proximal to the former gas plant) when compared to either similar counties (RR = 0.89, 95% CI: 0.86-0.93) or national standardized rates of cancer (SIR = 0.88, 95% CI: 0.85-0.91).

Conclusions: This historical cancer assessment did not find an increased risk of total cancer or specific cancer types in communities near a former manufactured gas plant site.

Strength and limitations of this study:

- The validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program.
- Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law.
- A priori, we developed a systematic protocol for identifying comparable counties. We matched counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level) to control for confounding.
- Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors associated with cancer such as physical activity, family history of disease, or body mass index that may have influenced the results.
- The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected.

INTRODUCTION

The production of manufactured gas is widely considered one of the key developments in our industrial history, with an extensive chronology beginning in the late 1700s and spanning into the 1960s. Manufactured gas consisted largely of the gasification of coal, and less frequently, the combustion of other materials such as wood and oil. Historically, the manufactured gas industry grew significantly in the early 1800s due to the production of lighting for the progress and development of cities. However, later in the 19th century, this industry diversified into heating, refrigeration, and cooking. During the early to mid-20th century, the advent of natural gas obviated the gasification of coal, ultimately leading to the conversion or closure of manufactured gas plants. Pipelines transported natural gas directly from the well to gas distribution systems, and natural gas was considered more economical, efficient, and environmentally friendly. Most manufactured gas plants in the U.S. were terminated by1966 with few exceptions, and as a result of the manufactured gas demise, over 1,500 plant sites are suggested to remain dormant or vacant in the U.S. today.

Numerous health concerns have been raised regarding possible environmental exposures stemming from manufactured gas plant sites. Foremost among the concerns is that contamination and waste products from the manufacturing gas process leaked into the adjacent soil and groundwater, thus posing health risks in the nearby residential areas and communities [1]. The process of coal carbonization generates coal tar, which are complex mixtures of heterocyclic compounds, phenols, and polycyclic aromatic hydrocarbons (PAHs). Indeed, both volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs) from coal tar and petroleum products are derived from the coal gasification process [1]. The VOCs contain a mixture of BTEX, or benzene, toluene, ethylbenzene, and xylene isomers among other

compounds, while the SVOCs consist of a mixture of compounds, such as benzo(a)pyrene, benzo(e)pyrene, naphthalene, and 2-methyl naphthalene. In addition, principal component analyses have identified heavy metals at former manufactured gas plant sites [2, 3]. As a result of these gas process by-products, the U.S. Environmental Protection Agency (EPA) and other regulatory agencies have focused on assessing the potential for soil and groundwater contamination at former manufactured gas plant sites, as well as evaluating the potential for health risks among residents in nearby communities. The International Agency for Research on Cancer (IARC) lists many of the manufactured gas plant by-product compounds as known, probable, or possible carcinogens for specific cancers but the level and extent of community exposure to such compounds resulting from former manufactured gas plants is uncertain. Furthermore, sparse epidemiologic evidence exists on the potential public health risks associated with residing near former manufactured gas plant sites.

Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant on a 3.5 acre lot in northern Champaign, IL. The plant, in operation from 1887 until 1953, manufactured gas by heating coal. Coal tar and other production wastes were suggested to remain on site until the closing of the plant. AmerenIP has registered this site with the Illinois EPA under their Site Remediation Program. However, the potential long-term health effects of residents in the nearby community are unknown. Therefore, we conducted a historical cancer incidence and mortality assessment using publicly available cancer data and census tract information to evaluate the occurrence of cancer in the community where the former manufactured gas plant was located compared with other communities with and without former gas plants that have similar demographic and lifestyle characteristics. In

addition, we conducted standardized incidence analyses for Champaign County and the study zip codes using nationally representative cancer data.

METHODS

All data used in this study are publicly available. Specifically, the cancer incidence data were obtained from the Illinois Department of Public Health and from the Surveillance, Epidemiology, and End Results (SEER) Program, while cancer mortality data were obtained from SEER. Analyses for cancer incidence are presented at both the county and zip code level while analyses for cancer mortality are presented at the county level, which is the smallest area for which cancer mortality data are available. County and zip code demarcations were based on information provided by the U.S. Census Bureau.

Study Areas

The analytical and comparison population areas were characterized using census tract information. The former manufactured gas plant of interest was located in Champaign County, IL, and was circumscribed by zip codes 61820 and 61801; thus, these demarcated areas served as the analytical group. Our objective was to identify comparison counties in the state of Illinois with similar demographic and socioeconomic characteristics. Relevant characteristics included county setting (urban vs. rural), county population size, and percentages for black race, high school graduation, persons over age 65, persons unemployed, families below poverty level, urban residence, and ever smoking status. In addition, the median household income was utilized as a comparison factor. County selection was based on methods developed by the National Cancer Institute [4, 5].

Illinois Cancer Data

In concert with the Illinois State Cancer Registry (ICSR), the SEER program of the National Cancer Institute is the source of data for cancer mortality between 1986 and 2010 [6]. These data are grouped by age, sex, and race and are provided at the county level (the smallest available area for cancer mortality). The National Center for Health Statistics (NCHS) provides information on the underlying cause of death, coded to the International Classification of Diseases (ICD-9) [7] for all deaths for years 1986 through 1998 and the International Classification of Diseases (ICD-10) for all deaths for year 1999 and later [8]. Cancer mortality rates are available by single year for Illinois only, and deaths among non-residents and deaths of unknown age or sex are omitted from the database calculations. Because of NCHS policy, rates are not calculated for stratified sub-groups containing less than 10 deaths. For this analysis we used mortality data from 1990-2010 to be consistent with the census tract reporting periods.

Cancer incidence data for the direct community comparisons used in this study were collected by the ISCR and are available as a public use data set via the Illinois Department of Public Health for the years 1991-2010. All obtainable data are provided by the ISCR as a public service for the purpose of statistical reporting and analysis only. Case ascertainment is near complete as the identification and reporting of cancer cases is mandated by state law. Individual (personal) information has been de-identified, and the data have been aggregated into categories (e.g., age, race, Hispanic ethnicity, year of diagnosis and type of cancer) within individual records [9]. The number of cases reported in a particular region depends on the size of the geographic area in an effort to protect the privacy of individuals. The Illinois dataset contains sanitized records of cancer incidence among residents who were diagnosed between 1986 and

2011. Cancer incidence data at the county and zip code level are based on five-year interval groupings, and include data for invasive cancers only with the exception of bladder cancer. Non-melanoma skin cancers and reported cases with an unknown age or "other" sex category are omitted by the ISCR. Cancer incidence data used for the SIR analyses were obtained directly from the SEER program.

By using these data, we agreed to comply with the Illinois Health and Hazardous Substances Registry Act (410 ILCS 525/12).

Main Analyses

As indicated, we ascertained cancer rates from the ISCR and the SEER program. The rates provided by these sources were calculated using the SEER*Stat® software package, developed by the Information Management Services Inc. for the National Cancer Institute [10]. SEER expresses rates per 100,000 population, and rates are age-adjusted by the direct method adjusting to the 2000 U.S. standard million population. These data were then used to formulate the basis of our historical cancer assessment.

We calculated relative rate ratios (RRs) and 95% confidence intervals (CIs) to compare cancer mortality and incidence rates in Champaign County, IL and zip codes 61820 and 61801 encompassing the location of the former manufactured gas plant to counties that were similar demographically (i.e., Macon, Winnebago, and Sangamon counties). These comparisons served as the main analyses because they were very well-matched demographically to the study areas. The number of cancer cases and deaths were ascertained for the period 1990 through 2010, and the absolute rate of cancer occurrence was calculated based on the county and zip code population size according to the U.S. Census Bureau. The relative rate of cancer occurrence was

calculated by dividing the rate of cancer in Champaign County and the zip codes (for cancer incidence only) by the rate of cancer in the comparison counties. County-level analyses were statistically adjusted for age, sex, and race, and zip code-level analyses were adjusted for age and sex (race stratified data were not available at the zip code level, and mortality analyses were adjusted for age only).

Sensitivity analyses

Although the comparison counties in the main analyses were very-well matched to Champaign County, they had former gas plants, which raises concern about potential bias resulting from similar chemical exposures in the comparison counties. To address this concern, we conducted several sensitivity analyses by comparing rates of cancer in Champaign County and the study zip codes with other populations. First, we reviewed an Environmental Protection Agency (EPA) report on manufactured gas plant production [11], the EPA website, and the following website link: http://www.hatheway.net/state_site_pages/il_epa.htm to identify additional comparison counties. Illinois counties with relatively similar demographic characteristics but without former gas plants (i.e., Brown, Douglas, Menard, Randolph counties) were selected. Evaluations of cancer mortality and cancer incidence, using the same methodology as the main analyses, were conducted using these counties as comparisons.

Second, we calculated standardized incidence ratios (SIRs) for cancer sites in Champaign County and the zip codes of interest. The numbers of observed cancers in Champaign County and in the study zip codes were compared with those expected on the basis of standardized rates of cancer in the general population using data obtained from SEER [12]. The number of observed cancers was determined by sex, race, and 5-year age groups (the zip codes were

standardized by age and sex groups) for each year from 1991-2010. Expected numbers of cases were calculated by multiplying the estimated population for Champaign County and for the study zip codes for each year of study by annual SEER cancer rates, stratified by 5-year age groups, race, and sex. Observed and expected counts were then generated for Champaign County and for the study zip codes, and SIRs were calculated by dividing the observed number by the expected number.

A final concern was the possibility of surveillance bias being introduced during the analytical study period. In the mid-2000s, a neighborhood advocacy group formed to increase awareness about the potential health effects from the abandoned gas plant [13]. In order to limit potential bias associated with the formation of this group, we conducted analyses for the years 1990-2000, prior to the formation of this group.

All analyses were performed using SAS statistical software.

RESULTS

Study Counties

The characteristics of the study county and the comparison counties are reported in Tables 1 and 2 for the 1990 and 2000 census periods, respectively.

Table 1. Characteristics of Study County and Comparison Counties based on 1990 Census.

Characteristic	Champaign County	Comparison counties		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	9.64	8.11	12.14	9.29
Percent did not graduate high school	12.50	18.23	23.79	23.70
Percent over age 65 years	8.74	13.71	14.57	12.67
Percent unemployed	4.24	4.36	6.60	5.20
Percent below poverty	8.03	7.19	9.84	7.71
Median household income (in tens)	2654	3035	2860	3134
Percent Urban	81.41	78.32	81.74	87.41

Table 2. Characteristics of Study county and Comparison counties based on 2000 census.

Characteristic	Champaign County	Comparison counties		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	11.82	10.17	14.76	11.16
Percent did not graduate high school	9.02	11.93	16.83	18.57
Percent over age 65 years	9.72	13.51	15.24	12.73
Percent unemployed	5.52	4.07	7.15	5.83
Percent below poverty	6.92	6.49	9.28	6.92
Median household income (in tens)	3778	4296	3786	4389
Percent Urban	84.34	85.40	84.17	91.78
Percent ever smoke	44.89	52.46	52.59	52.38

Champaign County was very well-matched to the comparison counties with former gas plants on the variables of interest. Given the relatively high proportion of counties with former manufactured gas plants in Illinois, the availability of matching counties without former gas plants was more limited. However, based on our county scoring methodology and criteria, we were able to identify counties (i.e., Brown, Douglas, Menard, Randolph) without former gas plants to serve as comparison communities in our sensitivity analyses. These counties were not as closely matched on potential confounding factors (i.e., demographic characteristics) that may be associated with cancer as the counties used in our main analyses.

Cancer Mortality

The RR for total cancer mortality in Champaign County versus the comparison counties (Macon, Winnebago, and Sangamon) was significantly decreased (RR = 0.91, 95% CI: 0.88-0.94) during 1990-2010 (Table 3). Similarly, statistically significant deficits in mortality were observed for cancers of the esophagus (RR = 0.80, 95% CI: 0.65-0.98), colorectum (RR = 0.88, 95% CI: 0.80-0.97), pancreas (RR = 0.78, 95% CI: 0.68-0.89), and lung & bronchus (RR = 0.85, 95% CI: 0.80-0.89). In fact, out of all 22 cancer site groupings, 17 RRs represented reduced risks, one RR was 1.0, no data were available for one site (testicular cancer), and three RRs were slightly elevated. None of these elevated cancer sites was statistically significant, with RRs of 1.03 (melanoma), 1.06 (prostate), and 1.05 (leukemias) (Table 3).

Table 3. Age adjusted mortality rates, RRs and 95% CI† in 1990-2010

	Champaign County			Comparison counties			Rate Ratio	95% CI
	No. of Deaths	Rate	95% CI	No. of Deaths	Rate	95% CI		
All Cancer	5,611	187.2	182.3-192.2	27,170	206.1	203.6-208.5	0.91*	0.88-0.94
Oral Cavity & Pharynx	64	2.1	1.6-2.7	358	2.7	2.4-3.0	0.78	0.59-1.03
Esophagus	118	4.0	3.3-4.7	650	4.9	4.5-5.3	0.80*	0.65-0.98
Stomach	94	3.1	2.5-3.8	494	3.7	3.4-4.1	0.84	0.67-1.05
Colorectal	551	18.4	16.9-20.0	2,765	20.8	20.1-21.6	0.88*	0.80-0.97
Liver	87	2.9	2.3-3.6	420	3.2	2.9-3.5	0.91	0.71-1.15
Pancreas	267	9.0	7.9-10.1	1,526	11.5	11-12.1	0.78*	0.68-0.89
Lung & Bronchus	1,526	51.3	48.7-53.9	7,990	60.6	59.2-61.9	0.85*	0.80-0.89
Bone & Joint	12	0.3	0.2-0.6	43	0.3	0.2-0.4	0.94	0.42-1.89
Melanomas	81	2.7	2.1-3.3	339	2.6	2.3-2.9	1.03	0.80-1.31
Breast‡	438	25.6	23.3-28.2	2,045	27.5	26.3-28.7	0.93	0.84-1.03
Prostate‡‡	348	31.4	28.1-34.9	1,427	29.7	28.1-31.3	1.06	0.94-1.19
Testis‡‡	-	-	-	-	-	-	-	-
Cervix‡	39	2.3	1.6-3.2	177	2.6	2.2-3.0	0.89	0.61-1.27
Uterine‡	72	4.2	3.2-5.2	323	4.2	3.7-4.6	1.00	0.76-1.29
Ovary‡	159	9.3	7.9-10.8	716	9.5	8.8-10.2	0.98	0.82-1.17
Kidney & Renal Pelvis	136	4.5	3.8-5.4	618	4.7	4.3-5.1	0.97	0.80-1.17
Bladder	131	4.4	3.7-5.3	610	4.6	4.2-5.0	0.97	0.79-1.17
Nervous System	119	3.8	3.2-4.6	596	4.6	4.2-5.0	0.83	0.68-1.02
Hodgkins Lymphomas	13	0.4	0.2-0.7	61	0.5	0.4-0.6	0.88	0.44-1.61
NHL	230	7.6	6.7-8.7	1,096	8.3	7.8-8.8	0.92	0.79-1.06
Myelomas	110	3.7	3.0-4.5	510	3.8	3.5-4.2	0.96	0.77-1.18
Leukemias	251	8.2	7.3-9.3	1,029	7.8	7.4-8.3	1.05	0.91-1.21

†Tiwariet al. 2006 modification for CIs
‡Female only, ‡‡ Male only
*p < 0.05

Similar results for Champaign County were observed when compared with counties without former manufactured gas plants. Total cancer was associated with an RR of 0.96 (95% CI: 0.92-1.00), and statistically significant reduced rates of colorectal and pancreatic cancer mortality were observed (data not tabulated). Relative risks for most cancer sites were 1.0 or lower, with few weakly positive, albeit non-significant associations. Taken together, results based on analyses using communities with and without former gas plants are not supportive of an increased risk of cancer mortality.

Cancer Incidence

A statistically significant reduced rate of total cancer incidence was observed in Champaign County versus the comparison counties (RR = 0.95, 95% CI: 0.94-0.97) during 1991-2010 (Table 4). Decreased incidence rates were observed for nineteen of 23 cancer site groupings based on analyses during 1991-2010. Incidence rates for cancers of the colorectum, pancreas, lung & bronchus, testis, cervix, nervous system, and "other" sites (list of cancers in this category are shown in Table 4) were all significantly lower versus the rates in the comparison counties. In contrast, statistically significant slightly elevated rates were observed for melanoma (RR = 1.12, 95% CI: 1.02-1.24) and prostate cancer (RR = 1.20, 95% CI: 1.14-1.25). Restricting the analytical period to 1991-2000 in Champaign County in order to reduce potential bias associated with the formation of the neighborhood advocacy group did not appreciably modify the results; the RR for melanoma was 1.17 (95% CI: 0.99-1.38) and the RR for prostate cancer was 1.17 (95% CI: 1.09-1.26) (data not tabulated). Incidence rates were significantly reduced for total, colorectal, pancreatic, lung & bronchus, testicular, and cervical cancers during 1991-2000.

Table 4. Age, sex, and race-adjusted incidence rate by county, RRs and 95% CI† in 1991-2010

	Champaign County			Comparison counties			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All cancer	13978	499.55	491.17-507.93	61184	524.18	520.03-528.34	0.95*	0.94-0.97
Oral cavity & pharynx	332	11.94	10.64-13.23	1484	12.71	12.07-13.36	0.94	0.83-1.06
Esophagus	141	5.21	4.35-6.08	696	5.96	5.52-6.41	0.87	0.73-1.05
Stomach	177	6.38	5.43-7.33	809	6.93	6.45-7.41	0.92	0.78-1.09
Colorectal	1442	52.87	50.11-55.62	7140	61.17	59.75-62.59	0.86*	0.82-0.91
Liver	112	3.94	3.20-4.67	486	4.16	3.79-4.53	0.95	0.77-1.16
Pancreas	291	10.69	9.45-11.92	1558	13.35	12.69-14.01	0.80*	0.71-0.91
Lung & Bronchus	1945	71.76	68.55-74.96	10063	86.21	84.53-87.90	0.83*	0.79-0.87
Bone	23	0.68	0.39-0.97	80	0.69	0.54-0.84	1.00	0.62-1.60
Melanomas	539	17.62	16.10-19.14	1834	15.71	14.99-16.43	1.12*	1.02-1.24
Breast-invasive‡	2184	150.65	144.25-157.04	9158	151.54	148.43-154.64	0.99	0.95-1.04
Prostate‡‡	2254	172.52	165.38-179.66	8125	144.35	141.21-147.48	1.20*	1.14-1.25
Testis‡‡	89	4.05	3.18-4.93	337	5.99	5.35-6.63	0.68*	0.53-0.86
Cervix‡	114	6.84	5.54-8.14	561	9.28	8.51-10.05	0.74*	0.60-0.91
Uterus‡	406	28.53	25.74-31.33	1801	29.80	28.42-31.18	0.96	0.86-1.07
Ovary‡	228	15.52	13.48-17.57	1022	16.91	15.87-17.95	0.92	0.79-1.06
Kidney	425	15.10	13.64-16.55	1945	16.66	15.92-17.40	0.91	0.81-1.01
Bladder	363	13.56	12.16-14.96	1725	14.78	14.08-15.48	0.92	0.82-1.03
Nervous System	164	5.53	4.66-6.39	797	6.83	6.35-7.30	0.81*	0.68-0.96
Hodgkins Lymphomas	93	2.51	1.98-3.04	341	2.92	2.61-3.23	0.86	0.68-1.09
NHL	556	19.64	17.98-21.29	2490	21.33	20.49-22.17	0.92	0.84-1.01
Myelomas	183	6.68	5.71-7.66	758	6.49	6.03-6.96	1.03	0.88-1.21
Leukemias	433	15.32	13.86-16.79	1678	14.38	13.69-15.06	1.07	0.96-1.19
All Other Sites‡‡‡	1484	50.63	48.00-53.26	6296	53.94	52.61-55.27	0.94*	0.89-0.99

†Breslow and Day 1987
‡Female only, ‡‡ Male only
‡‡‡Includes small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, breast-invasive male only, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.
*$p < 0.05$

Fewer cancer sub-groupings were available at the zip code level. Nevertheless, results similar to those in the county-level analyses were observed. Total cancer incidence was 11% lower in the study zip codes versus the comparison counties, resulting in a statistically significant RR of 0.89 (95% CI: 0.86-0.93) during 1991-2010 (Table 5). Of the 10 cancer site groupings, nine incidence rates were decreased versus comparison counties, including statistically significant reductions for colorectal (RR = 0.85, 95% CI: 0.76-0.95), breast (invasive) (RR =

0.86, 95% CI: 0.78-0.95), and "other" (RR = 0.86, 95% CI: 0.79-0.92) cancers. The only elevated incidence rate was for prostate cancer, with a significant RR of 1.13 (95% CI: 1.03-1.24), based on 500 diagnosed cases during 1991-2010. However, no significant association was found for prostate cancer (RR = 1.07, 95% CI: 0.95-1.21) in the analysis for the period 1991-2000 (data not tabulated). During this period, rates for colorectal, breast, and "other" remained significantly decreased, while significant deficits for lung & bronchus (RR = 0.75, 95% CI: 0.66-0.86) and central nervous system cancers (RR = 0.55, 95% CI: 0.33-0.93) were observed as well.

Table 5. Age and sex-adjusted incidence rate by zip code, RRs and 95% CI[†] in 1991-2010.

	Zip 61820, 61801			Comparison counties			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All Cancer	3191	468.15	451.25-485.06	61184	524.18	520.03-528.34	0.89*	0.86-0.93
Oral Cavity & Pharynx	81	12.40	9.62-15.19	1484	12.71	12.07-13.36	0.98	0.77-1.23
Colorectal	349	51.93	46.32-57.53	7140	61.17	59.75-62.59	0.85*	0.76-0.95
Lung & Bronchus	440	67.81	61.34-74.27	10063	86.21	84.53-87.90	0.79	0.71-0.87
Breast-Invasive[‡]	464	130.16	117.79-142.52	9158	151.54	148.43-154.64	0.86*	0.78-0.95
Cervix[‡]	38	8.22	5.33-11.12	561	9.28	8.51-10.05	0.89	0.62-1.27
Prostate[‡‡]	500	163.09	148.61-177.57	8125	144.35	141.21-147.48	1.13*	1.03-1.24
Urinary System	186	28.87	24.61-33.13	3670	31.44	30.42-32.46	0.92	0.79-1.07
Central Nervous System	38	5.47	3.63-7.31	797	6.83	6.35-7.30	0.80	0.57-1.13
Leukemias and Lymphomas	267	36.55	31.88-41.22	4509	38.63	37.50-39.76	0.95	0.83-1.08
All other cancers[‡‡‡]	828	114.84	106.51-123.17	15677	134.31	132.21-136.41	0.86*	0.79-0.92

[†]Breslow and Day 1987

[‡]Female only, [‡‡] Male only

[‡‡‡] Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

*$p < 0.05$

Additional sub-group analyses for the cancer sites were conducted by individual zip codes and by analytical periods. The rate of prostate cancer during 1991-2010 was elevated with marginal significance for zip code 61820 (RR = 1.15, 95% CI: 1.00-1.32, based on 211 cases) but not for zip code 61801 (RR = 1.12, 95% CI: 0.99-1.26) (data not tabulated). No effect modification was apparent by zip code as the CIs for prostate cancer largely overlapped. No other statistically significantly cancer rates were observed during 1991-2010 but rates were modified in the inverse direction for colorectal (RR for zip code 61820 = 0.98, 95% CI: 0.84-1.15; zip code 61801 = 0.76, 95% CI: 0.65-0.88) and lung & bronchus (RR for zip code 61820 = 0.98, 95% CI: 0.86-1.13; zip code 61801 = 0.65, 95% CI: 0.57-0.75) cancers (data not tabulated). Interestingly, when analyses were conducted for the period 1991-2000, prostate cancer rates were modified by zip code (RR for zip code 61820 = 1.23, 95% CI: 1.02-1.48; zip code 61801 = 0.98, 95% CI: 0.83-1.16).

Findings were again similar in the sensitivity analyses when counties without former manufactured gas plants were used as the comparison (data not tabulated). No difference in total cancer was found between Champaign County and the comparison counties without former gas plants (RR = 1.00, 95% CI: 0.97-1.02). Of 22 cancer site groupings, 12 had reduced rates in Champaign County, with statistically significant deficits for colorectal and cervical cancer. As with the main analyses, prostate cancer incidence was elevated slightly and significantly (RR = 1.14, 95% CI: 1.06-1.23) in Champaign County, but it was not significant in the study zip code analysis (RR = 1.09, 95% CI: 0.98-1.21). The only other statistically significant positive association in the county sensitivity analysis was for esophageal cancer (RR = 1.46, 95% CI: 1.07-1.99), but this finding was not substantiated in other analyses. Total cancer was significantly reduced in the study zip codes versus the comparison counties without former gas

plants (RR = 0.94, 95% CI: 0.90-0.98). Moreover, seven of 10 cancer sites were associated with reduced rates in the study zip codes, while three were slightly positive and not significant.

Standardized Incidence Ratio (SIR) Analyses

During the period, 1991-2010, 13,978 total cancers were observed in Champaign County with 14,150 expected based on nationally standardized rates, resulting in an SIR of 0.99 (95% CI: 0.97-1.00) (data not tabulated). Of 23 cancer site groupings, 14 had expected or lower than expected cases of cancer, with statistically significant deficits observed for stomach, liver, pancreas, bone, melanoma, testicular, bladder, nervous system, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. A slightly greater than expected number of lung & bronchus (SIR = 1.07, 95% CI: 1.02-1.11) and kidney (SIR = 1.13, 95% CI: 1.03-1.25) cancer cases were observed in Champaign County, but these findings were not supported by the other analyses. In fact, a slight deficit of lung & bronchus cancer cases was observed in the study zip codes (SIR = 0.98, 95% CI: 0.89-1.07), and urinary system cancer (includes kidney cancer) was reduced significantly (SIR = 0.78, 95% CI: 0.67-0.90) in the study zip codes (Table 6). Significantly fewer than expected total cancer cases were observed in the study zip codes (SIR = 0.88, 95% CI: 0.85-0.91) (the SIRs for the cancer sites in the study zip codes are summarized in Table 6).

Table 6. Standardized incidence ratios (SIRs) and 95% CI of Zip code 61820 and 61801, 1991-2010

Cancer Sites	Obs	Exp	SIR	95% CI
All Cancer	3191	3612	0.88	0.85-0.91
Oral Cavity & Pharynx	81	82	0.98	0.78-1.22
Colorectal	349	378	0.92	0.83-1.03
Lung & Bronchus	440	450	0.98	0.89-1.07
Breast-Invasive‡	464	511	0.91	0.83-0.99
Cervix‡	38	36	1.04	0.74-1.43
Prostate‡‡	500	525	0.95	0.87-1.04
Urinary System	186	239	0.78	0.67-0.90
Central Nervous System	38	63	0.60	0.43-0.83
Leukemias and Lymphomas	267	320	0.84	0.74-0.94
All other cancers‡‡‡	828	1008	0.82	0.77-0.88

†Breslow and Day 1987
‡Female only, ‡‡ Male only
‡‡‡ Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

DISCUSSION

We observed statistically significant reductions in total cancer mortality and incidence in Champaign County, IL, and the zip code study areas compared with counties that were similar demographically and socioeconomically, and based on nationally standardized rates. Furthermore, cancer occurrence was lower in the study area for most cancer types, with several statistically significant reductions in cancer rates. Results were largely consistent within and across analyses, with a few exceptions. Indeed, the lower mortality rates for most cancers in the study area versus the comparison counties were in accordance with the lower cancer incidence rates observed in Champaign County and the study zip codes. The only noteworthy positive associations in the primary analyses were for prostate cancer and melanoma. Neither prostate cancer mortality nor melanoma mortality was significantly elevated. However, incidence rates for these cancers were significantly increased in Champaign County. It is not clear why elevated

rates were observed, although based on chance alone, it would be expected that some cancer rates would be statistically significant in both the positive and inverse directions. As indicated, we observed several statistically significant inverse associations (i.e. RRs below the null value of 1.0), such as for lung & bronchus, colorectal, and breast cancers. However, only two cancer types (prostate cancer and melanoma; incidence only) were associated with statistically significant positive associations. Thus, significant associations may have been observed due to multiple comparisons – a statistical phenomenon whereby one out of 20 associations is statistically significant due to chance [14, 15]. In our analysis, we generated over 100 unique RRs.

Prostate cancer is the most common cancer among men in the U.S., and 238,590 incident cases and 29,720 deaths were estimated to occur in 2013 [16, 17]. The figures for prostate cancer represent 14.4% of all new cancer cases and 5.1% of all cancer deaths in the U.S. [17]. Increasing age, African American race, family history of prostate cancer, and genetic variations and mutations are established risk factors for prostate cancer, although the etiology is largely unknown despite an extensive effort to identify causes of this malignancy [16, 17]. The role of lifestyle and dietary factors are thought to play a role in prostate cancer risk, as past research has identified obesity, physical inactivity, and smoking as significant modifiable risk factors for this malignancy [18-21]. Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors such as physical activity, family history of disease, or body mass index that may have influenced the results. Based on a review of the literature and statements by prominent cancer organizations [16, 17], no manufactured gas plant by-product compound has been clearly or consistently associated with prostate cancer risk.

Perhaps the most likely reason for the elevation in prostate cancer incidence during 1991-2010 is the increased rate of prostate-specific antigen (PSA) screening in Champaign County versus the comparison counties. Indeed, based on the Behavioral Risk Factor Surveillance System (BRFSS) survey from the Centers for Disease Control and Prevention (CDC) and administered by the Illinois Department of Public Health [9], the percent of men who underwent PSA screening was higher in Champaign County than Sangamon, Macon, and Winnebago counties (as a composite percentage) during the study period. Furthermore, composite rates of PSA screening were higher in Champaign County than the counties without former gas plants. It is well-established and well-publicized that screening for prostate cancer results in an increase in incidence rates, whereas a proportion of prostate cancers may otherwise go undetected without screening [22-24]. In a sentinel review paper on the epidemiologic impact of screening on the incidence and mortality of prostate cancer in the U.S., it was suggested that PSA testing was the likely cause of the dramatic increase in prostate cancer incidence during the 1990s [23]. Although PSA testing is useful for early diagnosis, its value as a screening tool has been under scrutiny because the theoretical benefit on mortality is questionable [24]. According to a recent study from the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized screening trial, men who underwent annual prostate cancer screening with PSA testing and digital rectal examination had a 12 percent higher incidence rate of prostate cancer compared with men in the control group (who did not undergo PSA testing) [25]. However, approximately the same rate of death from prostate cancer was observed between groups, and no evidence of a mortality benefit was found in age or pre-trial PSA testing strata [25]. In our assessment, we observed a statistically significant increase in prostate cancer incidence in Champaign County (where a greater

proportion of individuals underwent PSA testing) but no statistically significant difference in prostate cancer mortality versus the comparison counties.

Melanoma was also associated with a statistically significant positive association (incidence only). Cancer incidence data for melanoma were not available at the zip code level, thus, it is uncertain if melanoma occurrence was higher in the areas directly circumscribing the abandoned plant. Approximately 21.3 out of 100,000 men and women are diagnosed annually with melanoma, and it is about twenty times more common in whites than blacks [17]. The major risk factor for melanoma is exposure to ultraviolet (UV) rays (sunlight is the primary source of UV rays), particularly among persons with fair skin. Other risk factors include having a large number of moles, having one or more first-degree relatives who have had melanoma, and being immunosuppressed [16]. It has been hypothesized that malignant melanoma may occur as a result of exposure to occupational or environmental chemicals (e.g., vinyl chloride, arsenic, polychlorinated biphenyls, petrochemicals, pesticides), particularly because malignancy can develop in cutaneous areas that have not been exposed to sunlight [26]. However, the epidemiologic evidence relating chemical exposures to melanoma risk is inconsistent. Thus, it is unclear whether the positive incidence rate ratio in Champaign County is the result of an artifactual finding from multiple comparisons, or has been confounded by sun exposure or other factors, such as immunosuppression. Moreover, general health concerns that the local population may have about living next to a former gas manufacturing site may lead to surveillance bias due to increased screening. Furthermore, a statistically significant deficit of melanoma was observed in Champaign County based on SIR analyses, and no statistically significant associations for melanoma were found based on comparisons with counties that did not have a former gas plant. Finally, esophageal cancer incidence was elevated when Champaign County was compared with

the non-gas plant counties in our sensitivity analysis of cancer incidence, but this observation was not substantiated by the main analyses, the sensitivity analysis of cancer mortality, or by the SIR analysis.

Alternatively, an unknown manufactured gas product compound may have produced the slight elevations in prostate cancer and/or melanoma incidence in the main analyses. This scenario is unlikely, however, given the plausible explanations listed above and because reduced rates were observed for cancers with known environmental or chemical relationships. That is, no "indicator" cancer types with established environmental or chemical etiology were observed in excess. For example, IARC has classified "coke production" as carcinogenic to humans (Group 1) for lung cancer because of exposure to PAHs in the industry (although associations from the occupational studies are somewhat tenuous) [27-29]. In our assessment, we observed statistically significant reduced mortality and incidence rates of 15% and 17%, respectively, for lung & bronchus cancers.

It is unclear as to why there was a preponderance of inverse associations in Champaign County and the study zip codes versus the comparison counties. *A priori*, we developed a systematic protocol for identifying comparable counties. We identified counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level). Based on the 2000 census information, there were approximately 7% fewer 'ever' smokers in Champaign County versus the comparison counties. This may explain, in part, the observation of lower cancer rates, particularly for lung & bronchus, in Champaign County. In addition, the prevalence of other potentially important factors, such as alcohol consumption or obesity, in these counties may have confounded the observed associations. However, relatively similar patterns of associations were

observed in sensitivity analyses comparing Champaign County and the study zip codes with counties that did not have a former gas plant, and based on SIR analyses using nationally representative cancer data from the SEER program.

Most of the literature on manufactured gas plants focuses on the environmental and ecological impacts of the gas process residues and waste products. As such, considerable literature exists on the methodological, toxicological, elemental chemistry, and extracting techniques involving remediation and compound evaluations from abandoned sites [30-33]. While potentially hazardous compounds may have been produced as part of the gas manufacturing process, the extent and level to which compound residues persist at the sites is unclear. In certain cases, potential hazards may be overestimated as samples in some studies have been consistent with background levels or below the assumed level [1, 34]. As mentioned previously, the literature on direct or indirect human health risks from an epidemiologic standpoint, is sparse. DeHate et al. [1] investigated soil vapor intrusion at 10 commercial buildings and 26 single family and multi-family residential properties overlying and/or adjacent to three former manufactured gas plant sites. Soil vapor samples and indoor/outdoor air were analyzed for VOCs, and comparative risks were evaluated based on maximum and mean concentrations for BTEX relative to background levels. All hazard indices were less than one or were comparable to mean and maximum background levels, and there was no evidence of manufactured gas plant-related soil vapor intrusion from any of the 36 sites. Based on these findings, the authors reported that no increased public health risks were associated with occupied residential or commercial properties overlying or surrounding former manufactured gas plant facilities [1]. Occupational epidemiologic studies involving postulated gas plant exposures, such as PAHs [27], BTEX [35-37], and coal tar [38-40], are extensive but none have evaluated

potential disease outcomes resulting from residing in a community that includes a former manufactured gas plant site.

Our historical cancer assessment has limitations that are commonplace with analyzing population-level data. Prime among the limitations is that we did not have individual-level information on lifestyle, dietary, medical, or occupational factors. In addition, we did not have personal information regarding potential exposures (e.g., to soil, groundwater, or air) from the manufactured gas process. We were, however, able to adjust cancer estimates for age, sex, and race. Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law. The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected. Despite these limitations, we found no clear or consistent evidence of an increase in cancer occurrence among residents in a community circumscribing a former manufactured gas plant. Furthermore, the validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program.

We conducted a community cancer assessment for the purpose of appraising the public health regarding the occurrence of cancer among residents in a community with a former manufactured gas plant. Although this study did not include individual-level information, rates of total cancer and most cancer sites in the Champaign County area and zip codes circumscribing the abandoned facility were lower versus similar comparison areas, and based on nationally

standardized rates of cancer. The primary exception is for prostate cancer, although there may be relevant explanations for the higher rates aside from potential exposure emanating from the former manufactured gas plant site, such as an incidence spike due to higher PSA testing rates in Champaign County, a statistical artifact based on multiple comparisons, or confounding by unmeasured factors. Furthermore, a review of the literature did not reveal any known relation between the potential gas plant compounds and prostate cancer risk. In conclusion, the results from this retrospective cancer mortality and incidence assessment do not support an increase in cancer occurrence in communities surrounding a former manufactured gas plant in Champaign, IL.

AUTHOR CONTRIBUTION: DDA, DHG, and JPF were responsible for conception and design of the research. Statistical analyses were carried out by XJ. DDA, XJ, LCB, DHG, SRI, and JPF were responsible for development of the manuscript, critical revision and intellectual content.

FUNDING: This work was supported by Ameren Corporation.

COMPETING INTERESTS: DHG has served as an expert witness on behalf of Ameren in litigation related to manufactured gas plants. DDA, XJ, LCB, DHG, SRI, and JPF are employed by EpidStat Institute, all of whom were contracted by Ameren Corporation to support the study.

DATA SHARING STATEMENT: The full data set is available by emailing the corresponding author of the study.

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BMJ Open

Historical Cancer Incidence and Mortality Assessment in an Illinois Community Proximal to a Former Manufactured Gas Plant

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006713.R1
Article Type:	Research
Date Submitted by the Author:	13-Nov-2014
Complete List of Authors:	Alexander, Dominik Jiang, Xiaohui Garabrant, David Irvin, Sarah Fryzek, Jon; EpidStat Institute,
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	natural gas manufacturing, community, ONCOLOGY

Historical Cancer Incidence and Mortality Assessment in an Illinois Community Proximal to a Former Manufactured Gas Plant

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Word count: 5,164 words

Abstract word count: (243 words)

Kewords: natural gas manufacturing, community, cancer incidence, epidemiology

ABSTRACT

Objectives: Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant in Champaign, IL. Thus, we compared historical rates of cancer in this area to comparison communities as well as with nationally standardized rates.

Design: Retrospective population-based community cancer assessment during 1990-2010

Setting: Champaign County, IL, and zip codes encompassing the location of the former manufactured gas plant to counties that were similar demographically.

Participants: Residents of the counties and zip codes studied between 1990-2010.

Main outcome measures: The relative risk (RR) and 95% confidence interval (CI) were used to compare cancer incidence and mortality in the areas near the gas compression site to the comparison counties. Standardized incidence ratios (SIR) were calculated to compare rates in the areas near the gas compression site to expected rates based on overall United States cancer rates.

Results: Total cancer mortality (RR = 0.91, 95% CI: 0.88-0.94) and incidence (RR = 0.95, 95% CI: 0.94-0.97) were reduced significantly in Champaign County versus the comparison counties. Similarly, a reduced rate of total cancer was observed in analyses by zip code (proximal to the former gas plant) when compared to either similar counties (RR = 0.89, 95% CI: 0.86-0.93) or national standardized rates of cancer (SIR = 0.88, 95% CI: 0.85-0.91).

Conclusions: This historical cancer assessment did not find an increased risk of total cancer or specific cancer types in communities near a former manufactured gas plant site.

Strength and limitations of this study:

- The validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program.
- Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law.
- A priori, we developed a systematic protocol for identifying comparable counties. We matched counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level) to control for confounding.
- Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors associated with cancer such as physical activity, family history of disease, or body mass index that may have influenced the results.
- The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected.

INTRODUCTION

The production of manufactured gas is widely considered one of the key developments in our industrial history, with an extensive chronology beginning in the late 1700s and spanning into the 1960s. Manufactured gas consisted largely of the gasification of coal, and less frequently, the combustion of other materials such as wood and oil. Historically, the manufactured gas industry grew significantly in the early 1800s due to the production of lighting for the progress and development of cities. However, later in the 19th century, this industry diversified into heating, refrigeration, and cooking. During the early to mid-20th century, the advent of natural gas obviated the gasification of coal, ultimately leading to the conversion or closure of manufactured gas plants. Pipelines transported natural gas directly from the well to gas distribution systems, and natural gas was considered more economical, efficient, and environmentally friendly. Most manufactured gas plants in the U.S. were terminated by1966 with few exceptions, and as a result of the manufactured gas demise, over 1,500 plant sites are suggested to remain dormant or vacant in the U.S. today.

Numerous health concerns have been raised regarding possible environmental exposures stemming from manufactured gas plant sites. Foremost among the concerns is that contamination and waste products from the manufacturing gas process leaked into the adjacent soil and groundwater, thus posing health risks in the nearby residential areas and communities [1]. The process of coal carbonization generates coal tar, which are complex mixtures of heterocyclic compounds, phenols, and polycyclic aromatic hydrocarbons (PAHs). Indeed, both volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs) from coal tar and petroleum products are derived from the coal gasification process [1]. The VOCs contain a mixture of BTEX, or benzene, toluene, ethylbenzene, and xylene isomers among other

compounds, while the SVOCs consist of a mixture of compounds, such as benzo(a)pyrene, benzo(e)pyrene, naphthalene, and 2-methyl naphthalene. In addition, principal component analyses have identified heavy metals at former manufactured gas plant sites [2, 3]. As a result of these gas process by-products, the U.S. Environmental Protection Agency (EPA) and other regulatory agencies have focused on assessing the potential for soil and groundwater contamination at former manufactured gas plant sites, as well as evaluating the potential for health risks among residents in nearby communities. The International Agency for Research on Cancer (IARC) lists many of the manufactured gas plant by-product compounds as known, probable, or possible carcinogens for specific cancers but the level and extent of community exposure to such compounds resulting from former manufactured gas plants is uncertain. Furthermore, sparse epidemiologic evidence exists on the potential public health risks associated with residing near former manufactured gas plant sites.

Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant on a 3.5 acre lot in northern Champaign, IL. The plant, in operation from 1887 until 1953, manufactured gas by heating coal. Coal tar and other production wastes were suggested to remain on site until the closing of the plant. AmerenIP has registered this site with the Illinois EPA under their Site Remediation Program. However, the potential long-term health effects of residents in the nearby community are unknown. Therefore, we conducted a historical cancer incidence and mortality assessment using publicly available cancer data and census tract information to evaluate the occurrence of cancer in the community where the former manufactured gas plant was located compared with other communities with and without former gas plants that have similar demographic and lifestyle characteristics. In

addition, we conducted standardized incidence analyses for Champaign County and the study zip codes using nationally representative cancer data.

METHODS

All data used in this study are publicly available. Specifically, the cancer incidence data were obtained from the Illinois Department of Public Health and from the Surveillance, Epidemiology, and End Results (SEER) Program, while cancer mortality data were obtained from SEER. Analyses for cancer incidence are presented at both the county and zip code level while analyses for cancer mortality are presented at the county level, which is the smallest area for which cancer mortality data are available. County and zip code demarcations were based on information provided by the U.S. Census Bureau.

Study Areas

The analytical and comparison population areas were characterized using census tract information. The former manufactured gas plant of interest was located in Champaign County, IL, and was circumscribed by zip codes 61820 and 61801; thus, these demarcated areas served as the analytical group. Because our assessment was community-based and ecologic in nature, our objective was to identify comparison counties in the state of Illinois with similar demographic and socioeconomic characteristics. Relevant characteristics included county setting (urban vs. rural), county population size, and percentages for black race, high school graduation, persons over age 65, persons unemployed, families below poverty level, urban residence, and ever smoking status. In addition, the median household income was utilized as a comparison factor. County selection was based on methods developed by the National Cancer Institute [4, 5].

Illinois Cancer Data

In concert with the Illinois State Cancer Registry (ICSR), the SEER program of the National Cancer Institute is the source of data for cancer mortality between 1986 and 2010 [6]. These data are grouped by age, sex, and race and are provided at the county level (the smallest available area for cancer mortality). The National Center for Health Statistics (NCHS) provides information on the underlying cause of death, coded to the International Classification of Diseases (ICD-9) [7] for all deaths for years 1986 through 1998 and the International Classification of Diseases (ICD-10) for all deaths for year 1999 and later [8]. Cancer mortality rates are available by single year for Illinois only, and deaths among non-residents and deaths of unknown age or sex are omitted from the database calculations. Because of NCHS policy, rates are not calculated for stratified sub-groups containing less than 10 deaths. For this analysis we used mortality data from 1990-2010 to be consistent with the census tract reporting periods.

Cancer incidence data for the direct community comparisons used in this study were collected by the ISCR and are available as a public use data set via the Illinois Department of Public Health for the years 1991-2010. All obtainable data are provided by the ISCR as a public service for the purpose of statistical reporting and analysis only. Case ascertainment is near complete as the identification and reporting of cancer cases is mandated by state law. Individual (personal) information has been de-identified, and the data have been aggregated into categories (e.g., age, race, Hispanic ethnicity, year of diagnosis and type of cancer) within individual records [9]. The number of cases reported in a particular region depends on the size of the geographic area in an effort to protect the privacy of individuals. The Illinois dataset contains sanitized records of cancer incidence among residents who were diagnosed between 1986 and

2011. Cancer incidence data at the county and zip code level are based on five-year interval groupings, and include data for invasive cancers only with the exception of bladder cancer. Non-melanoma skin cancers and reported cases with an unknown age or "other" sex category are omitted by the ISCR. Cancer incidence data used for the SIR analyses were obtained directly from the SEER program.

By using these data, we agreed to comply with the Illinois Health and Hazardous Substances Registry Act (410 ILCS 525/12). All data used in our analyses are publically available, thus, informed consent was not required.

Statistical Analyses

As indicated, we ascertained cancer rates from the ISCR and the SEER program. The rates provided by these sources were calculated using the SEER*Stat® software package, developed by the Information Management Services Inc. for the National Cancer Institute [10]. SEER expresses rates per 100,000 population, and rates are age-adjusted by the direct method adjusting to the 2000 U.S. standard million population. These data were then used to formulate the basis of our historical cancer assessment.

Because of the ecologic nature of the community-based analyses, we conducted analyses in an effort to account for potential confounding at the aggregate level while considering the potential for exposure misclassification. Thus, we conducted analyses using three different comparison populations based on: 1) Illinois counties that were the most closely matched demographically (irrespective of having former gas plants), 2) counties without former gas plants (as part of the selection criteria) that were relatively similar demographically, and 3) nationally representative cancer data from the SEER program. By utilizing three different comparison

populations, we were able to enhance the validity of our analyses, examine the consistency of cancer rates across different groups, and facilitate the identification of potential sources of statistical heterogeneity (if present). All types of analyses serve as complementary comparisons to appreciate fully any observed associations.

In the first type of analysis, we calculated relative rate ratios (RRs) and 95% confidence intervals (CIs) to compare cancer mortality and incidence rates in Champaign County, IL and zip codes 61820 and 61801 encompassing the location of the former manufactured gas plant to counties that were the most similar demographically (i.e., Macon, Winnebago, and Sangamon counties). Although not part of the selection criteria, these counties had former gas plants but were the most demographically comparable based on our objective matching criteria. The number of cancer cases and deaths were ascertained for the period 1990 through 2010, and the absolute rate of cancer occurrence was calculated based on the county and zip code population size according to the U.S. Census Bureau. The relative rate of cancer occurrence was calculated by dividing the rate of cancer in Champaign County and the zip codes (for cancer incidence only) by the rate of cancer in the comparison counties. County-level analyses were statistically adjusted for age, sex, and race, and zip code-level analyses were adjusted for age and sex (race stratified data were not available at the zip code level, and mortality analyses were adjusted for age only).

Although the comparison counties in the first analyses were very-well matched demographically to Champaign County, they had former gas plants, which raises concern about potential bias resulting from similar chemical exposures in the comparison counties. To address this concern, our second analyses consisted of comparing rates of cancer in Champaign County and the study zip codes with areas that did not have former gas plants but had relatively similar

descriptive characteristics. To do this, we reviewed an Environmental Protection Agency (EPA) report on manufactured gas plant production [11], the EPA website, and the following website link: http://www.hatheway.net/state_site_pages/il_epa.htm to identify additional comparison counties. Illinois counties with relatively similar demographic characteristics but without former gas plants (i.e., Brown, Douglas, Menard, Randolph counties) were selected. Evaluations of cancer mortality and cancer incidence, using the same methodology as the first analyses, were conducted using these counties as comparisons.

In our final set of analyses, we calculated standardized incidence ratios (SIRs) for cancer sites in Champaign County and the zip codes of interest. The numbers of observed cancers in Champaign County and in the study zip codes were compared with those expected on the basis of standardized rates of cancer in the general population using data obtained from SEER [12]. The number of observed cancers was determined by sex, race, and 5-year age groups (the zip codes were standardized by age and sex groups) for each year from 1991-2010. Expected numbers of cases were calculated by multiplying the estimated population for Champaign County and for the study zip codes for each year of study by annual SEER cancer rates, stratified by 5-year age groups, race, and sex. Observed and expected counts were then generated for Champaign County and for the study zip codes, and SIRs were calculated by dividing the observed number by the expected number.

A final concern was the possibility of surveillance bias being introduced during the analytical study period. In the mid-2000s, a neighborhood advocacy group formed to increase awareness about the potential health effects from the abandoned gas plant [13]. In order to limit potential bias associated with the formation of this group, we conducted analyses for the years 1990-2000, prior to the formation of this group.

All analyses were performed using SAS statistical software.

RESULTS

Study Counties

The characteristics of the study county and the comparison counties (with the most similar demographic characteristics) are reported in Tables 1 and 2 for the 1990 and 2000 census periods, respectively.

Table 1. Characteristics of Study County and Comparison Counties based on 1990 Census.

Characteristic	Champaign County	Comparison counties most closely matched demographically		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	9.64	8.11	12.14	9.29
Percent did not graduate high school	12.50	18.23	23.79	23.70
Percent over age 65 years	8.74	13.71	14.57	12.67
Percent unemployed	4.24	4.36	6.60	5.20
Percent below poverty	8.03	7.19	9.84	7.71
Median household income (in tens)	2654	3035	2860	3134
Percent Urban	81.41	78.32	81.74	87.41

Table 2. Characteristics of Study county and Comparison counties based on 2000 census.

Characteristic	Champaign County	Comparison counties most closely matched demographically		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	11.82	10.17	14.76	11.16
Percent did not graduate high school	9.02	11.93	16.83	18.57
Percent over age 65 years	9.72	13.51	15.24	12.73
Percent unemployed	5.52	4.07	7.15	5.83
Percent below poverty	6.92	6.49	9.28	6.92
Median household income (in tens)	3778	4296	3786	4389
Percent Urban	84.34	85.40	84.17	91.78
Percent ever smoke	44.89	52.46	52.59	52.38

Champaign County was very well-matched to the comparison counties with former gas plants on the variables of interest. Given the relatively high proportion of counties with former manufactured gas plants in Illinois, the availability of matching counties without former gas plants was more limited. However, based on our county scoring methodology and criteria, we were able to identify counties (i.e., Brown, Douglas, Menard, Randolph) without former gas plants to serve as comparison communities in our second type of analyses. These counties were not as closely matched on potential confounding factors (i.e., demographic characteristics) that may be associated with cancer as the counties used in the first analyses.

Cancer Mortality

The RR for total cancer mortality in Champaign County versus the comparison counties most closely matched demographically (Macon, Winnebago, and Sangamon) was significantly decreased (RR = 0.91, 95% CI: 0.88-0.94) during 1990-2010 (Table 3). Similarly, statistically significant deficits in mortality were observed for cancers of the esophagus (RR = 0.80, 95% CI: 0.65-0.98), colorectum (RR = 0.88, 95% CI: 0.80-0.97), pancreas (RR = 0.78, 95% CI: 0.68-0.89), and lung & bronchus (RR = 0.85, 95% CI: 0.80-0.89). In fact, out of all 22 cancer site groupings, 17 RRs represented reduced risks, one RR was 1.0, no data were available for one site (testicular cancer), and three RRs were slightly elevated. None of these elevated cancer sites was statistically significant, with RRs of 1.03 (melanoma), 1.06 (prostate), and 1.05 (leukemias) (Table 3).

Table 3. Age adjusted mortality rates, RRs and 95% CI[†] in 1990-2010

	Champaign County			Comparison counties most closely matched demographically			Rate Ratio	95% CI
	No. of Deaths	Rate	95% CI	No. of Deaths	Rate	95% CI		
All Cancer	5,611	187.2	182.3-192.2	27,170	206.1	203.6-208.5	0.91*	0.88-0.94
Oral Cavity & Pharynx	64	2.1	1.6-2.7	358	2.7	2.4-3.0	0.78	0.59-1.03
Esophagus	118	4.0	3.3-4.7	650	4.9	4.5-5.3	0.80*	0.65-0.98
Stomach	94	3.1	2.5-3.8	494	3.7	3.4-4.1	0.84	0.67-1.05
Colorectal	551	18.4	16.9-20.0	2,765	20.8	20.1-21.6	0.88*	0.80-0.97
Liver	87	2.9	2.3-3.6	420	3.2	2.9-3.5	0.91	0.71-1.15
Pancreas	267	9.0	7.9-10.1	1,526	11.5	11-12.1	0.78*	0.68-0.89
Lung & Bronchus	1,526	51.3	48.7-53.9	7,990	60.6	59.2-61.9	0.85*	0.80-0.89
Bone & Joint	12	0.3	0.2-0.6	43	0.3	0.2-0.4	0.94	0.42-1.89
Melanomas	81	2.7	2.1-3.3	339	2.6	2.3-2.9	1.03	0.80-1.31
Breast[‡]	438	25.6	23.3-28.2	2,045	27.5	26.3-28.7	0.93	0.84-1.03
Prostate[‡‡]	348	31.4	28.1-34.9	1,427	29.7	28.1-31.3	1.06	0.94-1.19
Testis[‡‡]	-	-	-	-	-	-	-	-
Cervix[‡]	39	2.3	1.6-3.2	177	2.6	2.2-3.0	0.89	0.61-1.27
Uterine[‡]	72	4.2	3.2-5.2	323	4.2	3.7-4.6	1.00	0.76-1.29
Ovary[‡]	159	9.3	7.9-10.8	716	9.5	8.8-10.2	0.98	0.82-1.17
Kidney & Renal Pelvis	136	4.5	3.8-5.4	618	4.7	4.3-5.1	0.97	0.80-1.17
Bladder	131	4.4	3.7-5.3	610	4.6	4.2-5.0	0.97	0.79-1.17
Nervous System	119	3.8	3.2-4.6	596	4.6	4.2-5.0	0.83	0.68-1.02
Hodgkins Lymphomas	13	0.4	0.2-0.7	61	0.5	0.4-0.6	0.88	0.44-1.61
NHL	230	7.6	6.7-8.7	1,096	8.3	7.8-8.8	0.92	0.79-1.06
Myelomas	110	3.7	3.0-4.5	510	3.8	3.5-4.2	0.96	0.77-1.18
Leukemias	251	8.2	7.3-9.3	1,029	7.8	7.4-8.3	1.05	0.91-1.21

[†]Tiwariet al. 2006 modification for CIs
[‡]Female only, [‡‡] Male only
*p < 0.05

In our second set of analyses, similar results for Champaign County were observed when compared with counties without former manufactured gas plants. Total cancer was associated with an RR of 0.96 (95% CI: 0.92-1.00), and statistically significant reduced rates of colorectal (RR = 0.85, 95% CI: 0.75-0.97) and pancreatic cancer (RR = 0.81, 95% CI: 0.67-0.98) mortality were observed (data tables not shown, but available upon request). Relative risks for most cancer sites were 1.0 or lower, with few weakly positive, albeit non-significant associations. No statistically significant associations for the more common cancers – lung & bronchus (RR =

0.94, 95% CI: 0.87-1.02), breast (RR = 1.00, 95% CI: 0.85-1.18), or prostate (RR = 1.00, 95% CI: 0.84-1.19) were observed.

Taken together, results based on analyses using communities with and without former gas plants are not supportive of an increased risk of cancer mortality.

Cancer Incidence

A statistically significant reduced rate of total cancer incidence was observed in Champaign County versus the comparison counties most closely matched demographically (RR = 0.95, 95% CI: 0.94-0.97) during 1991-2010 (Table 4). Decreased incidence rates were observed for nineteen of 23 cancer site groupings based on analyses during 1991-2010. Incidence rates for cancers of the colorectum, pancreas, lung & bronchus, testis, cervix, nervous system, and "other" sites (list of cancers in this category are shown in Table 4) were all significantly lower versus the rates in the comparison counties. In contrast, statistically significant slightly elevated rates were observed for melanoma (RR = 1.12, 95% CI: 1.02-1.24) and prostate cancer (RR = 1.20, 95% CI: 1.14-1.25). Restricting the analytical period to 1991-2000 in Champaign County in order to reduce potential bias associated with the formation of the neighborhood advocacy group did not appreciably modify the results; the RR for melanoma was 1.17 (95% CI: 0.99-1.38) and the RR for prostate cancer was 1.17 (95% CI: 1.09-1.26) (data not tabulated). Incidence rates were significantly reduced for total, colorectal, pancreatic, lung & bronchus, testicular, and cervical cancers during 1991-2000.

Table 4. Age, sex, and race-adjusted incidence rate by county, RRs and 95% CI† in 1991-2010

	Champaign County			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All cancer	13978	499.55	491.17-507.93	61184	524.18	520.03-528.34	0.95*	0.94-0.97
Oral cavity & pharynx	332	11.94	10.64-13.23	1484	12.71	12.07-13.36	0.94	0.83-1.06
Esophagus	141	5.21	4.35-6.08	696	5.96	5.52-6.41	0.87	0.73-1.05
Stomach	177	6.38	5.43-7.33	809	6.93	6.45-7.41	0.92	0.78-1.09
Colorectal	1442	52.87	50.11-55.62	7140	61.17	59.75-62.59	0.86*	0.82-0.91
Liver	112	3.94	3.20-4.67	486	4.16	3.79-4.53	0.95	0.77-1.16
Pancreas	291	10.69	9.45-11.92	1558	13.35	12.69-14.01	0.80*	0.71-0.91
Lung & Bronchus	1945	71.76	68.55-74.96	10063	86.21	84.53-87.90	0.83*	0.79-0.87
Bone	23	0.68	0.39-0.97	80	0.69	0.54-0.84	1.00	0.62-1.60
Melanomas	539	17.62	16.10-19.14	1834	15.71	14.99-16.43	1.12*	1.02-1.24
Breast-invasive‡	2184	150.65	144.25-157.04	9158	151.54	148.43-154.64	0.99	0.95-1.04
Prostate‡‡	2254	172.52	165.38-179.66	8125	144.35	141.21-147.48	1.20*	1.14-1.25
Testis‡‡	89	4.05	3.18-4.93	337	5.99	5.35-6.63	0.68*	0.53-0.86
Cervix‡	114	6.84	5.54-8.14	561	9.28	8.51-10.05	0.74*	0.60-0.91
Uterus‡	406	28.53	25.74-31.33	1801	29.80	28.42-31.18	0.96	0.86-1.07
Ovary‡	228	15.52	13.48-17.57	1022	16.91	15.87-17.95	0.92	0.79-1.06
Kidney	425	15.10	13.64-16.55	1945	16.66	15.92-17.40	0.91	0.81-1.01
Bladder	363	13.56	12.16-14.96	1725	14.78	14.08-15.48	0.92	0.82-1.03
Nervous System	164	5.53	4.66-6.39	797	6.83	6.35-7.30	0.81*	0.68-0.96
Hodgkins Lymphomas	93	2.51	1.98-3.04	341	2.92	2.61-3.23	0.86	0.68-1.09
NHL	556	19.64	17.98-21.29	2490	21.33	20.49-22.17	0.92	0.84-1.01
Myelomas	183	6.68	5.71-7.66	758	6.49	6.03-6.96	1.03	0.88-1.21
Leukemias	433	15.32	13.86-16.79	1678	14.38	13.69-15.06	1.07	0.96-1.19
All Other Sites‡‡‡	1484	50.63	48.00-53.26	6296	53.94	52.61-55.27	0.94*	0.89-0.99

†Breslow and Day 1987

‡Female only, ‡‡ Male only

‡‡‡Includes small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, breast-invasive male only, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

*$p < 0.05$

Fewer cancer sub-groupings were available at the zip code level. Nevertheless, results similar to those in the county-level analyses were observed. Total cancer incidence was 11% lower in the study zip codes versus the most closely matched comparison counties, resulting in a statistically significant RR of 0.89 (95% CI: 0.86-0.93) during 1991-2010 (Table 5). Of the 10 cancer site groupings, nine incidence rates were decreased versus comparison counties, including statistically significant reductions for colorectal (RR = 0.85, 95% CI: 0.76-0.95), breast

(invasive) (RR = 0.86, 95% CI: 0.78-0.95), and "other" (RR = 0.86, 95% CI: 0.79-0.92) cancers. The only elevated incidence rate was for prostate cancer, with a significant RR of 1.13 (95% CI: 1.03-1.24), based on 500 diagnosed cases during 1991-2010. However, no significant association was found for prostate cancer (RR = 1.07, 95% CI: 0.95-1.21) in the analysis for the period 1991-2000 (data not tabulated). During this period, rates for colorectal, breast, and "other" remained significantly decreased, while significant deficits for lung & bronchus (RR = 0.75, 95% CI: 0.66-0.86) and central nervous system cancers (RR = 0.55, 95% CI: 0.33-0.93) were observed as well.

Table 5. Age and sex-adjusted incidence rate by zip code, RRs and 95% CI[†] in 1991-2010.

	Zip 61820, 61801			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All Cancer	3191	468.15	451.25-485.06	61184	524.18	520.03-528.34	0.89*	0.86-0.93
Oral Cavity & Pharynx	81	12.40	9.62-15.19	1484	12.71	12.07-13.36	0.98	0.77-1.23
Colorectal	349	51.93	46.32-57.53	7140	61.17	59.75-62.59	0.85*	0.76-0.95
Lung & Bronchus	440	67.81	61.34-74.27	10063	86.21	84.53-87.90	0.79	0.71-0.87
Breast-Invasive[‡]	464	130.16	117.79-142.52	9158	151.54	148.43-154.64	0.86*	0.78-0.95
Cervix[‡]	38	8.22	5.33-11.12	561	9.28	8.51-10.05	0.89	0.62-1.27
Prostate[‡‡]	500	163.09	148.61-177.57	8125	144.35	141.21-147.48	1.13*	1.03-1.24
Urinary System	186	28.87	24.61-33.13	3670	31.44	30.42-32.46	0.92	0.79-1.07
Central Nervous System	38	5.47	3.63-7.31	797	6.83	6.35-7.30	0.80	0.57-1.13
Leukemias and Lymphomas	267	36.55	31.88-41.22	4509	38.63	37.50-39.76	0.95	0.83-1.08
All other cancers[‡‡‡]	828	114.84	106.51-123.17	15677	134.31	132.21-136.41	0.86*	0.79-0.92

[†]Breslow and Day 1987

[‡]Female only, [‡‡] Male only

[‡‡‡] Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva,

other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.
*p < 0.05

Additional sub-group analyses for the cancer sites were conducted by individual zip codes and by analytical periods. The rate of prostate cancer during 1991-2010 was elevated with marginal significance for zip code 61820 (RR = 1.15, 95% CI: 1.00-1.32, based on 211 cases) but not for zip code 61801 (RR = 1.12, 95% CI: 0.99-1.26) (data not tabulated). No effect modification was apparent by zip code as the CIs for prostate cancer largely overlapped. No other statistically significantly cancer rates were observed during 1991-2010 but rates were modified in the inverse direction for colorectal (RR for zip code 61820 = 0.98, 95% CI: 0.84-1.15; zip code 61801 = 0.76, 95% CI: 0.65-0.88) and lung & bronchus (RR for zip code 61820 = 0.98, 95% CI: 0.86-1.13; zip code 61801 = 0.65, 95% CI: 0.57-0.75) cancers (data not tabulated). Interestingly, when analyses were conducted for the period 1991-2000, prostate cancer rates were modified by zip code (RR for zip code 61820 = 1.23, 95% CI: 1.02-1.48; zip code 61801 = 0.98, 95% CI: 0.83-1.16).

In the second type of analysis, counties without former manufactured gas plants were used as the comparison (data tables not shown, but available upon request). No difference in total cancer was found between Champaign County and the comparison counties without former gas plants (RR = 1.00, 95% CI: 0.97-1.02). Of 22 cancer site groupings, 12 had reduced rates in Champaign County, with statistically significant deficits for colorectal (RR = 0.83, 95% CI: 0.76-0.90) and cervical cancer (RR = 0.66, 95% CI: 0.49-0.90). Respiratory system cancers (lung & bronchus RR = 0.95), urinary tract cancers (kidney RR = 0.99; bladder RR = 1.01), and lymphohematopoietic malignancies (Hodgkins lymphomas RR = 0.89; non-Hodgkins lymphomas RR = 0.96; myelomas RR = 0.99; leukemias RR = 1.03) were not elevated in

Champaign County compared with the counties that did not have former gas plants. As with the first set of analyses, prostate cancer incidence was elevated slightly and significantly (RR = 1.14, 95% CI: 1.06-1.23) in Champaign County, but it was not significant in the study zip code analysis (RR = 1.09, 95% CI: 0.98-1.21). The only other statistically significant positive association in the county analysis was for esophageal cancer (RR = 1.46, 95% CI: 1.07-1.99), but this finding was not substantiated in other analyses. Total cancer was significantly reduced in the study zip codes versus the comparison counties without former gas plants (RR = 0.94, 95% CI: 0.90-0.98). Moreover, seven of 10 cancer sites were associated with reduced rates in the study zip codes, while three were slightly positive and not significant.

Standardized Incidence Ratio (SIR) Analyses

During the period, 1991-2010, 13,978 total cancers were observed in Champaign County with 14,150 expected based on nationally standardized rates, resulting in an SIR of 0.99 (95% CI: 0.97-1.00) (data not tabulated). Of 23 cancer site groupings, 14 had expected or lower than expected cases of cancer, with statistically significant deficits observed for stomach, liver, pancreas, bone, melanoma, testicular, bladder, nervous system, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. A slightly greater than expected number of lung & bronchus (SIR = 1.07, 95% CI: 1.02-1.11) and kidney (SIR = 1.13, 95% CI: 1.03-1.25) cancer cases were observed in Champaign County, but these findings were not supported by the other analyses. In fact, a slight deficit of lung & bronchus cancer cases was observed in the study zip codes (SIR = 0.98, 95% CI: 0.89-1.07), and urinary system cancer (includes kidney cancer) was reduced significantly (SIR = 0.78, 95% CI: 0.67-0.90) in the study zip codes (Table 6). Significantly fewer than

expected total cancer cases were observed in the study zip codes (SIR = 0.88, 95% CI: 0.85-0.91) (the SIRs for the cancer sites in the study zip codes are summarized in Table 6).

Table 6. Standardized incidence ratios (SIRs) and 95% CI of Zip code 61820 and 61801, 1991-2010

Cancer Sites	Obs	Exp	SIR	95% CI
All Cancer	3191	3612	0.88	0.85-0.91
Oral Cavity & Pharynx	81	82	0.98	0.78-1.22
Colorectal	349	378	0.92	0.83-1.03
Lung & Bronchus	440	450	0.98	0.89-1.07
Breast-Invasive‡	464	511	0.91	0.83-0.99
Cervix‡	38	36	1.04	0.74-1.43
Prostate‡‡	500	525	0.95	0.87-1.04
Urinary System	186	239	0.78	0.67-0.90
Central Nervous System	38	63	0.60	0.43-0.83
Leukemias and Lymphomas	267	320	0.84	0.74-0.94
All other cancers‡‡‡	828	1008	0.82	0.77-0.88

†Breslow and Day 1987
‡Female only, ‡‡ Male only
‡‡‡ Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

DISCUSSION

We observed statistically significant reductions in total cancer mortality and incidence in Champaign County, IL, and the zip code study areas compared with counties that were similar demographically and socioeconomically, and based on nationally standardized rates. Furthermore, cancer occurrence was lower in the study area for most cancer types, with several statistically significant reductions in cancer rates. Results were largely consistent within and across analyses, with a few exceptions. Indeed, the lower mortality rates for most cancers in the study area versus the comparison counties were in accordance with the lower cancer incidence rates observed in Champaign County and the study zip codes. The only noteworthy positive associations in the primary analyses were for prostate cancer and melanoma. Neither prostate

cancer mortality nor melanoma mortality was significantly elevated. However, incidence rates for these cancers were significantly increased in Champaign County. It is not clear why elevated rates were observed, although based on chance alone, it would be expected that some cancer rates would be statistically significant in both the positive and inverse directions. As indicated, we observed several statistically significant inverse associations (i.e. RRs below the null value of 1.0), such as for lung & bronchus, colorectal, and breast cancers. However, only two cancer types (prostate cancer and melanoma; incidence only) were associated with statistically significant positive associations. Thus, significant associations may have been observed due to multiple comparisons – a statistical phenomenon whereby one out of 20 associations is statistically significant due to chance [14, 15]. In our analysis, we generated over 100 unique RRs.

Prostate cancer is the most common cancer among men in the U.S., and 238,590 incident cases and 29,720 deaths were estimated to occur in 2013 [16, 17]. The figures for prostate cancer represent 14.4% of all new cancer cases and 5.1% of all cancer deaths in the U.S. [17]. Increasing age, African American race, family history of prostate cancer, and genetic variations and mutations are established risk factors for prostate cancer, although the etiology is largely unknown despite an extensive effort to identify causes of this malignancy [16, 17]. The role of lifestyle and dietary factors are thought to play a role in prostate cancer risk, as past research has identified obesity, physical inactivity, and smoking as significant modifiable risk factors for this malignancy [18-21]. Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors such as physical activity, family history of disease, or body mass index that may have influenced the results. Based on a review of the literature and

statements by prominent cancer organizations [16, 17], no manufactured gas plant by-product compound has been clearly or consistently associated with prostate cancer risk.

Perhaps the most likely reason for the elevation in prostate cancer incidence during 1991-2010 is the increased rate of prostate-specific antigen (PSA) screening in Champaign County versus the comparison counties. Indeed, based on the Behavioral Risk Factor Surveillance System (BRFSS) survey from the Centers for Disease Control and Prevention (CDC) and administered by the Illinois Department of Public Health [9], the percent of men who underwent PSA screening was higher in Champaign County than Sangamon, Macon, and Winnebago counties (as a composite percentage) during the study period. Furthermore, composite rates of PSA screening were higher in Champaign County than the counties without former gas plants. It is well-established and well-publicized that screening for prostate cancer results in an increase in incidence rates, whereas a proportion of prostate cancers may otherwise go undetected without screening [22-24]. In a sentinel review paper on the epidemiologic impact of screening on the incidence and mortality of prostate cancer in the U.S., it was suggested that PSA testing was the likely cause of the dramatic increase in prostate cancer incidence during the 1990s [23]. Although PSA testing is useful for early diagnosis, its value as a screening tool has been under scrutiny because the theoretical benefit on mortality is questionable [24]. According to a recent study from the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized screening trial, men who underwent annual prostate cancer screening with PSA testing and digital rectal examination had a 12 percent higher incidence rate of prostate cancer compared with men in the control group (who did not undergo PSA testing) [25]. However, approximately the same rate of death from prostate cancer was observed between groups, and no evidence of a mortality benefit was found in age or pre-trial PSA testing strata [25]. In our assessment, we observed a statistically

significant increase in prostate cancer incidence in Champaign County (where a greater proportion of individuals underwent PSA testing) but no statistically significant difference in prostate cancer mortality versus the comparison counties.

Melanoma was also associated with a statistically significant positive association (incidence only). Cancer incidence data for melanoma were not available at the zip code level, thus, it is uncertain if melanoma occurrence was higher in the areas directly circumscribing the abandoned plant. Approximately 21.3 out of 100,000 men and women are diagnosed annually with melanoma, and it is about twenty times more common in whites than blacks [17]. The major risk factor for melanoma is exposure to ultraviolet (UV) rays (sunlight is the primary source of UV rays), particularly among persons with fair skin. Other risk factors include having a large number of moles, having one or more first-degree relatives who have had melanoma, and being immunosuppressed [16]. It has been hypothesized that malignant melanoma may occur as a result of exposure to occupational or environmental chemicals (e.g., vinyl chloride, arsenic, polychlorinated biphenyls, petrochemicals, pesticides), particularly because malignancy can develop in cutaneous areas that have not been exposed to sunlight [26]. However, the epidemiologic evidence relating chemical exposures to melanoma risk is inconsistent. Thus, it is unclear whether the positive incidence rate ratio in Champaign County is the result of an artifactual finding from multiple comparisons, or has been confounded by sun exposure or other factors, such as immunosuppression. Moreover, general health concerns that the local population may have about living next to a former gas manufacturing site may lead to surveillance bias due to increased screening. Furthermore, a statistically significant deficit of melanoma was observed in Champaign County based on SIR analyses, and no statistically significant associations for melanoma were found based on comparisons with counties that did not have a former gas plant.

Finally, esophageal cancer incidence was elevated when Champaign County was compared with the non-gas plant counties in our sensitivity analysis of cancer incidence, but this observation was not substantiated by the main analyses, the sensitivity analysis of cancer mortality, or by the SIR analysis.

Alternatively, an unknown manufactured gas product compound may have produced the slight elevations in prostate cancer and/or melanoma incidence in the main analyses. This scenario is unlikely, however, given the plausible explanations listed above and because reduced rates were observed for cancers with known environmental or chemical relationships. That is, no "indicator" cancer types with established environmental or chemical etiology were observed in excess. For example, IARC has classified "coke production" as carcinogenic to humans (Group 1) for lung cancer because of exposure to PAHs in the industry (although associations from the occupational studies are somewhat tenuous) [27-29]. In a quantitative review of occupational exposures to PAHs, lung cancer and bladder cancer risk was elevated significantly among workers in the coal gasification industry [30]. However, in our assessment, we observed statistically significant reduced mortality and incidence rates of 15% and 17%, respectively, for lung & bronchus cancers, and no associations for urinary system and bladder cancers Moreover, our analyses were based on rates of cancer at the community level, not among workers likely exposed to much higher concentrations of possible chemical exposures.

It is unclear as to why there was a preponderance of inverse associations in Champaign County and the study zip codes versus the comparison counties. *A priori*, we developed a systematic protocol for identifying comparable counties. We identified counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level). Based on the 2000 census

information, there were approximately 7% fewer 'ever' smokers in Champaign County versus the comparison counties. This may explain, in part, the observation of lower cancer rates, particularly for lung & bronchus, in Champaign County. In addition, the prevalence of other potentially important factors, such as alcohol consumption or obesity, in these counties may have confounded the observed associations. However, relatively similar patterns of associations were observed in sensitivity analyses comparing Champaign County and the study zip codes with counties that did not have a former gas plant, and based on SIR analyses using nationally representative cancer data from the SEER program.

Most of the literature on manufactured gas plants focuses on the environmental and ecological impacts of the gas process residues and waste products. As such, considerable literature exists on the methodological, toxicological, elemental chemistry, and extracting techniques involving remediation and compound evaluations from abandoned sites [31-34]. While potentially hazardous compounds may have been produced as part of the gas manufacturing process, the extent and level to which compound residues persist at the sites is unclear. In certain cases, potential hazards may be overestimated as samples in some studies have been consistent with background levels or below the assumed level [1, 35]. As mentioned previously, the literature on direct or indirect human health risks from an epidemiologic standpoint, is sparse. DeHate et al. [1] investigated soil vapor intrusion at 10 commercial buildings and 26 single family and multi-family residential properties overlying and/or adjacent to three former manufactured gas plant sites. Soil vapor samples and indoor/outdoor air were analyzed for VOCs, and comparative risks were evaluated based on maximum and mean concentrations for BTEX relative to background levels. All hazard indices were less than one or were comparable to mean and maximum background levels, and there was no evidence of

manufactured gas plant-related soil vapor intrusion from any of the 36 sites. Based on these findings, the authors reported that no increased public health risks were associated with occupied residential or commercial properties overlying or surrounding former manufactured gas plant facilities [1]. Occupational epidemiologic studies involving postulated gas plant exposures, such as PAHs [27, 30], BTEX [36-38], and coal tar [30, 39-41], are extensive but none have evaluated potential disease outcomes resulting from residing in a community that includes a former manufactured gas plant site.

Our historical cancer assessment has limitations that are commonplace with analyzing population-level data. Prime among the limitations is that we did not have individual-level information on lifestyle, dietary, medical, or occupational factors. In addition, we did not have personal information regarding potential exposures (e.g., to soil, groundwater, or air) from the manufactured gas process. We were, however, able to adjust cancer estimates for age, sex, and race. Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law. The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected. The gas plant ceased operations in 1953, and although immediate release of potential compounds may have diminished at that time, concern about the persistence of compounds over time in the vicinity has been raised. Our analyses were conducted on the basis of publically available aggregate-level data. We began our analytical period at the earliest time point possible that enabled us to merge cancer data and census data. Given our analytical periods, there is sufficient latency to observe a carcinogenic effect, if one exists.

However, we were not able to capture cases that occurred in earlier time periods, with possible greater exposures. It may be possible that our analyses are not sensitive enough to identify small effects of plant exposures because of the nature of residential exposure classification. Despite these limitations, we found no clear or consistent evidence of an increase in cancer occurrence among residents in a community circumscribing a former manufactured gas plant.

The validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program. These three types of analyses serve as complementary comparisons to examine the consistency of findings across different population metrics. We implemented an objective methodological approach to identify counties in the state of Illinois that were the most closely matched (demographically) to the analytical zones. By using this approach, we were able to account for some prominent confounding factors at the aggregate level. However, the most closely matched comparison areas also had former gas plants. Therefore, we conducted a second analysis by matching demographic factors that was restricted to counties without former gas plants. Finally, we conducted analyses using nationally standardized rates of cancer. Despite the variation in analytical approaches, results were consistent between techniques.

We conducted a community cancer assessment for the purpose of appraising the public health regarding the occurrence of cancer among residents in a community with a former manufactured gas plant. Although this study did not include individual-level information, rates of total cancer and most cancer sites in the Champaign County area and zip codes circumscribing the abandoned facility were lower versus similar comparison areas, and based on nationally standardized rates of cancer. The primary exception is for prostate cancer, although there may be

relevant explanations for the higher rates aside from potential exposure emanating from the former manufactured gas plant site, such as an incidence spike due to higher PSA testing rates in Champaign County, a statistical artifact based on multiple comparisons, or confounding by unmeasured factors. Furthermore, a review of the literature did not reveal any known relation between the potential gas plant compounds and prostate cancer risk. Interpretation of results from our analyses should be made in the context of the many limitations of ecological-based study designs. However, the results from this retrospective cancer mortality and incidence assessment do not support an increase in cancer occurrence in communities surrounding a former manufactured gas plant in Champaign, IL.

AUTHOR CONTRIBUTION: DDA, DHG, and JPF were responsible for conception and design of the research. Statistical analyses were carried out by XJ. DDA, XJ, LCB, DHG, SRI, and JPF were responsible for development of the manuscript, critical revision and intellectual content.

FUNDING: This work was supported by Ameren Corporation.

COMPETING INTERESTS: DHG has served as an expert witness on behalf of Ameren in litigation related to manufactured gas plants. DDA, XJ, LCB, DHG, SRI, and JPF are employed by EpidStat Institute, all of whom were contracted by Ameren Corporation to support the study.

DATA SHARING STATEMENT: The full data set is available by emailing the corresponding author of the study.

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Historical Cancer Incidence and Mortality Assessment in an Illinois Community Proximal to a Former Manufactured Gas Plant

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Word count: 5,164 words

Abstract word count: (243 words)

Kewords: natural gas manufacturing, community, cancer incidence, epidemiology

Formatted: Highlight

ABSTRACT

Objectives: Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant in Champaign, IL. Thus, we compared historical rates of cancer in this area to comparison communities as well as with nationally standardized rates.

Design: Retrospective population-based community cancer assessment during 1990-2010

Setting: Champaign County, IL, and zip codes encompassing the location of the former manufactured gas plant to counties that were similar demographically.

Participants: Residents of the counties and zip codes studied between 1990-2010.

Main outcome measures: The relative risk (RR) and 95% confidence interval (CI) were used to compare cancer incidence and mortality in the areas near the gas compression site to the comparison counties. Standardized incidence ratios (SIR) were calculated to compare rates in the areas near the gas compression site to expected rates based on overall United States cancer rates.

Results: Total cancer mortality (RR = 0.91, 95% CI: 0.88-0.94) and incidence (RR = 0.95, 95% CI: 0.94-0.97) were reduced significantly in Champaign County versus the comparison counties. Similarly, a reduced rate of total cancer was observed in analyses by zip code (proximal to the former gas plant) when compared to either similar counties (RR = 0.89, 95% CI: 0.86-0.93) or national standardized rates of cancer (SIR = 0.88, 95% CI: 0.85-0.91).

Conclusions: This historical cancer assessment did not find an increased risk of total cancer or specific cancer types in communities near a former manufactured gas plant site.

Strength and limitations of this study:

- The validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program.
- Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law.
- A priori, we developed a systematic protocol for identifying comparable counties. We matched counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level) to control for confounding.
- Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors associated with cancer such as physical activity, family history of disease, or body mass index that may have influenced the results.
- The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected.

INTRODUCTION

The production of manufactured gas is widely considered one of the key developments in our industrial history, with an extensive chronology beginning in the late 1700s and spanning into the 1960s. Manufactured gas consisted largely of the gasification of coal, and less frequently, the combustion of other materials such as wood and oil. Historically, the manufactured gas industry grew significantly in the early 1800s due to the production of lighting for the progress and development of cities. However, later in the 19th century, this industry diversified into heating, refrigeration, and cooking. During the early to mid-20th century, the advent of natural gas obviated the gasification of coal, ultimately leading to the conversion or closure of manufactured gas plants. Pipelines transported natural gas directly from the well to gas distribution systems, and natural gas was considered more economical, efficient, and environmentally friendly. Most manufactured gas plants in the U.S. were terminated by1966 with few exceptions, and as a result of the manufactured gas demise, over 1,500 plant sites are suggested to remain dormant or vacant in the U.S. today.

Numerous health concerns have been raised regarding possible environmental exposures stemming from manufactured gas plant sites. Foremost among the concerns is that contamination and waste products from the manufacturing gas process leaked into the adjacent soil and groundwater, thus posing health risks in the nearby residential areas and communities [1]. The process of coal carbonization generates coal tar, which are complex mixtures of heterocyclic compounds, phenols, and polycyclic aromatic hydrocarbons (PAHs). Indeed, both volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs) from coal tar and petroleum products are derived from the coal gasification process [1]. The VOCs contain a mixture of BTEX, or benzene, toluene, ethylbenzene, and xylene isomers among other

compounds, while the SVOCs consist of a mixture of compounds, such as benzo(a)pyrene, benzo(e)pyrene, naphthalene, and 2-methyl naphthalene. In addition, principal component analyses have identified heavy metals at former manufactured gas plant sites [2, 3]. As a result of these gas process by-products, the U.S. Environmental Protection Agency (EPA) and other regulatory agencies have focused on assessing the potential for soil and groundwater contamination at former manufactured gas plant sites, as well as evaluating the potential for health risks among residents in nearby communities. The International Agency for Research on Cancer (IARC) lists many of the manufactured gas plant by-product compounds as known, probable, or possible carcinogens for specific cancers but the level and extent of community exposure to such compounds resulting from former manufactured gas plants is uncertain. Furthermore, sparse epidemiologic evidence exists on the potential public health risks associated with residing near former manufactured gas plant sites.

Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant on a 3.5 acre lot in northern Champaign, IL. The plant, in operation from 1887 until 1953, manufactured gas by heating coal. Coal tar and other production wastes were suggested to remain on site until the closing of the plant. AmerenIP has registered this site with the Illinois EPA under their Site Remediation Program. However, the potential long-term health effects of residents in the nearby community are unknown. Therefore, we conducted a historical cancer incidence and mortality assessment using publicly available cancer data and census tract information to evaluate the occurrence of cancer in the community where the former manufactured gas plant was located compared with other communities with and without former gas plants that have similar demographic and lifestyle characteristics. In

addition, we conducted standardized incidence analyses for Champaign County and the study zip codes using nationally representative cancer data.

METHODS

All data used in this study are publicly available. Specifically, the cancer incidence data were obtained from the Illinois Department of Public Health and from the Surveillance, Epidemiology, and End Results (SEER) Program, while cancer mortality data were obtained from SEER. Analyses for cancer incidence are presented at both the county and zip code level while analyses for cancer mortality are presented at the county level, which is the smallest area for which cancer mortality data are available. County and zip code demarcations were based on information provided by the U.S. Census Bureau.

Study Areas

The analytical and comparison population areas were characterized using census tract information. The former manufactured gas plant of interest was located in Champaign County, IL, and was circumscribed by zip codes 61820 and 61801; thus, these demarcated areas served as the analytical group. Because our assessment was community-based and ecologic in nature, ~~O~~our objective was to identify comparison counties in the state of Illinois with similar demographic and socioeconomic characteristics. Relevant characteristics included county setting (urban vs. rural), county population size, and percentages for black race, high school graduation, persons over age 65, persons unemployed, families below poverty level, urban residence, and ever smoking status. In addition, the median household income was utilized as a comparison factor. County selection was based on methods developed by the National Cancer Institute [4, 5].

Illinois Cancer Data

In concert with the Illinois State Cancer Registry (ICSR), the SEER program of the National Cancer Institute is the source of data for cancer mortality between 1986 and 2010 [6]. These data are grouped by age, sex, and race and are provided at the county level (the smallest available area for cancer mortality). The National Center for Health Statistics (NCHS) provides information on the underlying cause of death, coded to the International Classification of Diseases (ICD-9) [7] for all deaths for years 1986 through 1998 and the International Classification of Diseases (ICD-10) for all deaths for year 1999 and later [8]. Cancer mortality rates are available by single year for Illinois only, and deaths among non-residents and deaths of unknown age or sex are omitted from the database calculations. Because of NCHS policy, rates are not calculated for stratified sub-groups containing less than 10 deaths. For this analysis we used mortality data from 1990-2010 to be consistent with the census tract reporting periods.

Cancer incidence data for the direct community comparisons used in this study were collected by the ISCR and are available as a public use data set via the Illinois Department of Public Health for the years 1991-2010. All obtainable data are provided by the ISCR as a public service for the purpose of statistical reporting and analysis only. Case ascertainment is near complete as the identification and reporting of cancer cases is mandated by state law. Individual (personal) information has been de-identified, and the data have been aggregated into categories (e.g., age, race, Hispanic ethnicity, year of diagnosis and type of cancer) within individual records [9]. The number of cases reported in a particular region depends on the size of the geographic area in an effort to protect the privacy of individuals. The Illinois dataset contains sanitized records of cancer incidence among residents who were diagnosed between 1986 and

2011. Cancer incidence data at the county and zip code level are based on five-year interval groupings, and include data for invasive cancers only with the exception of bladder cancer. Non-melanoma skin cancers and reported cases with an unknown age or "other" sex category are omitted by the ISCR. Cancer incidence data used for the SIR analyses were obtained directly from the SEER program.

By using these data, we agreed to comply with the Illinois Health and Hazardous Substances Registry Act (410 ILCS 525/12). All data used in our analyses are publically available, thus, informed consent was not required.

Statistical~~Main~~ Analyses

As indicated, we ascertained cancer rates from the ISCR and the SEER program. The rates provided by these sources were calculated using the SEER*Stat® software package, developed by the Information Management Services Inc. for the National Cancer Institute [10]. SEER expresses rates per 100,000 population, and rates are age-adjusted by the direct method adjusting to the 2000 U.S. standard million population. These data were then used to formulate the basis of our historical cancer assessment.

Because of the ecologic nature of the community-based analyses, we conducted analyses in an effort to account for potential confounding at the aggregate level while considering the potential for exposure misclassification. Thus, we conducted analyses using three different comparison populations based on: 1) Illinois counties that were the most closely matched demographically (irrespective of having former gas plants), 2) counties without former gas plants (as part of the selection criteria) that were relatively similar demographically, and 3) nationally representative cancer data from the SEER program. By utilizing three different comparison

populations, we were able to enhance the validity of our analyses, examine the consistency of cancer rates across different groups, and facilitate the identification of potential sources of statistical heterogeneity (if present). All types of analyses serve as complementary comparisons to appreciate fully any observed associations.

In the first type of analysis, ~~W~~we calculated relative rate ratios (RRs) and 95% confidence intervals (CIs) to compare cancer mortality and incidence rates in Champaign County, IL and zip codes 61820 and 61801 encompassing the location of the former manufactured gas plant to counties that were the most similar demographically (i.e., Macon, Winnebago, and Sangamon counties). Although not part of the selection criteria, these counties had former gas plants but were the most demographically comparable based on our objective matching criteria. ~~These comparisons served as the main analyses because they were very well-matched demographically to the study areas.~~ The number of cancer cases and deaths were ascertained for the period 1990 through 2010, and the absolute rate of cancer occurrence was calculated based on the county and zip code population size according to the U.S. Census Bureau. The relative rate of cancer occurrence was calculated by dividing the rate of cancer in Champaign County and the zip codes (for cancer incidence only) by the rate of cancer in the comparison counties. County-level analyses were statistically adjusted for age, sex, and race, and zip code-level analyses were adjusted for age and sex (race stratified data were not available at the zip code level, and mortality analyses were adjusted for age only).

~~Sensitivity analyses~~

Although the comparison counties in the first ~~main~~ analyses were very-well matched demographically to Champaign County, they had former gas plants, which raises concern about

potential bias resulting from similar chemical exposures in the comparison counties. To address this concern, our second ~~we conducted several sensitivity~~ analyses consisted of~~by~~ comparing rates of cancer in Champaign County and the study zip codes with areas that did not have former gas plants but had relatively similar descriptive characteristics~~other populations~~. To do this~~First~~, we reviewed an Environmental Protection Agency (EPA) report on manufactured gas plant production [11], the EPA website, and the following website link: http://www.hatheway.net/state_site_pages/il_epa.htm to identify additional comparison counties. Illinois counties with relatively similar demographic characteristics but without former gas plants (i.e., Brown, Douglas, Menard, Randolph counties) were selected. Evaluations of cancer mortality and cancer incidence, using the same methodology as the first~~main~~ analyses, were conducted using these counties as comparisons.

In our final set of analyses~~Second~~, we calculated standardized incidence ratios (SIRs) for cancer sites in Champaign County and the zip codes of interest. The numbers of observed cancers in Champaign County and in the study zip codes were compared with those expected on the basis of standardized rates of cancer in the general population using data obtained from SEER [12]. The number of observed cancers was determined by sex, race, and 5-year age groups (the zip codes were standardized by age and sex groups) for each year from 1991-2010. Expected numbers of cases were calculated by multiplying the estimated population for Champaign County and for the study zip codes for each year of study by annual SEER cancer rates, stratified by 5-year age groups, race, and sex. Observed and expected counts were then generated for Champaign County and for the study zip codes, and SIRs were calculated by dividing the observed number by the expected number.

A final concern was the possibility of surveillance bias being introduced during the analytical study period. In the mid-2000s, a neighborhood advocacy group formed to increase awareness about the potential health effects from the abandoned gas plant [13]. In order to limit potential bias associated with the formation of this group, we conducted analyses for the years 1990-2000, prior to the formation of this group.

All analyses were performed using SAS statistical software.

RESULTS

Study Counties

The characteristics of the study county and the comparison counties (with the most similar demographic characteristics) are reported in Tables 1 and 2 for the 1990 and 2000 census periods, respectively.

Table 1. Characteristics of Study County and Comparison Counties based on 1990 Census.

Characteristic	Champaign County	Comparison counties most closely matched demographically		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	9.64	8.11	12.14	9.29
Percent did not graduate high school	12.50	18.23	23.79	23.70
Percent over age 65 years	8.74	13.71	14.57	12.67
Percent unemployed	4.24	4.36	6.60	5.20
Percent below poverty	8.03	7.19	9.84	7.71
Median household income (in tens)	2654	3035	2860	3134
Percent Urban	81.41	78.32	81.74	87.41

Table 2. Characteristics of Study county and Comparison counties based on 2000 census.

Characteristic	Champaign County	Comparison counties most closely matched demographically		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	11.82	10.17	14.76	11.16
Percent did not graduate high school	9.02	11.93	16.83	18.57
Percent over age 65 years	9.72	13.51	15.24	12.73
Percent unemployed	5.52	4.07	7.15	5.83
Percent below poverty	6.92	6.49	9.28	6.92
Median household income (in tens)	3778	4296	3786	4389
Percent Urban	84.34	85.40	84.17	91.78
Percent ever smoke	44.89	52.46	52.59	52.38

Champaign County was very well-matched to the comparison counties with former gas plants on the variables of interest. Given the relatively high proportion of counties with former manufactured gas plants in Illinois, the availability of matching counties without former gas plants was more limited. However, based on our county scoring methodology and criteria, we were able to identify counties (i.e., Brown, Douglas, Menard, Randolph) without former gas plants to serve as comparison communities in our second type of~~sensitivity~~ analyses. These counties were not as closely matched on potential confounding factors (i.e., demographic

characteristics) that may be associated with cancer as the counties used in the first~~our main~~ analyses.

Cancer Mortality

The RR for total cancer mortality in Champaign County versus the comparison counties most closely matched demographically (Macon, Winnebago, and Sangamon) was significantly decreased (RR = 0.91, 95% CI: 0.88-0.94) during 1990-2010 (Table 3). Similarly, statistically significant deficits in mortality were observed for cancers of the esophagus (RR = 0.80, 95% CI: 0.65-0.98), colorectum (RR = 0.88, 95% CI: 0.80-0.97), pancreas (RR = 0.78, 95% CI: 0.68-0.89), and lung & bronchus (RR = 0.85, 95% CI: 0.80-0.89). In fact, out of all 22 cancer site groupings, 17 RRs represented reduced risks, one RR was 1.0, no data were available for one site (testicular cancer), and three RRs were slightly elevated. None of these elevated cancer sites was statistically significant, with RRs of 1.03 (melanoma), 1.06 (prostate), and 1.05 (leukemias) (Table 3).

Table 3. Age adjusted mortality rates, RRs and 95% CI† in 1990-2010

	Champaign County			Comparison counties most closely matched demographically			Rate Ratio	95% CI
	No. of Deaths	Rate	95% CI	No. of Deaths	Rate	95% CI		
All Cancer	5,611	187.2	182.3-192.2	27,170	206.1	203.6-208.5	0.91*	0.88-0.94
Oral Cavity & Pharynx	64	2.1	1.6-2.7	358	2.7	2.4-3.0	0.78	0.59-1.03
Esophagus	118	4.0	3.3-4.7	650	4.9	4.5-5.3	0.80*	0.65-0.98
Stomach	94	3.1	2.5-3.8	494	3.7	3.4-4.1	0.84	0.67-1.05
Colorectal	551	18.4	16.9-20.0	2,765	20.8	20.1-21.6	0.88*	0.80-0.97
Liver	87	2.9	2.3-3.6	420	3.2	2.9-3.5	0.91	0.71-1.15
Pancreas	267	9.0	7.9-10.1	1,526	11.5	11-12.1	0.78*	0.68-0.89
Lung & Bronchus	1,526	51.3	48.7-53.9	7,990	60.6	59.2-61.9	0.85*	0.80-0.89
Bone & Joint	12	0.3	0.2-0.6	43	0.3	0.2-0.4	0.94	0.42-1.89
Melanomas	81	2.7	2.1-3.3	339	2.6	2.3-2.9	1.03	0.80-1.31
Breast‡	438	25.6	23.3-28.2	2,045	27.5	26.3-28.7	0.93	0.84-1.03
Prostate‡‡	348	31.4	28.1-34.9	1,427	29.7	28.1-31.3	1.06	0.94-1.19
Testis‡‡	-	-	-	-	-	-	-	-
Cervix‡	39	2.3	1.6-3.2	177	2.6	2.2-3.0	0.89	0.61-1.27
Uterine‡	72	4.2	3.2-5.2	323	4.2	3.7-4.6	1.00	0.76-1.29
Ovary‡	159	9.3	7.9-10.8	716	9.5	8.8-10.2	0.98	0.82-1.17
Kidney & Renal Pelvis	136	4.5	3.8-5.4	618	4.7	4.3-5.1	0.97	0.80-1.17
Bladder	131	4.4	3.7-5.3	610	4.6	4.2-5.0	0.97	0.79-1.17
Nervous System	119	3.8	3.2-4.6	596	4.6	4.2-5.0	0.83	0.68-1.02
Hodgkins Lymphomas	13	0.4	0.2-0.7	61	0.5	0.4-0.6	0.88	0.44-1.61
NHL	230	7.6	6.7-8.7	1,096	8.3	7.8-8.8	0.92	0.79-1.06
Myelomas	110	3.7	3.0-4.5	510	3.8	3.5-4.2	0.96	0.77-1.18
Leukemias	251	8.2	7.3-9.3	1,029	7.8	7.4-8.3	1.05	0.91-1.21

†Tiwariet al. 2006 modification for CIs
‡Female only, ‡‡ Male only
*p < 0.05

In our second set of analyses, ~~S~~similar results for Champaign County were observed when compared with counties without former manufactured gas plants. Total cancer was associated with an RR of 0.96 (95% CI: 0.92-1.00), and statistically significant reduced rates of colorectal (RR = 0.85, 95% CI: 0.75-0.97) and pancreatic cancer (RR = 0.81, 95% CI: 0.67-0.98) mortality were observed (data ~~not tabulated~~tables not shown, but available upon request). Relative risks for most cancer sites were 1.0 or lower, with few weakly positive, albeit non-significant associations. No statistically significant associations for the more common cancers –

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lung & bronchus (RR = 0.94, 95% CI: 0.87-1.02), breast (RR = 1.00, 95% CI: 0.85-1.18), or prostate (RR = 1.00, 95% CI: 0.84-1.19) were observed.

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Taken together, results based on analyses using communities with and without former gas plants are not supportive of an increased risk of cancer mortality.

Cancer Incidence

A statistically significant reduced rate of total cancer incidence was observed in Champaign County versus the comparison counties most closely matched demographically (RR = 0.95, 95% CI: 0.94-0.97) during 1991-2010 (Table 4). Decreased incidence rates were observed for nineteen of 23 cancer site groupings based on analyses during 1991-2010. Incidence rates for cancers of the colorectum, pancreas, lung & bronchus, testis, cervix, nervous system, and "other" sites (list of cancers in this category are shown in Table 4) were all significantly lower versus the rates in the comparison counties. In contrast, statistically significant slightly elevated rates were observed for melanoma (RR = 1.12, 95% CI: 1.02-1.24) and prostate cancer (RR = 1.20, 95% CI: 1.14-1.25). Restricting the analytical period to 1991-2000 in Champaign County in order to reduce potential bias associated with the formation of the neighborhood advocacy group did not appreciably modify the results; the RR for melanoma was 1.17 (95% CI: 0.99-1.38) and the RR for prostate cancer was 1.17 (95% CI: 1.09-1.26) (data not tabulated). Incidence rates were significantly reduced for total, colorectal, pancreatic, lung & bronchus, testicular, and cervical cancers during 1991-2000.

Table 4. Age, sex, and race-adjusted incidence rate by county, RRs and 95% CI[†] in 1991-2010

	Champaign County			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All cancer	13978	499.55	491.17-507.93	61184	524.18	520.03-528.34	0.95*	0.94-0.97
Oral cavity & pharynx	332	11.94	10.64-13.23	1484	12.71	12.07-13.36	0.94	0.83-1.06
Esophagus	141	5.21	4.35-6.08	696	5.96	5.52-6.41	0.87	0.73-1.05
Stomach	177	6.38	5.43-7.33	809	6.93	6.45-7.41	0.92	0.78-1.09
Colorectal	1442	52.87	50.11-55.62	7140	61.17	59.75-62.59	0.86*	0.82-0.91
Liver	112	3.94	3.20-4.67	486	4.16	3.79-4.53	0.95	0.77-1.16
Pancreas	291	10.69	9.45-11.92	1558	13.35	12.69-14.01	0.80*	0.71-0.91
Lung & Bronchus	1945	71.76	68.55-74.96	10063	86.21	84.53-87.90	0.83*	0.79-0.87
Bone	23	0.68	0.39-0.97	80	0.69	0.54-0.84	1.00	0.62-1.60
Melanomas	539	17.62	16.10-19.14	1834	15.71	14.99-16.43	1.12*	1.02-1.24
Breast-invasive[‡]	2184	150.65	144.25-157.04	9158	151.54	148.43-154.64	0.99	0.95-1.04
Prostate[‡‡]	2254	172.52	165.38-179.66	8125	144.35	141.21-147.48	1.20*	1.14-1.25
Testis[‡‡]	89	4.05	3.18-4.93	337	5.99	5.35-6.63	0.68*	0.53-0.86
Cervix[‡]	114	6.84	5.54-8.14	561	9.28	8.51-10.05	0.74*	0.60-0.91
Uterus[‡]	406	28.53	25.74-31.33	1801	29.80	28.42-31.18	0.96	0.86-1.07
Ovary[‡]	228	15.52	13.48-17.57	1022	16.91	15.87-17.95	0.92	0.79-1.06
Kidney	425	15.10	13.64-16.55	1945	16.66	15.92-17.40	0.91	0.81-1.01
Bladder	363	13.56	12.16-14.96	1725	14.78	14.08-15.48	0.92	0.82-1.03
Nervous System	164	5.53	4.66-6.39	797	6.83	6.35-7.30	0.81*	0.68-0.96
Hodgkins Lymphomas	93	2.51	1.98-3.04	341	2.92	2.61-3.23	0.86	0.68-1.09
NHL	556	19.64	17.98-21.29	2490	21.33	20.49-22.17	0.92	0.84-1.01
Myelomas	183	6.68	5.71-7.66	758	6.49	6.03-6.96	1.03	0.88-1.21
Leukemias	433	15.32	13.86-16.79	1678	14.38	13.69-15.06	1.07	0.96-1.19
All Other Sites[‡‡‡]	1484	50.63	48.00-53.26	6296	53.94	52.61-55.27	0.94*	0.89-0.99

[†]Breslow and Day 1987
[‡]Female only, [‡‡] Male only
[‡‡‡]Includes small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, breast-invasive male only, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.
*$p < 0.05$

Fewer cancer sub-groupings were available at the zip code level. Nevertheless, results similar to those in the county-level analyses were observed. Total cancer incidence was 11% lower in the study zip codes versus the most closely matched comparison counties, resulting in a statistically significant RR of 0.89 (95% CI: 0.86-0.93) during 1991-2010 (Table 5). Of the 10 cancer site groupings, nine incidence rates were decreased versus comparison counties, including statistically significant reductions for colorectal (RR = 0.85, 95% CI: 0.76-0.95), breast

(invasive) (RR = 0.86, 95% CI: 0.78-0.95), and "other" (RR = 0.86, 95% CI: 0.79-0.92) cancers. The only elevated incidence rate was for prostate cancer, with a significant RR of 1.13 (95% CI: 1.03-1.24), based on 500 diagnosed cases during 1991-2010. However, no significant association was found for prostate cancer (RR = 1.07, 95% CI: 0.95-1.21) in the analysis for the period 1991-2000 (data not tabulated). During this period, rates for colorectal, breast, and "other" remained significantly decreased, while significant deficits for lung & bronchus (RR = 0.75, 95% CI: 0.66-0.86) and central nervous system cancers (RR = 0.55, 95% CI: 0.33-0.93) were observed as well.

Table 5. Age and sex-adjusted incidence rate by zip code, RRs and 95% CI† in 1991-2010.

	Zip 61820, 61801			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All Cancer	3191	468.15	451.25-485.06	61184	524.18	520.03-528.34	0.89*	0.86-0.93
Oral Cavity & Pharynx	81	12.40	9.62-15.19	1484	12.71	12.07-13.36	0.98	0.77-1.23
Colorectal	349	51.93	46.32-57.53	7140	61.17	59.75-62.59	0.85*	0.76-0.95
Lung & Bronchus	440	67.81	61.34-74.27	10063	86.21	84.53-87.90	0.79	0.71-0.87
Breast-Invasive‡	464	130.16	117.79-142.52	9158	151.54	148.43-154.64	0.86*	0.78-0.95
Cervix‡	38	8.22	5.33-11.12	561	9.28	8.51-10.05	0.89	0.62-1.27
Prostate‡‡	500	163.09	148.61-177.57	8125	144.35	141.21-147.48	1.13*	1.03-1.24
Urinary System	186	28.87	24.61-33.13	3670	31.44	30.42-32.46	0.92	0.79-1.07
Central Nervous System	38	5.47	3.63-7.31	797	6.83	6.35-7.30	0.80	0.57-1.13
Leukemias and Lymphomas	267	36.55	31.88-41.22	4509	38.63	37.50-39.76	0.95	0.83-1.08
All other cancers‡‡‡	828	114.84	106.51-123.17	15677	134.31	132.21-136.41	0.86*	0.79-0.92

†Breslow and Day 1987

‡Female only, ‡‡ Male only

‡‡‡ Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva,

other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.
*p < 0.05

Additional sub-group analyses for the cancer sites were conducted by individual zip codes and by analytical periods. The rate of prostate cancer during 1991-2010 was elevated with marginal significance for zip code 61820 (RR = 1.15, 95% CI: 1.00-1.32, based on 211 cases) but not for zip code 61801 (RR = 1.12, 95% CI: 0.99-1.26) (data not tabulated). No effect modification was apparent by zip code as the CIs for prostate cancer largely overlapped. No other statistically significantly cancer rates were observed during 1991-2010 but rates were modified in the inverse direction for colorectal (RR for zip code 61820 = 0.98, 95% CI: 0.84-1.15; zip code 61801 = 0.76, 95% CI: 0.65-0.88) and lung & bronchus (RR for zip code 61820 = 0.98, 95% CI: 0.86-1.13; zip code 61801 = 0.65, 95% CI: 0.57-0.75) cancers (data not tabulated). Interestingly, when analyses were conducted for the period 1991-2000, prostate cancer rates were modified by zip code (RR for zip code 61820 = 1.23, 95% CI: 1.02-1.48; zip code 61801 = 0.98, 95% CI: 0.83-1.16).

In the second type of analysis, ~~Findings were again similar in the sensitivity analyses when~~ counties without former manufactured gas plants were used as the comparison (data tables not shown ~~not tabulated~~, but available upon request). No difference in total cancer was found between Champaign County and the comparison counties without former gas plants (RR = 1.00, 95% CI: 0.97-1.02). Of 22 cancer site groupings, 12 had reduced rates in Champaign County, with statistically significant deficits for colorectal (RR = 0.83, 95% CI: 0.76-0.90) and cervical cancer (RR = 0.66, 95% CI: 0.49-0.90). Respiratory system cancers (lung & bronchus RR = 0.95), urinary tract cancers (kidney RR = 0.99; bladder RR = 1.01), and lymphohematopoietic malignancies (Hodgkins lymphomas RR = 0.89; non-Hodgkins lymphomas RR = 0.96;

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myelomas RR = 0.99; leukemias RR = 1.03) were not elevated in Champaign County compared with the counties that did not have former gas plants. As with the first set of~~main~~ analyses, prostate cancer incidence was elevated slightly and significantly (RR = 1.14, 95% CI: 1.06-1.23) in Champaign County, but it was not significant in the study zip code analysis (RR = 1.09, 95% CI: 0.98-1.21). The only other statistically significant positive association in the county ~~sensitivity~~ analysis was for esophageal cancer (RR = 1.46, 95% CI: 1.07-1.99), but this finding was not substantiated in other analyses. Total cancer was significantly reduced in the study zip codes versus the comparison counties without former gas plants (RR = 0.94, 95% CI: 0.90-0.98). Moreover, seven of 10 cancer sites were associated with reduced rates in the study zip codes, while three were slightly positive and not significant.

Standardized Incidence Ratio (SIR) Analyses

During the period, 1991-2010, 13,978 total cancers were observed in Champaign County with 14,150 expected based on nationally standardized rates, resulting in an SIR of 0.99 (95% CI: 0.97-1.00) (data not tabulated). Of 23 cancer site groupings, 14 had expected or lower than expected cases of cancer, with statistically significant deficits observed for stomach, liver, pancreas, bone, melanoma, testicular, bladder, nervous system, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. A slightly greater than expected number of lung & bronchus (SIR = 1.07, 95% CI: 1.02-1.11) and kidney (SIR = 1.13, 95% CI: 1.03-1.25) cancer cases were observed in Champaign County, but these findings were not supported by the other analyses. In fact, a slight deficit of lung & bronchus cancer cases was observed in the study zip codes (SIR = 0.98, 95% CI: 0.89-1.07), and urinary system cancer (includes kidney cancer) was reduced significantly (SIR = 0.78, 95% CI: 0.67-0.90) in the study zip codes (Table 6). Significantly fewer than

expected total cancer cases were observed in the study zip codes (SIR = 0.88, 95% CI: 0.85-0.91) (the SIRs for the cancer sites in the study zip codes are summarized in Table 6).

Table 6. Standardized incidence ratios (SIRs) and 95% CI of Zip code 61820 and 61801, 1991-2010

Cancer Sites	Obs	Exp	SIR	95% CI
All Cancer	3191	3612	0.88	0.85-0.91
Oral Cavity & Pharynx	81	82	0.98	0.78-1.22
Colorectal	349	378	0.92	0.83-1.03
Lung & Bronchus	440	450	0.98	0.89-1.07
Breast-Invasive‡	464	511	0.91	0.83-0.99
Cervix‡	38	36	1.04	0.74-1.43
Prostate‡‡	500	525	0.95	0.87-1.04
Urinary System	186	239	0.78	0.67-0.90
Central Nervous System	38	63	0.60	0.43-0.83
Leukemias and Lymphomas	267	320	0.84	0.74-0.94
All other cancers‡‡‡	828	1008	0.82	0.77-0.88

†Breslow and Day 1987
‡Female only, ‡‡ Male only
‡‡‡ Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

DISCUSSION

We observed statistically significant reductions in total cancer mortality and incidence in Champaign County, IL, and the zip code study areas compared with counties that were similar demographically and socioeconomically, and based on nationally standardized rates. Furthermore, cancer occurrence was lower in the study area for most cancer types, with several statistically significant reductions in cancer rates. Results were largely consistent within and across analyses, with a few exceptions. Indeed, the lower mortality rates for most cancers in the study area versus the comparison counties were in accordance with the lower cancer incidence rates observed in Champaign County and the study zip codes. The only noteworthy positive associations in the primary analyses were for prostate cancer and melanoma. Neither prostate

cancer mortality nor melanoma mortality was significantly elevated. However, incidence rates for these cancers were significantly increased in Champaign County. It is not clear why elevated rates were observed, although based on chance alone, it would be expected that some cancer rates would be statistically significant in both the positive and inverse directions. As indicated, we observed several statistically significant inverse associations (i.e. RRs below the null value of 1.0), such as for lung & bronchus, colorectal, and breast cancers. However, only two cancer types (prostate cancer and melanoma; incidence only) were associated with statistically significant positive associations. Thus, significant associations may have been observed due to multiple comparisons – a statistical phenomenon whereby one out of 20 associations is statistically significant due to chance [14, 15]. In our analysis, we generated over 100 unique RRs.

Prostate cancer is the most common cancer among men in the U.S., and 238,590 incident cases and 29,720 deaths were estimated to occur in 2013 [16, 17]. The figures for prostate cancer represent 14.4% of all new cancer cases and 5.1% of all cancer deaths in the U.S. [17]. Increasing age, African American race, family history of prostate cancer, and genetic variations and mutations are established risk factors for prostate cancer, although the etiology is largely unknown despite an extensive effort to identify causes of this malignancy [16, 17]. The role of lifestyle and dietary factors are thought to play a role in prostate cancer risk, as past research has identified obesity, physical inactivity, and smoking as significant modifiable risk factors for this malignancy [18-21]. Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors such as physical activity, family history of disease, or body mass index that may have influenced the results. Based on a review of the literature and

statements by prominent cancer organizations [16, 17], no manufactured gas plant by-product compound has been clearly or consistently associated with prostate cancer risk.

Perhaps the most likely reason for the elevation in prostate cancer incidence during 1991-2010 is the increased rate of prostate-specific antigen (PSA) screening in Champaign County versus the comparison counties. Indeed, based on the Behavioral Risk Factor Surveillance System (BRFSS) survey from the Centers for Disease Control and Prevention (CDC) and administered by the Illinois Department of Public Health [9], the percent of men who underwent PSA screening was higher in Champaign County than Sangamon, Macon, and Winnebago counties (as a composite percentage) during the study period. Furthermore, composite rates of PSA screening were higher in Champaign County than the counties without former gas plants. It is well-established and well-publicized that screening for prostate cancer results in an increase in incidence rates, whereas a proportion of prostate cancers may otherwise go undetected without screening [22-24]. In a sentinel review paper on the epidemiologic impact of screening on the incidence and mortality of prostate cancer in the U.S., it was suggested that PSA testing was the likely cause of the dramatic increase in prostate cancer incidence during the 1990s [23]. Although PSA testing is useful for early diagnosis, its value as a screening tool has been under scrutiny because the theoretical benefit on mortality is questionable [24]. According to a recent study from the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized screening trial, men who underwent annual prostate cancer screening with PSA testing and digital rectal examination had a 12 percent higher incidence rate of prostate cancer compared with men in the control group (who did not undergo PSA testing) [25]. However, approximately the same rate of death from prostate cancer was observed between groups, and no evidence of a mortality benefit was found in age or pre-trial PSA testing strata [25]. In our assessment, we observed a statistically

significant increase in prostate cancer incidence in Champaign County (where a greater proportion of individuals underwent PSA testing) but no statistically significant difference in prostate cancer mortality versus the comparison counties.

Melanoma was also associated with a statistically significant positive association (incidence only). Cancer incidence data for melanoma were not available at the zip code level, thus, it is uncertain if melanoma occurrence was higher in the areas directly circumscribing the abandoned plant. Approximately 21.3 out of 100,000 men and women are diagnosed annually with melanoma, and it is about twenty times more common in whites than blacks [17]. The major risk factor for melanoma is exposure to ultraviolet (UV) rays (sunlight is the primary source of UV rays), particularly among persons with fair skin. Other risk factors include having a large number of moles, having one or more first-degree relatives who have had melanoma, and being immunosuppressed [16]. It has been hypothesized that malignant melanoma may occur as a result of exposure to occupational or environmental chemicals (e.g., vinyl chloride, arsenic, polychlorinated biphenyls, petrochemicals, pesticides), particularly because malignancy can develop in cutaneous areas that have not been exposed to sunlight [26]. However, the epidemiologic evidence relating chemical exposures to melanoma risk is inconsistent. Thus, it is unclear whether the positive incidence rate ratio in Champaign County is the result of an artifactual finding from multiple comparisons, or has been confounded by sun exposure or other factors, such as immunosuppression. Moreover, general health concerns that the local population may have about living next to a former gas manufacturing site may lead to surveillance bias due to increased screening. Furthermore, a statistically significant deficit of melanoma was observed in Champaign County based on SIR analyses, and no statistically significant associations for melanoma were found based on comparisons with counties that did not have a former gas plant.

Finally, esophageal cancer incidence was elevated when Champaign County was compared with the non-gas plant counties in our sensitivity analysis of cancer incidence, but this observation was not substantiated by the main analyses, the sensitivity analysis of cancer mortality, or by the SIR analysis.

Alternatively, an unknown manufactured gas product compound may have produced the slight elevations in prostate cancer and/or melanoma incidence in the main analyses. This scenario is unlikely, however, given the plausible explanations listed above and because reduced rates were observed for cancers with known environmental or chemical relationships. That is, no "indicator" cancer types with established environmental or chemical etiology were observed in excess. For example, IARC has classified "coke production" as carcinogenic to humans (Group 1) for lung cancer because of exposure to PAHs in the industry (although associations from the occupational studies are somewhat tenuous) [27-29]. In a quantitative review of occupational exposures to PAHs, lung cancer and bladder cancer risk was elevated significantly among workers in the coal gasification industry [30]. However, ~~I~~in our assessment, we observed statistically significant reduced mortality and incidence rates of 15% and 17%, respectively, for lung & bronchus cancers, and no associations for urinary system and bladder cancers. Moreover, our analyses were based on rates of cancer at the community level, not among workers likely exposed to much higher concentrations of possible chemical exposures.

It is unclear as to why there was a preponderance of inverse associations in Champaign County and the study zip codes versus the comparison counties. *A priori*, we developed a systematic protocol for identifying comparable counties. We identified counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level). Based on the 2000 census

information, there were approximately 7% fewer 'ever' smokers in Champaign County versus the comparison counties. This may explain, in part, the observation of lower cancer rates, particularly for lung & bronchus, in Champaign County. In addition, the prevalence of other potentially important factors, such as alcohol consumption or obesity, in these counties may have confounded the observed associations. However, relatively similar patterns of associations were observed in sensitivity analyses comparing Champaign County and the study zip codes with counties that did not have a former gas plant, and based on SIR analyses using nationally representative cancer data from the SEER program.

Most of the literature on manufactured gas plants focuses on the environmental and ecological impacts of the gas process residues and waste products. As such, considerable literature exists on the methodological, toxicological, elemental chemistry, and extracting techniques involving remediation and compound evaluations from abandoned sites [31-34]. While potentially hazardous compounds may have been produced as part of the gas manufacturing process, the extent and level to which compound residues persist at the sites is unclear. In certain cases, potential hazards may be overestimated as samples in some studies have been consistent with background levels or below the assumed level [1, 35]. As mentioned previously, the literature on direct or indirect human health risks from an epidemiologic standpoint, is sparse. DeHate et al. [1] investigated soil vapor intrusion at 10 commercial buildings and 26 single family and multi-family residential properties overlying and/or adjacent to three former manufactured gas plant sites. Soil vapor samples and indoor/outdoor air were analyzed for VOCs, and comparative risks were evaluated based on maximum and mean concentrations for BTEX relative to background levels. All hazard indices were less than one or were comparable to mean and maximum background levels, and there was no evidence of

manufactured gas plant-related soil vapor intrusion from any of the 36 sites. Based on these findings, the authors reported that no increased public health risks were associated with occupied residential or commercial properties overlying or surrounding former manufactured gas plant facilities [1]. Occupational epidemiologic studies involving postulated gas plant exposures, such as PAHs [27, 30], BTEX [36-38], and coal tar [30, 39-41], are extensive but none have evaluated potential disease outcomes resulting from residing in a community that includes a former manufactured gas plant site.

Our historical cancer assessment has limitations that are commonplace with analyzing population-level data. Prime among the limitations is that we did not have individual-level information on lifestyle, dietary, medical, or occupational factors. In addition, we did not have personal information regarding potential exposures (e.g., to soil, groundwater, or air) from the manufactured gas process. We were, however, able to adjust cancer estimates for age, sex, and race. Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law. The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected. The gas plant ceased operations in 1953, and although immediate release of potential compounds may have diminished at that time, concern about the persistence of compounds over time in the vicinity has been raised. Our analyses were conducted on the basis of publically available aggregate-level data. We began our analytical period at the earliest time point possible that enabled us to merge cancer data and census data. Given our analytical periods, there is sufficient latency to observe a carcinogenic effect, if one exists.

However, we were not able to capture cases that occurred in earlier time periods, with possible greater exposures. It may be possible that our analyses are not sensitive enough to identify small effects of plant exposures because of the nature of residential exposure classification. Despite these limitations, we found no clear or consistent evidence of an increase in cancer occurrence among residents in a community circumscribing a former manufactured gas plant. ~~Furthermore,~~

T~~t~~he validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program. These three types of analyses serve as complementary comparisons to examine the consistency of findings across different population metrics. We implemented an objective methodological approach to identify counties in the state of Illinois that were the most closely matched (demographically) to the analytical zones. By using this approach, we were able to account for some prominent confounding factors at the aggregate level. However, the most closely matched comparison areas also had former gas plants. Therefore, we conducted a second analysis by matching demographic factors that was restricted to counties without former gas plants. Finally, we conducted analyses using nationally standardized rates of cancer. Despite the variation in analytical approaches, results were consistent between techniques.

We conducted a community cancer assessment for the purpose of appraising the public health regarding the occurrence of cancer among residents in a community with a former manufactured gas plant. Although this study did not include individual-level information, rates of total cancer and most cancer sites in the Champaign County area and zip codes circumscribing the abandoned facility were lower versus similar comparison areas, and based on nationally standardized rates of cancer. The primary exception is for prostate cancer, although there may be

relevant explanations for the higher rates aside from potential exposure emanating from the former manufactured gas plant site, such as an incidence spike due to higher PSA testing rates in Champaign County, a statistical artifact based on multiple comparisons, or confounding by unmeasured factors. Furthermore, a review of the literature did not reveal any known relation between the potential gas plant compounds and prostate cancer risk. Interpretation of results from our analyses should be made in the context of the many limitations of ecological-based study designs. However, ~~In conclusion,~~ the results from this retrospective cancer mortality and incidence assessment do not support an increase in cancer occurrence in communities surrounding a former manufactured gas plant in Champaign, IL.

AUTHOR CONTRIBUTION: DDA, DHG, and JPF were responsible for conception and design of the research. Statistical analyses were carried out by XJ. DDA, XJ, LCB, DHG, SRI, and JPF were responsible for development of the manuscript, critical revision and intellectual content.

FUNDING: This work was supported by Ameren Corporation.

COMPETING INTERESTS: DHG has served as an expert witness on behalf of Ameren in litigation related to manufactured gas plants. DDA, XJ, LCB, DHG, SRI, and JPF are employed by EpidStat Institute, all of whom were contracted by Ameren Corporation to support the study.

DATA SHARING STATEMENT: The full data set is available by emailing the corresponding author of the study.

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BMJ Open

Historical Cancer Incidence and Mortality Assessment in an Illinois Community Proximal to a Former Manufactured Gas Plant

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006713.R2
Article Type:	Research
Date Submitted by the Author:	04-Dec-2014
Complete List of Authors:	Alexander, Dominik; EpidStat Institute, Jiang, Xiaohui; EpidStat Institute, Bylsma, Lauren; EpidStat Institute, Garabrant, David; EpidStat Institute, Irvin, Sarah; EpidStat Institute, Fryzek, Jon; EpidStat Institute,
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	natural gas manufacturing, community, ONCOLOGY

Historical Cancer Incidence and Mortality Assessment in an Illinois Community Proximal to a Former Manufactured Gas Plant

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Word count: 5,164 words

Abstract word count: (243 words)

Kewords: natural gas manufacturing, community, cancer incidence, epidemiology

ABSTRACT

Objectives: Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant in Champaign, IL. Thus, we compared historical rates of cancer in this area to comparison communities as well as with nationally standardized rates.

Design: Retrospective population-based community cancer assessment during 1990-2010

Setting: Champaign County, IL, and zip codes encompassing the location of the former manufactured gas plant to counties that were similar demographically.

Participants: Residents of the counties and zip codes studied between 1990-2010.

Main outcome measures: The relative risk (RR) and 95% confidence interval (CI) were used to compare cancer incidence and mortality in the areas near the gas compression site to the comparison counties. Standardized incidence ratios (SIR) were calculated to compare rates in the areas near the gas compression site to expected rates based on overall United States cancer rates.

Results: Total cancer mortality (RR = 0.91, 95% CI: 0.88-0.94) and incidence (RR = 0.95, 95% CI: 0.94-0.97) were reduced significantly in Champaign County versus the comparison counties. Similarly, a reduced rate of total cancer was observed in analyses by zip code (proximal to the former gas plant) when compared to either similar counties (RR = 0.89, 95% CI: 0.86-0.93) or national standardized rates of cancer (SIR = 0.88, 95% CI: 0.85-0.91).

Conclusions: This historical cancer assessment did not find an increased risk of total cancer or specific cancer types in communities near a former manufactured gas plant site.

Strength and limitations of this study:

- The validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program.
- Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law.
- A priori, we developed a systematic protocol for identifying comparable counties. We matched counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level) to control for confounding.
- Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors associated with cancer such as physical activity, family history of disease, or body mass index that may have influenced the results.
- The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected.

INTRODUCTION

The production of manufactured gas is widely considered one of the key developments in our industrial history, with an extensive chronology beginning in the late 1700s and spanning into the 1960s. Manufactured gas consisted largely of the gasification of coal, and less frequently, the combustion of other materials such as wood and oil. Historically, the manufactured gas industry grew significantly in the early 1800s due to the production of lighting for the progress and development of cities. However, later in the 19th century, this industry diversified into heating, refrigeration, and cooking. During the early to mid-20th century, the advent of natural gas obviated the gasification of coal, ultimately leading to the conversion or closure of manufactured gas plants. Pipelines transported natural gas directly from the well to gas distribution systems, and natural gas was considered more economical, efficient, and environmentally friendly. Most manufactured gas plants in the U.S. were terminated by1966 with few exceptions, and as a result of the manufactured gas demise, over 1,500 plant sites are suggested to remain dormant or vacant in the U.S. today.

Numerous health concerns have been raised regarding possible environmental exposures stemming from manufactured gas plant sites. Foremost among the concerns is that contamination and waste products from the manufacturing gas process leaked into the adjacent soil and groundwater, thus posing health risks in the nearby residential areas and communities [1]. The process of coal carbonization generates coal tar, which are complex mixtures of heterocyclic compounds, phenols, and polycyclic aromatic hydrocarbons (PAHs). Indeed, both volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs) from coal tar and petroleum products are derived from the coal gasification process [1]. The VOCs contain a mixture of BTEX, or benzene, toluene, ethylbenzene, and xylene isomers among other

compounds, while the SVOCs consist of a mixture of compounds, such as benzo(a)pyrene, benzo(e)pyrene, naphthalene, and 2-methyl naphthalene. In addition, principal component analyses have identified heavy metals at former manufactured gas plant sites [2, 3]. As a result of these gas process by-products, the U.S. Environmental Protection Agency (EPA) and other regulatory agencies have focused on assessing the potential for soil and groundwater contamination at former manufactured gas plant sites, as well as evaluating the potential for health risks among residents in nearby communities. The International Agency for Research on Cancer (IARC) lists many of the manufactured gas plant by-product compounds as known, probable, or possible carcinogens for specific cancers but the level and extent of community exposure to such compounds resulting from former manufactured gas plants is uncertain. Furthermore, sparse epidemiologic evidence exists on the potential public health risks associated with residing near former manufactured gas plant sites.

Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant on a 3.5 acre lot in northern Champaign, IL. The plant, in operation from 1887 until 1953, manufactured gas by heating coal. Coal tar and other production wastes were suggested to remain on site until the closing of the plant. AmerenIP has registered this site with the Illinois EPA under their Site Remediation Program. However, the potential long-term health effects of residents in the nearby community are unknown. Therefore, we conducted a historical cancer incidence and mortality assessment using publicly available cancer data and census tract information to evaluate the occurrence of cancer in the community where the former manufactured gas plant was located compared with other communities with and without former gas plants that have similar demographic and lifestyle characteristics. In

addition, we conducted standardized incidence analyses for Champaign County and the study zip codes using nationally representative cancer data.

METHODS

All data used in this study are publicly available. Specifically, the cancer incidence data were obtained from the Illinois Department of Public Health and from the Surveillance, Epidemiology, and End Results (SEER) Program, while cancer mortality data were obtained from SEER. Analyses for cancer incidence are presented at both the county and zip code level while analyses for cancer mortality are presented at the county level, which is the smallest area for which cancer mortality data are available. County and zip code demarcations were based on information provided by the U.S. Census Bureau.

Study Areas

The analytical and comparison population areas were characterized using census tract information. The former manufactured gas plant of interest was located in Champaign County, IL, and was circumscribed by zip codes 61820 and 61801; thus, these demarcated areas served as the analytical group. Because our assessment was community-based and ecologic in nature, our objective was to identify comparison counties in the state of Illinois with similar demographic and socioeconomic characteristics. Relevant characteristics included county setting (urban vs. rural), county population size, and percentages for black race, high school graduation, persons over age 65, persons unemployed, families below poverty level, urban residence, and ever smoking status. In addition, the median household income was utilized as a comparison factor. County selection was based on methods developed by the National Cancer Institute [4, 5].

Illinois Cancer Data

In concert with the Illinois State Cancer Registry (ICSR), the SEER program of the National Cancer Institute is the source of data for cancer mortality between 1986 and 2010 [6]. These data are grouped by age, sex, and race and are provided at the county level (the smallest available area for cancer mortality). The National Center for Health Statistics (NCHS) provides information on the underlying cause of death, coded to the International Classification of Diseases (ICD-9) [7] for all deaths for years 1986 through 1998 and the International Classification of Diseases (ICD-10) for all deaths for year 1999 and later [8]. Cancer mortality rates are available by single year for Illinois only, and deaths among non-residents and deaths of unknown age or sex are omitted from the database calculations. Because of NCHS policy, rates are not calculated for stratified sub-groups containing less than 10 deaths. For this analysis we used mortality data from 1990-2010 to be consistent with the census tract reporting periods.

Cancer incidence data for the direct community comparisons used in this study were collected by the ISCR and are available as a public use data set via the Illinois Department of Public Health for the years 1991-2010. All obtainable data are provided by the ISCR as a public service for the purpose of statistical reporting and analysis only. Case ascertainment is near complete as the identification and reporting of cancer cases is mandated by state law. Individual (personal) information has been de-identified, and the data have been aggregated into categories (e.g., age, race, Hispanic ethnicity, year of diagnosis and type of cancer) within individual records [9]. The number of cases reported in a particular region depends on the size of the geographic area in an effort to protect the privacy of individuals. The Illinois dataset contains sanitized records of cancer incidence among residents who were diagnosed between 1986 and

2011. Cancer incidence data at the county and zip code level are based on five-year interval groupings, and include data for invasive cancers only with the exception of bladder cancer. Non-melanoma skin cancers and reported cases with an unknown age or "other" sex category are omitted by the ISCR. Cancer incidence data used for the SIR analyses were obtained directly from the SEER program.

By using these data, we agreed to comply with the Illinois Health and Hazardous Substances Registry Act (410 ILCS 525/12). All data used in our analyses are publically available, thus, informed consent was not required.

Statistical Analyses

As indicated, we ascertained cancer rates from the ISCR and the SEER program. The rates provided by these sources were calculated using the SEER*Stat® software package, developed by the Information Management Services Inc. for the National Cancer Institute [10]. SEER expresses rates per 100,000 population, and rates are age-adjusted by the direct method adjusting to the 2000 U.S. standard million population. These data were then used to formulate the basis of our historical cancer assessment.

Because of the ecologic nature of the community-based analyses, we conducted analyses in an effort to account for potential confounding at the aggregate level while considering the potential for exposure misclassification. Thus, we conducted analyses using three different comparison populations based on: 1) Illinois counties that were the most closely matched demographically (irrespective of having former gas plants), 2) counties without former gas plants (as part of the selection criteria) that were relatively similar demographically, and 3) nationally representative cancer data from the SEER program. By utilizing three different comparison

populations, we were able to enhance the validity of our analyses, examine the consistency of cancer rates across different groups, and facilitate the identification of potential sources of statistical heterogeneity (if present). All types of analyses serve as complementary comparisons to appreciate fully any observed associations.

In the first type of analysis, we calculated relative rate ratios (RRs) and 95% confidence intervals (CIs) to compare cancer mortality and incidence rates in Champaign County, IL and zip codes 61820 and 61801 encompassing the location of the former manufactured gas plant to counties that were the most similar demographically (i.e., Macon, Winnebago, and Sangamon counties). Although not part of the selection criteria, these counties had former gas plants but were the most demographically comparable based on our objective matching criteria. The number of cancer cases and deaths were ascertained for the period 1990 through 2010, and the absolute rate of cancer occurrence was calculated based on the county and zip code population size according to the U.S. Census Bureau. The relative rate of cancer occurrence was calculated by dividing the rate of cancer in Champaign County and the zip codes (for cancer incidence only) by the rate of cancer in the comparison counties. County-level analyses were statistically adjusted for age, sex, and race, and zip code-level analyses were adjusted for age and sex (race stratified data were not available at the zip code level, and mortality analyses were adjusted for age only).

Although the comparison counties in the first analyses were very-well matched demographically to Champaign County, they had former gas plants, which raises concern about potential bias resulting from similar chemical exposures in the comparison counties. To address this concern, our second analyses consisted of comparing rates of cancer in Champaign County and the study zip codes with areas that did not have former gas plants but had relatively similar

descriptive characteristics. To do this, we reviewed an Environmental Protection Agency (EPA) report on manufactured gas plant production [11], the EPA website, and the following website link: http://www.hatheway.net/state_site_pages/il_epa.htm to identify additional comparison counties. Illinois counties with relatively similar demographic characteristics but without former gas plants (i.e., Brown, Douglas, Menard, Randolph counties) were selected. Evaluations of cancer mortality and cancer incidence, using the same methodology as the first analyses, were conducted using these counties as comparisons.

In our final set of analyses, we calculated standardized incidence ratios (SIRs) for cancer sites in Champaign County and the zip codes of interest. The numbers of observed cancers in Champaign County and in the study zip codes were compared with those expected on the basis of standardized rates of cancer in the general population using data obtained from SEER [12]. The number of observed cancers was determined by sex, race, and 5-year age groups (the zip codes were standardized by age and sex groups) for each year from 1991-2010. Expected numbers of cases were calculated by multiplying the estimated population for Champaign County and for the study zip codes for each year of study by annual SEER cancer rates, stratified by 5-year age groups, race, and sex. Observed and expected counts were then generated for Champaign County and for the study zip codes, and SIRs were calculated by dividing the observed number by the expected number.

A final concern was the possibility of surveillance bias being introduced during the analytical study period. In the mid-2000s, a neighborhood advocacy group formed to increase awareness about the potential health effects from the abandoned gas plant [13]. In order to limit potential bias associated with the formation of this group, we conducted analyses for the years 1990-2000, prior to the formation of this group.

All analyses were performed using SAS statistical software.

RESULTS

Study Counties

The characteristics of the study county and the comparison counties (with the most similar demographic characteristics) are reported in Table 1 for the 1990 and 2000 census periods.

Table 1. Characteristics of Study County and Comparison Counties Most Closely Matched Demographically Based on 1990 and 2000 Census.

Characteristic	Year of Census	Champaign County	Comparison counties most closely matched demographically		
			Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	1990	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
	2000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	1990	9.64	8.11	12.14	9.29
	2000	11.82	10.17	14.76	11.16
Percent did not graduate high school	1990	12.50	18.23	23.79	23.70
	2000	9.02	11.93	16.83	18.57
Percent over age 65 years	1990	8.74	13.71	14.57	12.67
	2000	9.72	13.51	15.24	12.73
Percent unemployed	1990	4.24	4.36	6.60	5.20
	2000	5.52	4.07	7.15	5.83
Percent below poverty	1990	8.03	7.19	9.84	7.71
	2000	6.92	6.49	9.28	6.92
Median household income (in tens)	1990	2654	3035	2860	3134
	2000	3778	4296	3786	4389
Percent Urban	1990	81.41	78.32	81.74	87.41
	2000	84.34	85.40	84.17	91.78
Percent ever smoke	1990	Not Available	Not Available	Not Available	Not Available
	2000	44.89	52.46	52.59	52.38

Champaign County was very well-matched to the comparison counties with former gas plants on the variables of interest. Given the relatively high proportion of counties with former manufactured gas plants in Illinois, the availability of matching counties without former gas

plants was more limited. However, based on our county scoring methodology and criteria, we were able to identify counties (i.e., Brown, Douglas, Menard, Randolph) without former gas plants to serve as comparison communities in our second type of analyses. These counties were not as closely matched on potential confounding factors (i.e., demographic characteristics) that may be associated with cancer as the counties used in the first analyses (Table 2).

Table 2. Characteristics of Study County and Comparison Counties Without Former Gas Plants on 1990 and 2000 Census.

Characteristic	Year of Census	Champaign County	Comparison counties without former gas plants			
			Brown	Douglas	Menard	Randolph
Rural-Urban Continuum Code	1990	Counties in metropolitan areas of <250,000	Comp rural < 2,500 urban pop, not adjacent to metro area	Urban pop of 2,500 to 19,999, adjacent to a metro area	Counties in metropolitan areas of <250,000	Urban pop of 2,500 to 19,999, adjacent to a metro area
	2000	Counties in metropolitan areas of <250,000	Urban pop of 2,500 to 19,999, not adjacent to a metro area	Urban pop of 2,500 to 19,999, adjacent to a metro area	Counties in metropolitan areas of <250,000	Urban pop of 2,500 to 19,999, adjacent to a metro area
Percent Black	1990	9.64	9.37	0.05	0.05	8.26
	2000	11.82	18.29	0.43	0.46	9.56
Percent did not graduate high school	1990	12.50	31.14	25.97	22.69	35.78
	2000	9.02	36.75	20.69	11.67	28.67
Percent over age 65 years	1990	8.74	16.83	15.26	15.06	15.33
	2000	9.72	12.69	15.96	13.17	15.61
Percent unemployed	1990	4.24	6.03	4.4	4.35	6.46
	2000	5.52	3.47	2.78	3.88	5.69
Percent below poverty	1990	8.03	10.47	6.92	7.13	8.75
	2000	6.92	4.84	4.21	6.11	7.06
Median household income (in tens)	1990	2654	2045	2676	2933	2586
	2000	3778	3545	3944	4660	3701
Percent Urban	1990	81.41	0.00	49.13	0.00	46.16
	2000	84.34	58.66	36.69	24.66	57.3
Percent ever smoke	1990	Not Available	Not Available	Not Available	Not Available	Not Available
	2000	44.89	49.76	48.98	50.81	55.14

Cancer Mortality

The RR for total cancer mortality in Champaign County versus the comparison counties most closely matched demographically (Macon, Winnebago, and Sangamon) was significantly

decreased (RR = 0.91, 95% CI: 0.88-0.94) during 1990-2010 (Table 3). Similarly, statistically significant deficits in mortality were observed for cancers of the esophagus (RR = 0.80, 95% CI: 0.65-0.98), colorectum (RR = 0.88, 95% CI: 0.80-0.97), pancreas (RR = 0.78, 95% CI: 0.68-0.89), and lung & bronchus (RR = 0.85, 95% CI: 0.80-0.89). In fact, out of all 22 cancer site groupings, 17 RRs represented reduced risks, one RR was 1.0, no data were available for one site (testicular cancer), and three RRs were slightly elevated. None of these elevated cancer sites was statistically significant, with RRs of 1.03 (melanoma), 1.06 (prostate), and 1.05 (leukemias) (Table 3).

Table 3. Age adjusted mortality rates, RRs and 95% CI[†] in 1990-2010

	Champaign County			Comparison counties most closely matched demographically			Rate Ratio	95% CI
	No. of Deaths	Rate	95% CI	No. of Deaths	Rate	95% CI		
All Cancer	5,611	187.2	182.3-192.2	27,170	206.1	203.6-208.5	0.91*	0.88-0.94
Oral Cavity & Pharynx	64	2.1	1.6-2.7	358	2.7	2.4-3.0	0.78	0.59-1.03
Esophagus	118	4.0	3.3-4.7	650	4.9	4.5-5.3	0.80*	0.65-0.98
Stomach	94	3.1	2.5-3.8	494	3.7	3.4-4.1	0.84	0.67-1.05
Colorectal	551	18.4	16.9-20.0	2,765	20.8	20.1-21.6	0.88*	0.80-0.97
Liver	87	2.9	2.3-3.6	420	3.2	2.9-3.5	0.91	0.71-1.15
Pancreas	267	9.0	7.9-10.1	1,526	11.5	11-12.1	0.78*	0.68-0.89
Lung & Bronchus	1,526	51.3	48.7-53.9	7,990	60.6	59.2-61.9	0.85*	0.80-0.89
Bone & Joint	12	0.3	0.2-0.6	43	0.3	0.2-0.4	0.94	0.42-1.89
Melanomas	81	2.7	2.1-3.3	339	2.6	2.3-2.9	1.03	0.80-1.31
Breast[‡]	438	25.6	23.3-28.2	2,045	27.5	26.3-28.7	0.93	0.84-1.03
Prostate[‡‡]	348	31.4	28.1-34.9	1,427	29.7	28.1-31.3	1.06	0.94-1.19
Testis[‡‡]	-	-	-	-	-	-	-	-
Cervix[‡]	39	2.3	1.6-3.2	177	2.6	2.2-3.0	0.89	0.61-1.27
Uterine[‡]	72	4.2	3.2-5.2	323	4.2	3.7-4.6	1.00	0.76-1.29
Ovary[‡]	159	9.3	7.9-10.8	716	9.5	8.8-10.2	0.98	0.82-1.17
Kidney & Renal Pelvis	136	4.5	3.8-5.4	618	4.7	4.3-5.1	0.97	0.80-1.17
Bladder	131	4.4	3.7-5.3	610	4.6	4.2-5.0	0.97	0.79-1.17
Nervous System	119	3.8	3.2-4.6	596	4.6	4.2-5.0	0.83	0.68-1.02
Hodgkins Lymphomas	13	0.4	0.2-0.7	61	0.5	0.4-0.6	0.88	0.44-1.61
NHL	230	7.6	6.7-8.7	1,096	8.3	7.8-8.8	0.92	0.79-1.06
Myelomas	110	3.7	3.0-4.5	510	3.8	3.5-4.2	0.96	0.77-1.18
Leukemias	251	8.2	7.3-9.3	1,029	7.8	7.4-8.3	1.05	0.91-1.21

[†]Tiwariet al. 2006 modification for CIs
[‡]Female only, [‡‡] Male only
*p < 0.05

In our second set of analyses, similar results for Champaign County were observed when compared with counties without former manufactured gas plants. Total cancer was associated with an RR of 0.96 (95% CI: 0.92-1.00), and statistically significant reduced rates of colorectal (RR = 0.85, 95% CI: 0.75-0.97) and pancreatic cancer (RR = 0.81, 95% CI: 0.67-0.98) mortality were observed (data tables not shown, but available upon request). Relative risks for most cancer sites were 1.0 or lower, with few weakly positive, albeit non-significant associations. No statistically significant associations for the more common cancers – lung & bronchus (RR =

0.94, 95% CI: 0.87-1.02), breast (RR = 1.00, 95% CI: 0.85-1.18), or prostate (RR = 1.00, 95% CI: 0.84-1.19) were observed.

Taken together, results based on analyses using communities with and without former gas plants are not supportive of an increased risk of cancer mortality.

Cancer Incidence

A statistically significant reduced rate of total cancer incidence was observed in Champaign County versus the comparison counties most closely matched demographically (RR = 0.95, 95% CI: 0.94-0.97) during 1991-2010 (Table 4). Decreased incidence rates were observed for nineteen of 23 cancer site groupings based on analyses during 1991-2010. Incidence rates for cancers of the colorectum, pancreas, lung & bronchus, testis, cervix, nervous system, and "other" sites (list of cancers in this category are shown in Table 4) were all significantly lower versus the rates in the comparison counties. In contrast, statistically significant slightly elevated rates were observed for melanoma (RR = 1.12, 95% CI: 1.02-1.24) and prostate cancer (RR = 1.20, 95% CI: 1.14-1.25). Restricting the analytical period to 1991-2000 in Champaign County in order to reduce potential bias associated with the formation of the neighborhood advocacy group did not appreciably modify the results; the RR for melanoma was 1.17 (95% CI: 0.99-1.38) and the RR for prostate cancer was 1.17 (95% CI: 1.09-1.26) (data not tabulated). Incidence rates were significantly reduced for total, colorectal, pancreatic, lung & bronchus, testicular, and cervical cancers during 1991-2000.

Table 4. Age, sex, and race-adjusted incidence rate by county, RRs and 95% CI† in 1991-2010

	Champaign County			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All cancer	13978	499.55	491.17-507.93	61184	524.18	520.03-528.34	0.95*	0.94-0.97
Oral cavity & pharynx	332	11.94	10.64-13.23	1484	12.71	12.07-13.36	0.94	0.83-1.06
Esophagus	141	5.21	4.35-6.08	696	5.96	5.52-6.41	0.87	0.73-1.05
Stomach	177	6.38	5.43-7.33	809	6.93	6.45-7.41	0.92	0.78-1.09
Colorectal	1442	52.87	50.11-55.62	7140	61.17	59.75-62.59	0.86*	0.82-0.91
Liver	112	3.94	3.20-4.67	486	4.16	3.79-4.53	0.95	0.77-1.16
Pancreas	291	10.69	9.45-11.92	1558	13.35	12.69-14.01	0.80*	0.71-0.91
Lung & Bronchus	1945	71.76	68.55-74.96	10063	86.21	84.53-87.90	0.83*	0.79-0.87
Bone	23	0.68	0.39-0.97	80	0.69	0.54-0.84	1.00	0.62-1.60
Melanomas	539	17.62	16.10-19.14	1834	15.71	14.99-16.43	1.12*	1.02-1.24
Breast-invasive‡	2184	150.65	144.25-157.04	9158	151.54	148.43-154.64	0.99	0.95-1.04
Prostate‡‡	2254	172.52	165.38-179.66	8125	144.35	141.21-147.48	1.20*	1.14-1.25
Testis‡‡	89	4.05	3.18-4.93	337	5.99	5.35-6.63	0.68*	0.53-0.86
Cervix‡	114	6.84	5.54-8.14	561	9.28	8.51-10.05	0.74*	0.60-0.91
Uterus‡	406	28.53	25.74-31.33	1801	29.80	28.42-31.18	0.96	0.86-1.07
Ovary‡	228	15.52	13.48-17.57	1022	16.91	15.87-17.95	0.92	0.79-1.06
Kidney	425	15.10	13.64-16.55	1945	16.66	15.92-17.40	0.91	0.81-1.01
Bladder	363	13.56	12.16-14.96	1725	14.78	14.08-15.48	0.92	0.82-1.03
Nervous System	164	5.53	4.66-6.39	797	6.83	6.35-7.30	0.81*	0.68-0.96
Hodgkins Lymphomas	93	2.51	1.98-3.04	341	2.92	2.61-3.23	0.86	0.68-1.09
NHL	556	19.64	17.98-21.29	2490	21.33	20.49-22.17	0.92	0.84-1.01
Myelomas	183	6.68	5.71-7.66	758	6.49	6.03-6.96	1.03	0.88-1.21
Leukemias	433	15.32	13.86-16.79	1678	14.38	13.69-15.06	1.07	0.96-1.19
All Other Sites‡‡‡	1484	50.63	48.00-53.26	6296	53.94	52.61-55.27	0.94*	0.89-0.99

†Breslow and Day 1987

‡Female only, ‡‡ Male only

‡‡‡Includes small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, breast-invasive male only, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

*$p < 0.05$

Fewer cancer sub-groupings were available at the zip code level. Nevertheless, results similar to those in the county-level analyses were observed. Total cancer incidence was 11% lower in the study zip codes versus the most closely matched comparison counties, resulting in a statistically significant RR of 0.89 (95% CI: 0.86-0.93) during 1991-2010 (Table 5). Of the 10 cancer site groupings, nine incidence rates were decreased versus comparison counties, including statistically significant reductions for colorectal (RR = 0.85, 95% CI: 0.76-0.95), breast

(invasive) (RR = 0.86, 95% CI: 0.78-0.95), and "other" (RR = 0.86, 95% CI: 0.79-0.92) cancers. The only elevated incidence rate was for prostate cancer, with a significant RR of 1.13 (95% CI: 1.03-1.24), based on 500 diagnosed cases during 1991-2010. However, no significant association was found for prostate cancer (RR = 1.07, 95% CI: 0.95-1.21) in the analysis for the period 1991-2000 (data not tabulated). During this period, rates for colorectal, breast, and "other" remained significantly decreased, while significant deficits for lung & bronchus (RR = 0.75, 95% CI: 0.66-0.86) and central nervous system cancers (RR = 0.55, 95% CI: 0.33-0.93) were observed as well.

Table 5. Age and sex-adjusted incidence rate by zip code, RRs and 95% CI[†] in 1991-2010.

	Zip 61820, 61801			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All Cancer	3191	468.15	451.25-485.06	61184	524.18	520.03-528.34	0.89*	0.86-0.93
Oral Cavity & Pharynx	81	12.40	9.62-15.19	1484	12.71	12.07-13.36	0.98	0.77-1.23
Colorectal	349	51.93	46.32-57.53	7140	61.17	59.75-62.59	0.85*	0.76-0.95
Lung & Bronchus	440	67.81	61.34-74.27	10063	86.21	84.53-87.90	0.79	0.71-0.87
Breast-Invasive[‡]	464	130.16	117.79-142.52	9158	151.54	148.43-154.64	0.86*	0.78-0.95
Cervix[‡]	38	8.22	5.33-11.12	561	9.28	8.51-10.05	0.89	0.62-1.27
Prostate[‡‡]	500	163.09	148.61-177.57	8125	144.35	141.21-147.48	1.13*	1.03-1.24
Urinary System	186	28.87	24.61-33.13	3670	31.44	30.42-32.46	0.92	0.79-1.07
Central Nervous System	38	5.47	3.63-7.31	797	6.83	6.35-7.30	0.80	0.57-1.13
Leukemias and Lymphomas	267	36.55	31.88-41.22	4509	38.63	37.50-39.76	0.95	0.83-1.08
All other cancers[‡‡‡]	828	114.84	106.51-123.17	15677	134.31	132.21-136.41	0.86*	0.79-0.92

[†]Breslow and Day 1987
[‡]Female only, [‡‡] Male only
[‡‡‡] Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva,

other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.
*p < 0.05

Additional sub-group analyses for the cancer sites were conducted by individual zip codes and by analytical periods. The rate of prostate cancer during 1991-2010 was elevated with marginal significance for zip code 61820 (RR = 1.15, 95% CI: 1.00-1.32, based on 211 cases) but not for zip code 61801 (RR = 1.12, 95% CI: 0.99-1.26) (data not tabulated). No effect modification was apparent by zip code as the CIs for prostate cancer largely overlapped. No other statistically significantly cancer rates were observed during 1991-2010 but rates were modified in the inverse direction for colorectal (RR for zip code 61820 = 0.98, 95% CI: 0.84-1.15; zip code 61801 = 0.76, 95% CI: 0.65-0.88) and lung & bronchus (RR for zip code 61820 = 0.98, 95% CI: 0.86-1.13; zip code 61801 = 0.65, 95% CI: 0.57-0.75) cancers (data not tabulated). Interestingly, when analyses were conducted for the period 1991-2000, prostate cancer rates were modified by zip code (RR for zip code 61820 = 1.23, 95% CI: 1.02-1.48; zip code 61801 = 0.98, 95% CI: 0.83-1.16).

In the second type of analysis, counties without former manufactured gas plants were used as the comparison (data tables not shown, but available upon request). No difference in total cancer was found between Champaign County and the comparison counties without former gas plants (RR = 1.00, 95% CI: 0.97-1.02). Of 22 cancer site groupings, 12 had reduced rates in Champaign County, with statistically significant deficits for colorectal (RR = 0.83, 95% CI: 0.76-0.90) and cervical cancer (RR = 0.66, 95% CI: 0.49-0.90). Respiratory system cancers (lung & bronchus RR = 0.95), urinary tract cancers (kidney RR = 0.99; bladder RR = 1.01), and lymphohematopoietic malignancies (Hodgkins lymphomas RR = 0.89; non-Hodgkins lymphomas RR = 0.96; myelomas RR = 0.99; leukemias RR = 1.03) were not elevated in

Champaign County compared with the counties that did not have former gas plants. As with the first set of analyses, prostate cancer incidence was elevated slightly and significantly (RR = 1.14, 95% CI: 1.06-1.23) in Champaign County, but it was not significant in the study zip code analysis (RR = 1.09, 95% CI: 0.98-1.21). The only other statistically significant positive association in the county analysis was for esophageal cancer (RR = 1.46, 95% CI: 1.07-1.99), but this finding was not substantiated in other analyses. Total cancer was significantly reduced in the study zip codes versus the comparison counties without former gas plants (RR = 0.94, 95% CI: 0.90-0.98). Moreover, seven of 10 cancer sites were associated with reduced rates in the study zip codes, while three were slightly positive and not significant.

Standardized Incidence Ratio (SIR) Analyses

During the period, 1991-2010, 13,978 total cancers were observed in Champaign County with 14,150 expected based on nationally standardized rates, resulting in an SIR of 0.99 (95% CI: 0.97-1.00) (data not tabulated). Of 23 cancer site groupings, 14 had expected or lower than expected cases of cancer, with statistically significant deficits observed for stomach, liver, pancreas, bone, melanoma, testicular, bladder, nervous system, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. A slightly greater than expected number of lung & bronchus (SIR = 1.07, 95% CI: 1.02-1.11) and kidney (SIR = 1.13, 95% CI: 1.03-1.25) cancer cases were observed in Champaign County, but these findings were not supported by the other analyses. In fact, a slight deficit of lung & bronchus cancer cases was observed in the study zip codes (SIR = 0.98, 95% CI: 0.89-1.07), and urinary system cancer (includes kidney cancer) was reduced significantly (SIR = 0.78, 95% CI: 0.67-0.90) in the study zip codes (Table 6). Significantly fewer than

expected total cancer cases were observed in the study zip codes (SIR = 0.88, 95% CI: 0.85-0.91) (the SIRs for the cancer sites in the study zip codes are summarized in Table 6).

Table 6. Standardized incidence ratios (SIRs) and 95% CI of Zip code 61820 and 61801, 1991-2010

Cancer Sites	Obs	Exp	SIR	95% CI
All Cancer	3191	3612	0.88	0.85-0.91
Oral Cavity & Pharynx	81	82	0.98	0.78-1.22
Colorectal	349	378	0.92	0.83-1.03
Lung & Bronchus	440	450	0.98	0.89-1.07
Breast-Invasive‡	464	511	0.91	0.83-0.99
Cervix‡	38	36	1.04	0.74-1.43
Prostate‡‡	500	525	0.95	0.87-1.04
Urinary System	186	239	0.78	0.67-0.90
Central Nervous System	38	63	0.60	0.43-0.83
Leukemias and Lymphomas	267	320	0.84	0.74-0.94
All other cancers‡‡‡	828	1008	0.82	0.77-0.88

†Breslow and Day 1987
‡Female only, ‡‡ Male only
‡‡‡ Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

DISCUSSION

We observed statistically significant reductions in total cancer mortality and incidence in Champaign County, IL, and the zip code study areas compared with counties that were similar demographically and socioeconomically, and based on nationally standardized rates. Furthermore, cancer occurrence was lower in the study area for most cancer types, with several statistically significant reductions in cancer rates. Results were largely consistent within and across analyses, with a few exceptions. Indeed, the lower mortality rates for most cancers in the study area versus the comparison counties were in accordance with the lower cancer incidence rates observed in Champaign County and the study zip codes. The only noteworthy positive associations in the primary analyses were for prostate cancer and melanoma. Neither prostate

cancer mortality nor melanoma mortality was significantly elevated. However, incidence rates for these cancers were significantly increased in Champaign County. It is not clear why elevated rates were observed, although based on chance alone, it would be expected that some cancer rates would be statistically significant in both the positive and inverse directions. As indicated, we observed several statistically significant inverse associations (i.e. RRs below the null value of 1.0), such as for lung & bronchus, colorectal, and breast cancers. However, only two cancer types (prostate cancer and melanoma; incidence only) were associated with statistically significant positive associations. Thus, significant associations may have been observed due to multiple comparisons – a statistical phenomenon whereby one out of 20 associations is statistically significant due to chance [14, 15]. In our analysis, we generated over 100 unique RRs.

Prostate cancer is the most common cancer among men in the U.S., and 238,590 incident cases and 29,720 deaths were estimated to occur in 2013 [16, 17]. The figures for prostate cancer represent 14.4% of all new cancer cases and 5.1% of all cancer deaths in the U.S. [17]. Increasing age, African American race, family history of prostate cancer, and genetic variations and mutations are established risk factors for prostate cancer, although the etiology is largely unknown despite an extensive effort to identify causes of this malignancy [16, 17]. The role of lifestyle and dietary factors are thought to play a role in prostate cancer risk, as past research has identified obesity, physical inactivity, and smoking as significant modifiable risk factors for this malignancy [18-21]. Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors such as physical activity, family history of disease, or body mass index that may have influenced the results. Based on a review of the literature and

statements by prominent cancer organizations [16, 17], no manufactured gas plant by-product compound has been clearly or consistently associated with prostate cancer risk.

Perhaps the most likely reason for the elevation in prostate cancer incidence during 1991-2010 is the increased rate of prostate-specific antigen (PSA) screening in Champaign County versus the comparison counties. Indeed, based on the Behavioral Risk Factor Surveillance System (BRFSS) survey from the Centers for Disease Control and Prevention (CDC) and administered by the Illinois Department of Public Health [9], the percent of men who underwent PSA screening was higher in Champaign County than Sangamon, Macon, and Winnebago counties (as a composite percentage) during the study period. Furthermore, composite rates of PSA screening were higher in Champaign County than the counties without former gas plants. It is well-established and well-publicized that screening for prostate cancer results in an increase in incidence rates, whereas a proportion of prostate cancers may otherwise go undetected without screening [22-24]. In a sentinel review paper on the epidemiologic impact of screening on the incidence and mortality of prostate cancer in the U.S., it was suggested that PSA testing was the likely cause of the dramatic increase in prostate cancer incidence during the 1990s [23]. Although PSA testing is useful for early diagnosis, its value as a screening tool has been under scrutiny because the theoretical benefit on mortality is questionable [24]. According to a recent study from the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized screening trial, men who underwent annual prostate cancer screening with PSA testing and digital rectal examination had a 12 percent higher incidence rate of prostate cancer compared with men in the control group (who did not undergo PSA testing) [25]. However, approximately the same rate of death from prostate cancer was observed between groups, and no evidence of a mortality benefit was found in age or pre-trial PSA testing strata [25]. In our assessment, we observed a statistically

significant increase in prostate cancer incidence in Champaign County (where a greater proportion of individuals underwent PSA testing) but no statistically significant difference in prostate cancer mortality versus the comparison counties.

Melanoma was also associated with a statistically significant positive association (incidence only). Cancer incidence data for melanoma were not available at the zip code level, thus, it is uncertain if melanoma occurrence was higher in the areas directly circumscribing the abandoned plant. Approximately 21.3 out of 100,000 men and women are diagnosed annually with melanoma, and it is about twenty times more common in whites than blacks [17]. The major risk factor for melanoma is exposure to ultraviolet (UV) rays (sunlight is the primary source of UV rays), particularly among persons with fair skin. Other risk factors include having a large number of moles, having one or more first-degree relatives who have had melanoma, and being immunosuppressed [16]. It has been hypothesized that malignant melanoma may occur as a result of exposure to occupational or environmental chemicals (e.g., vinyl chloride, arsenic, polychlorinated biphenyls, petrochemicals, pesticides), particularly because malignancy can develop in cutaneous areas that have not been exposed to sunlight [26]. However, the epidemiologic evidence relating chemical exposures to melanoma risk is inconsistent. Thus, it is unclear whether the positive incidence rate ratio in Champaign County is the result of an artifactual finding from multiple comparisons, or has been confounded by sun exposure or other factors, such as immunosuppression. Moreover, general health concerns that the local population may have about living next to a former gas manufacturing site may lead to surveillance bias due to increased screening. Furthermore, a statistically significant deficit of melanoma was observed in Champaign County based on SIR analyses, and no statistically significant associations for melanoma were found based on comparisons with counties that did not have a former gas plant.

Finally, esophageal cancer incidence was elevated when Champaign County was compared with the non-gas plant counties in our sensitivity analysis of cancer incidence, but this observation was not substantiated by the main analyses, the sensitivity analysis of cancer mortality, or by the SIR analysis.

Alternatively, an unknown manufactured gas product compound may have produced the slight elevations in prostate cancer and/or melanoma incidence in the main analyses. This scenario is unlikely, however, given the plausible explanations listed above and because reduced rates were observed for cancers with known environmental or chemical relationships. That is, no "indicator" cancer types with established environmental or chemical etiology were observed in excess. For example, IARC has classified "coke production" as carcinogenic to humans (Group 1) for lung cancer because of exposure to PAHs in the industry (although associations from the occupational studies are somewhat tenuous) [27-29]. In a quantitative review of occupational exposures to PAHs, lung cancer and bladder cancer risk was elevated significantly among workers in the coal gasification industry [30]. However, in our assessment, we observed statistically significant reduced mortality and incidence rates of 15% and 17%, respectively, for lung & bronchus cancers, and no associations for urinary system and bladder cancers Moreover, our analyses were based on rates of cancer at the community level, not among workers likely exposed to much higher concentrations of possible chemical exposures.

It is unclear as to why there was a preponderance of inverse associations in Champaign County and the study zip codes versus the comparison counties. *A priori*, we developed a systematic protocol for identifying comparable counties. We identified counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level). Based on the 2000 census

information, there were approximately 7% fewer 'ever' smokers in Champaign County versus the comparison counties. This may explain, in part, the observation of lower cancer rates, particularly for lung & bronchus, in Champaign County. In addition, the prevalence of other potentially important factors, such as alcohol consumption or obesity, in these counties may have confounded the observed associations. However, relatively similar patterns of associations were observed in sensitivity analyses comparing Champaign County and the study zip codes with counties that did not have a former gas plant, and based on SIR analyses using nationally representative cancer data from the SEER program.

Most of the literature on manufactured gas plants focuses on the environmental and ecological impacts of the gas process residues and waste products. As such, considerable literature exists on the methodological, toxicological, elemental chemistry, and extracting techniques involving remediation and compound evaluations from abandoned sites [31-34]. While potentially hazardous compounds may have been produced as part of the gas manufacturing process, the extent and level to which compound residues persist at the sites is unclear. In certain cases, potential hazards may be overestimated as samples in some studies have been consistent with background levels or below the assumed level [1, 35]. As mentioned previously, the literature on direct or indirect human health risks from an epidemiologic standpoint, is sparse. DeHate et al. [1] investigated soil vapor intrusion at 10 commercial buildings and 26 single family and multi-family residential properties overlying and/or adjacent to three former manufactured gas plant sites. Soil vapor samples and indoor/outdoor air were analyzed for VOCs, and comparative risks were evaluated based on maximum and mean concentrations for BTEX relative to background levels. All hazard indices were less than one or were comparable to mean and maximum background levels, and there was no evidence of

manufactured gas plant-related soil vapor intrusion from any of the 36 sites. Based on these findings, the authors reported that no increased public health risks were associated with occupied residential or commercial properties overlying or surrounding former manufactured gas plant facilities [1]. Occupational epidemiologic studies involving postulated gas plant exposures, such as PAHs [27, 30], BTEX [36-38], and coal tar [30, 39-41], are extensive but none have evaluated potential disease outcomes resulting from residing in a community that includes a former manufactured gas plant site.

Our historical cancer assessment has limitations that are commonplace with analyzing population-level data. Prime among the limitations is that we did not have individual-level information on lifestyle, dietary, medical, or occupational factors. In addition, we did not have personal information regarding potential exposures (e.g., to soil, groundwater, or air) from the manufactured gas process. We were, however, able to adjust cancer estimates for age, sex, and race. Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law. The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected. The gas plant ceased operations in 1953, and although immediate release of potential compounds may have diminished at that time, concern about the persistence of compounds over time in the vicinity has been raised. Our analyses were conducted on the basis of publically available aggregate-level data. We began our analytical period at the earliest time point possible that enabled us to merge cancer data and census data. Given our analytical periods, there is sufficient latency to observe a carcinogenic effect, if one exists.

However, we were not able to capture cases that occurred in earlier time periods, with possible greater exposures. It may be possible that our analyses are not sensitive enough to identify small effects of plant exposures because of the nature of residential exposure classification. Despite these limitations, we found no clear or consistent evidence of an increase in cancer occurrence among residents in a community circumscribing a former manufactured gas plant.

The validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program. These three types of analyses serve as complementary comparisons to examine the consistency of findings across different population metrics. We implemented an objective methodological approach to identify counties in the state of Illinois that were the most closely matched (demographically) to the analytical zones. By using this approach, we were able to account for some prominent confounding factors at the aggregate level. However, the most closely matched comparison areas also had former gas plants. Therefore, we conducted a second analysis by matching demographic factors that was restricted to counties without former gas plants. Finally, we conducted analyses using nationally standardized rates of cancer. Despite the variation in analytical approaches, results were consistent between techniques.

We conducted a community cancer assessment for the purpose of appraising the public health regarding the occurrence of cancer among residents in a community with a former manufactured gas plant. Although this study did not include individual-level information, rates of total cancer and most cancer sites in the Champaign County area and zip codes circumscribing the abandoned facility were lower versus similar comparison areas, and based on nationally standardized rates of cancer. The primary exception is for prostate cancer, although there may be

relevant explanations for the higher rates aside from potential exposure emanating from the former manufactured gas plant site, such as an incidence spike due to higher PSA testing rates in Champaign County, a statistical artifact based on multiple comparisons, or confounding by unmeasured factors. Furthermore, a review of the literature did not reveal any known relation between the potential gas plant compounds and prostate cancer risk. Interpretation of results from our analyses should be made in the context of the many limitations of ecological-based study designs. However, the results from this retrospective cancer mortality and incidence assessment do not support an increase in cancer occurrence in communities surrounding a former manufactured gas plant in Champaign, IL.

AUTHOR CONTRIBUTION: DDA, DHG, and JPF were responsible for conception and design of the research. Statistical analyses were carried out by XJ. DDA, XJ, LCB, DHG, SRI, and JPF were responsible for development of the manuscript, critical revision and intellectual content.

FUNDING: This work was supported by Ameren Corporation.

COMPETING INTERESTS: DHG has served as an expert witness on behalf of Ameren in litigation related to manufactured gas plants. DDA, XJ, LCB, DHG, SRI, and JPF are employed by EpidStat Institute, all of whom were contracted by Ameren Corporation to support the study.

DATA SHARING STATEMENT: The full data set is available by emailing the corresponding author of the study.

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Historical Cancer Incidence and Mortality Assessment in an Illinois Community Proximal to a Former Manufactured Gas Plant

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Word count: 5,164 words

Abstract word count: (243 words)

Kewords: natural gas manufacturing, community, cancer incidence, epidemiology

Formatted: Highlight

ABSTRACT

Objectives: Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant in Champaign, IL. Thus, we compared historical rates of cancer in this area to comparison communities as well as with nationally standardized rates.

Design: Retrospective population-based community cancer assessment during 1990-2010

Setting: Champaign County, IL, and zip codes encompassing the location of the former manufactured gas plant to counties that were similar demographically.

Participants: Residents of the counties and zip codes studied between 1990-2010.

Main outcome measures: The relative risk (RR) and 95% confidence interval (CI) were used to compare cancer incidence and mortality in the areas near the gas compression site to the comparison counties. Standardized incidence ratios (SIR) were calculated to compare rates in the areas near the gas compression site to expected rates based on overall United States cancer rates.

Results: Total cancer mortality (RR = 0.91, 95% CI: 0.88-0.94) and incidence (RR = 0.95, 95% CI: 0.94-0.97) were reduced significantly in Champaign County versus the comparison counties. Similarly, a reduced rate of total cancer was observed in analyses by zip code (proximal to the former gas plant) when compared to either similar counties (RR = 0.89, 95% CI: 0.86-0.93) or national standardized rates of cancer (SIR = 0.88, 95% CI: 0.85-0.91).

Conclusions: This historical cancer assessment did not find an increased risk of total cancer or specific cancer types in communities near a former manufactured gas plant site.

Strength and limitations of this study:

- The validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program.
- Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law.
- A priori, we developed a systematic protocol for identifying comparable counties. We matched counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level) to control for confounding.
- Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors associated with cancer such as physical activity, family history of disease, or body mass index that may have influenced the results.
- The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected.

INTRODUCTION

The production of manufactured gas is widely considered one of the key developments in our industrial history, with an extensive chronology beginning in the late 1700s and spanning into the 1960s. Manufactured gas consisted largely of the gasification of coal, and less frequently, the combustion of other materials such as wood and oil. Historically, the manufactured gas industry grew significantly in the early 1800s due to the production of lighting for the progress and development of cities. However, later in the 19th century, this industry diversified into heating, refrigeration, and cooking. During the early to mid-20th century, the advent of natural gas obviated the gasification of coal, ultimately leading to the conversion or closure of manufactured gas plants. Pipelines transported natural gas directly from the well to gas distribution systems, and natural gas was considered more economical, efficient, and environmentally friendly. Most manufactured gas plants in the U.S. were terminated by1966 with few exceptions, and as a result of the manufactured gas demise, over 1,500 plant sites are suggested to remain dormant or vacant in the U.S. today.

Numerous health concerns have been raised regarding possible environmental exposures stemming from manufactured gas plant sites. Foremost among the concerns is that contamination and waste products from the manufacturing gas process leaked into the adjacent soil and groundwater, thus posing health risks in the nearby residential areas and communities [1]. The process of coal carbonization generates coal tar, which are complex mixtures of heterocyclic compounds, phenols, and polycyclic aromatic hydrocarbons (PAHs). Indeed, both volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs) from coal tar and petroleum products are derived from the coal gasification process [1]. The VOCs contain a mixture of BTEX, or benzene, toluene, ethylbenzene, and xylene isomers among other

compounds, while the SVOCs consist of a mixture of compounds, such as benzo(a)pyrene, benzo(e)pyrene, naphthalene, and 2-methyl naphthalene. In addition, principal component analyses have identified heavy metals at former manufactured gas plant sites [2, 3]. As a result of these gas process by-products, the U.S. Environmental Protection Agency (EPA) and other regulatory agencies have focused on assessing the potential for soil and groundwater contamination at former manufactured gas plant sites, as well as evaluating the potential for health risks among residents in nearby communities. The International Agency for Research on Cancer (IARC) lists many of the manufactured gas plant by-product compounds as known, probable, or possible carcinogens for specific cancers but the level and extent of community exposure to such compounds resulting from former manufactured gas plants is uncertain. Furthermore, sparse epidemiologic evidence exists on the potential public health risks associated with residing near former manufactured gas plant sites.

Concern has been raised that the occurrence of cancer may be increased in neighborhoods around a former manufactured gas plant on a 3.5 acre lot in northern Champaign, IL. The plant, in operation from 1887 until 1953, manufactured gas by heating coal. Coal tar and other production wastes were suggested to remain on site until the closing of the plant. AmerenIP has registered this site with the Illinois EPA under their Site Remediation Program. However, the potential long-term health effects of residents in the nearby community are unknown. Therefore, we conducted a historical cancer incidence and mortality assessment using publicly available cancer data and census tract information to evaluate the occurrence of cancer in the community where the former manufactured gas plant was located compared with other communities with and without former gas plants that have similar demographic and lifestyle characteristics. In

addition, we conducted standardized incidence analyses for Champaign County and the study zip codes using nationally representative cancer data.

METHODS

All data used in this study are publicly available. Specifically, the cancer incidence data were obtained from the Illinois Department of Public Health and from the Surveillance, Epidemiology, and End Results (SEER) Program, while cancer mortality data were obtained from SEER. Analyses for cancer incidence are presented at both the county and zip code level while analyses for cancer mortality are presented at the county level, which is the smallest area for which cancer mortality data are available. County and zip code demarcations were based on information provided by the U.S. Census Bureau.

Study Areas

The analytical and comparison population areas were characterized using census tract information. The former manufactured gas plant of interest was located in Champaign County, IL, and was circumscribed by zip codes 61820 and 61801; thus, these demarcated areas served as the analytical group. Because our assessment was community-based and ecologic in nature, ~~O~~our objective was to identify comparison counties in the state of Illinois with similar demographic and socioeconomic characteristics. Relevant characteristics included county setting (urban vs. rural), county population size, and percentages for black race, high school graduation, persons over age 65, persons unemployed, families below poverty level, urban residence, and ever smoking status. In addition, the median household income was utilized as a comparison factor. County selection was based on methods developed by the National Cancer Institute [4, 5].

Illinois Cancer Data

In concert with the Illinois State Cancer Registry (ICSR), the SEER program of the National Cancer Institute is the source of data for cancer mortality between 1986 and 2010 [6]. These data are grouped by age, sex, and race and are provided at the county level (the smallest available area for cancer mortality). The National Center for Health Statistics (NCHS) provides information on the underlying cause of death, coded to the International Classification of Diseases (ICD-9) [7] for all deaths for years 1986 through 1998 and the International Classification of Diseases (ICD-10) for all deaths for year 1999 and later [8]. Cancer mortality rates are available by single year for Illinois only, and deaths among non-residents and deaths of unknown age or sex are omitted from the database calculations. Because of NCHS policy, rates are not calculated for stratified sub-groups containing less than 10 deaths. For this analysis we used mortality data from 1990-2010 to be consistent with the census tract reporting periods.

Cancer incidence data for the direct community comparisons used in this study were collected by the ISCR and are available as a public use data set via the Illinois Department of Public Health for the years 1991-2010. All obtainable data are provided by the ISCR as a public service for the purpose of statistical reporting and analysis only. Case ascertainment is near complete as the identification and reporting of cancer cases is mandated by state law. Individual (personal) information has been de-identified, and the data have been aggregated into categories (e.g., age, race, Hispanic ethnicity, year of diagnosis and type of cancer) within individual records [9]. The number of cases reported in a particular region depends on the size of the geographic area in an effort to protect the privacy of individuals. The Illinois dataset contains sanitized records of cancer incidence among residents who were diagnosed between 1986 and

2011. Cancer incidence data at the county and zip code level are based on five-year interval groupings, and include data for invasive cancers only with the exception of bladder cancer. Non-melanoma skin cancers and reported cases with an unknown age or "other" sex category are omitted by the ISCR. Cancer incidence data used for the SIR analyses were obtained directly from the SEER program.

By using these data, we agreed to comply with the Illinois Health and Hazardous Substances Registry Act (410 ILCS 525/12). All data used in our analyses are publically available, thus, informed consent was not required.

Statistical~~Main~~ Analyses

As indicated, we ascertained cancer rates from the ISCR and the SEER program. The rates provided by these sources were calculated using the SEER*Stat® software package, developed by the Information Management Services Inc. for the National Cancer Institute [10]. SEER expresses rates per 100,000 population, and rates are age-adjusted by the direct method adjusting to the 2000 U.S. standard million population. These data were then used to formulate the basis of our historical cancer assessment.

Because of the ecologic nature of the community-based analyses, we conducted analyses in an effort to account for potential confounding at the aggregate level while considering the potential for exposure misclassification. Thus, we conducted analyses using three different comparison populations based on: 1) Illinois counties that were the most closely matched demographically (irrespective of having former gas plants), 2) counties without former gas plants (as part of the selection criteria) that were relatively similar demographically, and 3) nationally representative cancer data from the SEER program. By utilizing three different comparison

populations, we were able to enhance the validity of our analyses, examine the consistency of cancer rates across different groups, and facilitate the identification of potential sources of statistical heterogeneity (if present). All types of analyses serve as complementary comparisons to appreciate fully any observed associations.

In the first type of analysis, ~~W~~we calculated relative rate ratios (RRs) and 95% confidence intervals (CIs) to compare cancer mortality and incidence rates in Champaign County, IL and zip codes 61820 and 61801 encompassing the location of the former manufactured gas plant to counties that were the most similar demographically (i.e., Macon, Winnebago, and Sangamon counties). Although not part of the selection criteria, these counties had former gas plants but were the most demographically comparable based on our objective matching criteria. ~~These comparisons served as the main analyses because they were very well-matched demographically to the study areas.~~ The number of cancer cases and deaths were ascertained for the period 1990 through 2010, and the absolute rate of cancer occurrence was calculated based on the county and zip code population size according to the U.S. Census Bureau. The relative rate of cancer occurrence was calculated by dividing the rate of cancer in Champaign County and the zip codes (for cancer incidence only) by the rate of cancer in the comparison counties. County-level analyses were statistically adjusted for age, sex, and race, and zip code-level analyses were adjusted for age and sex (race stratified data were not available at the zip code level, and mortality analyses were adjusted for age only).

~~Sensitivity analyses~~

Although the comparison counties in the first ~~main~~ analyses were very-well matched demographically to Champaign County, they had former gas plants, which raises concern about

potential bias resulting from similar chemical exposures in the comparison counties. To address this concern, our second ~~we conducted several sensitivity~~ analyses consisted of~~by~~ comparing rates of cancer in Champaign County and the study zip codes with areas that did not have former gas plants but had relatively similar descriptive characteristics~~other populations~~. To do this~~First~~, we reviewed an Environmental Protection Agency (EPA) report on manufactured gas plant production [11], the EPA website, and the following website link: http://www.hatheway.net/state_site_pages/il_epa.htm to identify additional comparison counties. Illinois counties with relatively similar demographic characteristics but without former gas plants (i.e., Brown, Douglas, Menard, Randolph counties) were selected. Evaluations of cancer mortality and cancer incidence, using the same methodology as the first~~main~~ analyses, were conducted using these counties as comparisons.

In our final set of analyses~~Second~~, we calculated standardized incidence ratios (SIRs) for cancer sites in Champaign County and the zip codes of interest. The numbers of observed cancers in Champaign County and in the study zip codes were compared with those expected on the basis of standardized rates of cancer in the general population using data obtained from SEER [12]. The number of observed cancers was determined by sex, race, and 5-year age groups (the zip codes were standardized by age and sex groups) for each year from 1991-2010. Expected numbers of cases were calculated by multiplying the estimated population for Champaign County and for the study zip codes for each year of study by annual SEER cancer rates, stratified by 5-year age groups, race, and sex. Observed and expected counts were then generated for Champaign County and for the study zip codes, and SIRs were calculated by dividing the observed number by the expected number.

A final concern was the possibility of surveillance bias being introduced during the analytical study period. In the mid-2000s, a neighborhood advocacy group formed to increase awareness about the potential health effects from the abandoned gas plant [13]. In order to limit potential bias associated with the formation of this group, we conducted analyses for the years 1990-2000, prior to the formation of this group.

All analyses were performed using SAS statistical software.

RESULTS

Study Counties

The characteristics of the study county and the comparison counties (with the most similar demographic characteristics) are reported in Tables ~~s~~ 1 ~~and 2~~ for the 1990 and 2000 census periods~~, respectively~~.

Table 1. Characteristics of Study County and Comparison Counties based on 1990 Census.

Characteristic	Champaign County	Comparison counties most closely matched demographically		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	9.64	8.11	12.14	9.29
Percent did not graduate high school	12.50	18.23	23.79	23.70
Percent over age 65 years	8.74	13.71	14.57	12.67
Percent unemployed	4.24	4.36	6.60	5.20
Percent below poverty	8.03	7.19	9.84	7.71
Median household income (in tens)	2654	3035	2860	3134
Percent Urban	81.41	78.32	81.74	87.41

Table 2. Characteristics of Study county and Comparison counties based on 2000 census.

Characteristic	Champaign County	Comparison counties most closely matched demographically		
		Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	11.82	10.17	14.76	11.16
Percent did not graduate high school	9.02	11.93	16.83	18.57
Percent over age 65 years	9.72	13.51	15.24	12.73
Percent unemployed	5.52	4.07	7.15	5.83
Percent below poverty	6.92	6.49	9.28	6.92
Median household income (in tens)	3778	4296	3786	4389
Percent Urban	84.34	85.40	84.17	91.78
Percent ever smoke	44.89	52.46	52.59	52.38

Table 1. Characteristics of Study County and Comparison Counties Most Closely Matched Demographically Based on 1990 and 2000 Census.

Characteristic	Year of Census	Champaign County	Comparison counties most closely matched demographically		
			Sangamon County	Macon County	Winnebago County
Rural-Urban Continuum Code	1990	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
	2000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of <250,000	Counties in metropolitan areas of 250,000-1,00,000
Percent Black	1990	9.64	8.11	12.14	9.29
	2000	11.82	10.17	14.76	11.16
Percent did not	1990	12.50	18.23	23.79	23.70

graduate high school	2000	9.02	11.93	16.83	18.57
Percent over age 65 years	1990	8.74	13.71	14.57	12.67
	2000	9.72	13.51	15.24	12.73
Percent unemployed	1990	4.24	4.36	6.60	5.20
	2000	5.52	4.07	7.15	5.83
Percent below poverty	1990	8.03	7.19	9.84	7.71
	2000	6.92	6.49	9.28	6.92
Median household income (in tens)	1990	2654	3035	2860	3134
	2000	3778	4296	3786	4389
Percent Urban	1990	81.41	78.32	81.74	87.41
	2000	84.34	85.40	84.17	91.78
Percent ever smoke	1990	Not Available	Not Available	Not Available	Not Available
	2000	44.89	52.46	52.59	52.38

Champaign County was very well-matched to the comparison counties with former gas plants on the variables of interest. Given the relatively high proportion of counties with former manufactured gas plants in Illinois, the availability of matching counties without former gas plants was more limited. However, based on our county scoring methodology and criteria, we were able to identify counties (i.e., Brown, Douglas, Menard, Randolph) without former gas plants to serve as comparison communities in our second type of~~sensitivity~~ analyses. These counties were not as closely matched on potential confounding factors (i.e., demographic characteristics) that may be associated with cancer as the counties used in the first~~our main~~ analyses (Table 2).

Table 2. Characteristics of Study County and Comparison Counties Without Former Gas Plants on 1990 and 2000 Census.

Characteristic	Year of Census	Champaign County	Comparison counties without former gas plants			
			Brown	Douglas	Menard	Randolph
Rural-Urban Continuum Code	1990	Counties in metropolitan areas of <250,000	Comp rural < 2,500 urban pop, not adjacent to metro area	Urban pop of 2,500 to 19,999, adjacent to a metro area	Counties in metropolitan areas of <250,000	Urban pop of 2,500 to 19,999, adjacent to a metro area
	2000	Counties in metropolitan areas of <250,000	Urban pop of 2,500 to 19,999, not adjacent to a metro area	Urban pop of 2,500 to 19,999, adjacent to a metro area	Counties in metropolitan areas of <250,000	Urban pop of 2,500 to 19,999, adjacent to a metro area

Percent Black	1990	9.64	9.37	0.05	0.05	8.26
	2000	11.82	18.29	0.43	0.46	9.56
Percent did not graduate high school	1990	12.50	31.14	25.97	22.69	35.78
	2000	9.02	36.75	20.69	11.67	28.67
Percent over age 65 years	1990	8.74	16.83	15.26	15.06	15.33
	2000	9.72	12.69	15.96	13.17	15.61
Percent unemployed	1990	4.24	6.03	4.4	4.35	6.46
	2000	5.52	3.47	2.78	3.88	5.69
Percent below poverty	1990	8.03	10.47	6.92	7.13	8.75
	2000	6.92	4.84	4.21	6.11	7.06
Median household income (in tens)	1990	2654	2045	2676	2933	2586
	2000	3778	3545	3944	4660	3701
Percent Urban	1990	81.41	0.00	49.13	0.00	46.16
	2000	84.34	58.66	36.69	24.66	57.3
Percent ever smoke	1990	Not Available	Not Available	Not Available	Not Available	Not Available
	2000	44.89	49.76	48.98	50.81	55.14

Cancer Mortality

The RR for total cancer mortality in Champaign County versus the comparison counties most closely matched demographically (Macon, Winnebago, and Sangamon) was significantly decreased (RR = 0.91, 95% CI: 0.88-0.94) during 1990-2010 (Table 3). Similarly, statistically significant deficits in mortality were observed for cancers of the esophagus (RR = 0.80, 95% CI: 0.65-0.98), colorectum (RR = 0.88, 95% CI: 0.80-0.97), pancreas (RR = 0.78, 95% CI: 0.68-0.89), and lung & bronchus (RR = 0.85, 95% CI: 0.80-0.89). In fact, out of all 22 cancer site groupings, 17 RRs represented reduced risks, one RR was 1.0, no data were available for one site (testicular cancer), and three RRs were slightly elevated. None of these elevated cancer sites was statistically significant, with RRs of 1.03 (melanoma), 1.06 (prostate), and 1.05 (leukemias) (Table 3).

Table 3. Age adjusted mortality rates, RRs and 95% CI† in 1990-2010

	Champaign County			Comparison counties most closely matched demographically			Rate Ratio	95% CI
	No. of Deaths	Rate	95% CI	No. of Deaths	Rate	95% CI		
All Cancer	5,611	187.2	182.3-192.2	27,170	206.1	203.6-208.5	0.91*	0.88-0.94
Oral Cavity & Pharynx	64	2.1	1.6-2.7	358	2.7	2.4-3.0	0.78	0.59-1.03
Esophagus	118	4.0	3.3-4.7	650	4.9	4.5-5.3	0.80*	0.65-0.98
Stomach	94	3.1	2.5-3.8	494	3.7	3.4-4.1	0.84	0.67-1.05
Colorectal	551	18.4	16.9-20.0	2,765	20.8	20.1-21.6	0.88*	0.80-0.97
Liver	87	2.9	2.3-3.6	420	3.2	2.9-3.5	0.91	0.71-1.15
Pancreas	267	9.0	7.9-10.1	1,526	11.5	11-12.1	0.78*	0.68-0.89
Lung & Bronchus	1,526	51.3	48.7-53.9	7,990	60.6	59.2-61.9	0.85*	0.80-0.89
Bone & Joint	12	0.3	0.2-0.6	43	0.3	0.2-0.4	0.94	0.42-1.89
Melanomas	81	2.7	2.1-3.3	339	2.6	2.3-2.9	1.03	0.80-1.31
Breast‡	438	25.6	23.3-28.2	2,045	27.5	26.3-28.7	0.93	0.84-1.03
Prostate‡‡	348	31.4	28.1-34.9	1,427	29.7	28.1-31.3	1.06	0.94-1.19
Testis‡‡	-	-	-	-	-	-	-	-
Cervix‡	39	2.3	1.6-3.2	177	2.6	2.2-3.0	0.89	0.61-1.27
Uterine‡	72	4.2	3.2-5.2	323	4.2	3.7-4.6	1.00	0.76-1.29
Ovary‡	159	9.3	7.9-10.8	716	9.5	8.8-10.2	0.98	0.82-1.17
Kidney & Renal Pelvis	136	4.5	3.8-5.4	618	4.7	4.3-5.1	0.97	0.80-1.17
Bladder	131	4.4	3.7-5.3	610	4.6	4.2-5.0	0.97	0.79-1.17
Nervous System	119	3.8	3.2-4.6	596	4.6	4.2-5.0	0.83	0.68-1.02
Hodgkins Lymphomas	13	0.4	0.2-0.7	61	0.5	0.4-0.6	0.88	0.44-1.61
NHL	230	7.6	6.7-8.7	1,096	8.3	7.8-8.8	0.92	0.79-1.06
Myelomas	110	3.7	3.0-4.5	510	3.8	3.5-4.2	0.96	0.77-1.18
Leukemias	251	8.2	7.3-9.3	1,029	7.8	7.4-8.3	1.05	0.91-1.21

†Tiwariet al. 2006 modification for CIs
‡Female only, ‡‡ Male only
*p < 0.05

In our second set of analyses, ~~S~~similar results for Champaign County were observed when compared with counties without former manufactured gas plants. Total cancer was associated with an RR of 0.96 (95% CI: 0.92-1.00), and statistically significant reduced rates of colorectal (RR = 0.85, 95% CI: 0.75-0.97) and pancreatic cancer (RR = 0.81, 95% CI: 0.67-0.98) mortality were observed (data ~~not tabulated~~tables not shown, but available upon request). Relative risks for most cancer sites were 1.0 or lower, with few weakly positive, albeit non-significant associations. No statistically significant associations for the more common cancers –

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lung & bronchus (RR = 0.94, 95% CI: 0.87-1.02), breast (RR = 1.00, 95% CI: 0.85-1.18), or prostate (RR = 1.00, 95% CI: 0.84-1.19) were observed.

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Taken together, results based on analyses using communities with and without former gas plants are not supportive of an increased risk of cancer mortality.

Cancer Incidence

A statistically significant reduced rate of total cancer incidence was observed in Champaign County versus the comparison counties most closely matched demographically (RR = 0.95, 95% CI: 0.94-0.97) during 1991-2010 (Table 4). Decreased incidence rates were observed for nineteen of 23 cancer site groupings based on analyses during 1991-2010. Incidence rates for cancers of the colorectum, pancreas, lung & bronchus, testis, cervix, nervous system, and "other" sites (list of cancers in this category are shown in Table 4) were all significantly lower versus the rates in the comparison counties. In contrast, statistically significant slightly elevated rates were observed for melanoma (RR = 1.12, 95% CI: 1.02-1.24) and prostate cancer (RR = 1.20, 95% CI: 1.14-1.25). Restricting the analytical period to 1991-2000 in Champaign County in order to reduce potential bias associated with the formation of the neighborhood advocacy group did not appreciably modify the results; the RR for melanoma was 1.17 (95% CI: 0.99-1.38) and the RR for prostate cancer was 1.17 (95% CI: 1.09-1.26) (data not tabulated). Incidence rates were significantly reduced for total, colorectal, pancreatic, lung & bronchus, testicular, and cervical cancers during 1991-2000.

Table 4. Age, sex, and race-adjusted incidence rate by county, RRs and 95% CI[†] in 1991-2010

	Champaign County			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All cancer	13978	499.55	491.17-507.93	61184	524.18	520.03-528.34	0.95*	0.94-0.97
Oral cavity & pharynx	332	11.94	10.64-13.23	1484	12.71	12.07-13.36	0.94	0.83-1.06
Esophagus	141	5.21	4.35-6.08	696	5.96	5.52-6.41	0.87	0.73-1.05
Stomach	177	6.38	5.43-7.33	809	6.93	6.45-7.41	0.92	0.78-1.09
Colorectal	1442	52.87	50.11-55.62	7140	61.17	59.75-62.59	0.86*	0.82-0.91
Liver	112	3.94	3.20-4.67	486	4.16	3.79-4.53	0.95	0.77-1.16
Pancreas	291	10.69	9.45-11.92	1558	13.35	12.69-14.01	0.80*	0.71-0.91
Lung & Bronchus	1945	71.76	68.55-74.96	10063	86.21	84.53-87.90	0.83*	0.79-0.87
Bone	23	0.68	0.39-0.97	80	0.69	0.54-0.84	1.00	0.62-1.60
Melanomas	539	17.62	16.10-19.14	1834	15.71	14.99-16.43	1.12*	1.02-1.24
Breast-invasive[‡]	2184	150.65	144.25-157.04	9158	151.54	148.43-154.64	0.99	0.95-1.04
Prostate[‡‡]	2254	172.52	165.38-179.66	8125	144.35	141.21-147.48	1.20*	1.14-1.25
Testis[‡‡]	89	4.05	3.18-4.93	337	5.99	5.35-6.63	0.68*	0.53-0.86
Cervix[‡]	114	6.84	5.54-8.14	561	9.28	8.51-10.05	0.74*	0.60-0.91
Uterus[‡]	406	28.53	25.74-31.33	1801	29.80	28.42-31.18	0.96	0.86-1.07
Ovary[‡]	228	15.52	13.48-17.57	1022	16.91	15.87-17.95	0.92	0.79-1.06
Kidney	425	15.10	13.64-16.55	1945	16.66	15.92-17.40	0.91	0.81-1.01
Bladder	363	13.56	12.16-14.96	1725	14.78	14.08-15.48	0.92	0.82-1.03
Nervous System	164	5.53	4.66-6.39	797	6.83	6.35-7.30	0.81*	0.68-0.96
Hodgkins Lymphomas	93	2.51	1.98-3.04	341	2.92	2.61-3.23	0.86	0.68-1.09
NHL	556	19.64	17.98-21.29	2490	21.33	20.49-22.17	0.92	0.84-1.01
Myelomas	183	6.68	5.71-7.66	758	6.49	6.03-6.96	1.03	0.88-1.21
Leukemias	433	15.32	13.86-16.79	1678	14.38	13.69-15.06	1.07	0.96-1.19
All Other Sites[‡‡‡]	1484	50.63	48.00-53.26	6296	53.94	52.61-55.27	0.94*	0.89-0.99

[†]Breslow and Day 1987

[‡]Female only, [‡‡] Male only

[‡‡‡]Includes small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, breast-invasive male only, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

*$p < 0.05$

Fewer cancer sub-groupings were available at the zip code level. Nevertheless, results similar to those in the county-level analyses were observed. Total cancer incidence was 11% lower in the study zip codes versus the most closely matched comparison counties, resulting in a statistically significant RR of 0.89 (95% CI: 0.86-0.93) during 1991-2010 (Table 5). Of the 10 cancer site groupings, nine incidence rates were decreased versus comparison counties, including statistically significant reductions for colorectal (RR = 0.85, 95% CI: 0.76-0.95), breast

(invasive) (RR = 0.86, 95% CI: 0.78-0.95), and "other" (RR = 0.86, 95% CI: 0.79-0.92) cancers. The only elevated incidence rate was for prostate cancer, with a significant RR of 1.13 (95% CI: 1.03-1.24), based on 500 diagnosed cases during 1991-2010. However, no significant association was found for prostate cancer (RR = 1.07, 95% CI: 0.95-1.21) in the analysis for the period 1991-2000 (data not tabulated). During this period, rates for colorectal, breast, and "other" remained significantly decreased, while significant deficits for lung & bronchus (RR = 0.75, 95% CI: 0.66-0.86) and central nervous system cancers (RR = 0.55, 95% CI: 0.33-0.93) were observed as well.

Table 5. Age and sex-adjusted incidence rate by zip code, RRs and 95% CI† in 1991-2010.

	Zip 61820, 61801			Comparison counties most closely matched demographically			Relative rate	95% CI
	No. of Cancers	Rate	95% CI	No. of Cancers	Rate	95% CI		
All Cancer	3191	468.15	451.25-485.06	61184	524.18	520.03-528.34	0.89*	0.86-0.93
Oral Cavity & Pharynx	81	12.40	9.62-15.19	1484	12.71	12.07-13.36	0.98	0.77-1.23
Colorectal	349	51.93	46.32-57.53	7140	61.17	59.75-62.59	0.85*	0.76-0.95
Lung & Bronchus	440	67.81	61.34-74.27	10063	86.21	84.53-87.90	0.79	0.71-0.87
Breast-Invasive‡	464	130.16	117.79-142.52	9158	151.54	148.43-154.64	0.86*	0.78-0.95
Cervix‡	38	8.22	5.33-11.12	561	9.28	8.51-10.05	0.89	0.62-1.27
Prostate‡‡	500	163.09	148.61-177.57	8125	144.35	141.21-147.48	1.13*	1.03-1.24
Urinary System	186	28.87	24.61-33.13	3670	31.44	30.42-32.46	0.92	0.79-1.07
Central Nervous System	38	5.47	3.63-7.31	797	6.83	6.35-7.30	0.80	0.57-1.13
Leukemias and Lymphomas	267	36.55	31.88-41.22	4509	38.63	37.50-39.76	0.95	0.83-1.08
All other cancers‡‡‡	828	114.84	106.51-123.17	15677	134.31	132.21-136.41	0.86*	0.79-0.92

†Breslow and Day 1987

‡Female only, ‡‡ Male only

‡‡‡ Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva,

other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.
*p < 0.05

Additional sub-group analyses for the cancer sites were conducted by individual zip codes and by analytical periods. The rate of prostate cancer during 1991-2010 was elevated with marginal significance for zip code 61820 (RR = 1.15, 95% CI: 1.00-1.32, based on 211 cases) but not for zip code 61801 (RR = 1.12, 95% CI: 0.99-1.26) (data not tabulated). No effect modification was apparent by zip code as the CIs for prostate cancer largely overlapped. No other statistically significantly cancer rates were observed during 1991-2010 but rates were modified in the inverse direction for colorectal (RR for zip code 61820 = 0.98, 95% CI: 0.84-1.15; zip code 61801 = 0.76, 95% CI: 0.65-0.88) and lung & bronchus (RR for zip code 61820 = 0.98, 95% CI: 0.86-1.13; zip code 61801 = 0.65, 95% CI: 0.57-0.75) cancers (data not tabulated). Interestingly, when analyses were conducted for the period 1991-2000, prostate cancer rates were modified by zip code (RR for zip code 61820 = 1.23, 95% CI: 1.02-1.48; zip code 61801 = 0.98, 95% CI: 0.83-1.16).

In the second type of analysis, ~~Findings were again similar in the sensitivity analyses when~~ counties without former manufactured gas plants were used as the comparison (data tables not shown ~~not tabulated~~, but available upon request). No difference in total cancer was found between Champaign County and the comparison counties without former gas plants (RR = 1.00, 95% CI: 0.97-1.02). Of 22 cancer site groupings, 12 had reduced rates in Champaign County, with statistically significant deficits for colorectal (RR = 0.83, 95% CI: 0.76-0.90) and cervical cancer (RR = 0.66, 95% CI: 0.49-0.90). Respiratory system cancers (lung & bronchus RR = 0.95), urinary tract cancers (kidney RR = 0.99; bladder RR = 1.01), and lymphohematopoietic malignancies (Hodgkins lymphomas RR = 0.89; non-Hodgkins lymphomas RR = 0.96;

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myelomas RR = 0.99; leukemias RR = 1.03) were not elevated in Champaign County compared with the counties that did not have former gas plants. As with the first set of~~main~~ analyses, prostate cancer incidence was elevated slightly and significantly (RR = 1.14, 95% CI: 1.06-1.23) in Champaign County, but it was not significant in the study zip code analysis (RR = 1.09, 95% CI: 0.98-1.21). The only other statistically significant positive association in the county ~~sensitivity~~ analysis was for esophageal cancer (RR = 1.46, 95% CI: 1.07-1.99), but this finding was not substantiated in other analyses. Total cancer was significantly reduced in the study zip codes versus the comparison counties without former gas plants (RR = 0.94, 95% CI: 0.90-0.98). Moreover, seven of 10 cancer sites were associated with reduced rates in the study zip codes, while three were slightly positive and not significant.

Standardized Incidence Ratio (SIR) Analyses

During the period, 1991-2010, 13,978 total cancers were observed in Champaign County with 14,150 expected based on nationally standardized rates, resulting in an SIR of 0.99 (95% CI: 0.97-1.00) (data not tabulated). Of 23 cancer site groupings, 14 had expected or lower than expected cases of cancer, with statistically significant deficits observed for stomach, liver, pancreas, bone, melanoma, testicular, bladder, nervous system, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. A slightly greater than expected number of lung & bronchus (SIR = 1.07, 95% CI: 1.02-1.11) and kidney (SIR = 1.13, 95% CI: 1.03-1.25) cancer cases were observed in Champaign County, but these findings were not supported by the other analyses. In fact, a slight deficit of lung & bronchus cancer cases was observed in the study zip codes (SIR = 0.98, 95% CI: 0.89-1.07), and urinary system cancer (includes kidney cancer) was reduced significantly (SIR = 0.78, 95% CI: 0.67-0.90) in the study zip codes (Table 6). Significantly fewer than

expected total cancer cases were observed in the study zip codes (SIR = 0.88, 95% CI: 0.85-0.91) (the SIRs for the cancer sites in the study zip codes are summarized in Table 6).

Table 6. Standardized incidence ratios (SIRs) and 95% CI of Zip code 61820 and 61801, 1991-2010

Cancer Sites	Obs	Exp	SIR	95% CI
All Cancer	3191	3612	0.88	0.85-0.91
Oral Cavity & Pharynx	81	82	0.98	0.78-1.22
Colorectal	349	378	0.92	0.83-1.03
Lung & Bronchus	440	450	0.98	0.89-1.07
Breast-Invasive‡	464	511	0.91	0.83-0.99
Cervix‡	38	36	1.04	0.74-1.43
Prostate‡‡	500	525	0.95	0.87-1.04
Urinary System	186	239	0.78	0.67-0.90
Central Nervous System	38	63	0.60	0.43-0.83
Leukemias and Lymphomas	267	320	0.84	0.74-0.94
All other cancers‡‡‡	828	1008	0.82	0.77-0.88

†Breslow and Day 1987
‡Female only, ‡‡ Male only
‡‡‡ Includes esophagus, stomach, liver, pancreas, bone, melanomas, uterus, ovary, testis, myelomas, breast-invasive male only, small intestine, anus, intrahepatic bile duct, gallbladder, other biliary, retroperitoneum, peritoneum, other digestive organs, nose, larynx, pleura, trachea, soft tissue including heart, other non-epithelial skin, vagina, vulva, other female genital organs, penis, other male genital organs, ureter, other urinary organs, eye, thyroid, other endocrine including thymus, mesothelioma, Kaposi sarcoma, and miscellaneous other sites.

DISCUSSION

We observed statistically significant reductions in total cancer mortality and incidence in Champaign County, IL, and the zip code study areas compared with counties that were similar demographically and socioeconomically, and based on nationally standardized rates. Furthermore, cancer occurrence was lower in the study area for most cancer types, with several statistically significant reductions in cancer rates. Results were largely consistent within and across analyses, with a few exceptions. Indeed, the lower mortality rates for most cancers in the study area versus the comparison counties were in accordance with the lower cancer incidence rates observed in Champaign County and the study zip codes. The only noteworthy positive associations in the primary analyses were for prostate cancer and melanoma. Neither prostate

cancer mortality nor melanoma mortality was significantly elevated. However, incidence rates for these cancers were significantly increased in Champaign County. It is not clear why elevated rates were observed, although based on chance alone, it would be expected that some cancer rates would be statistically significant in both the positive and inverse directions. As indicated, we observed several statistically significant inverse associations (i.e. RRs below the null value of 1.0), such as for lung & bronchus, colorectal, and breast cancers. However, only two cancer types (prostate cancer and melanoma; incidence only) were associated with statistically significant positive associations. Thus, significant associations may have been observed due to multiple comparisons – a statistical phenomenon whereby one out of 20 associations is statistically significant due to chance [14, 15]. In our analysis, we generated over 100 unique RRs.

Prostate cancer is the most common cancer among men in the U.S., and 238,590 incident cases and 29,720 deaths were estimated to occur in 2013 [16, 17]. The figures for prostate cancer represent 14.4% of all new cancer cases and 5.1% of all cancer deaths in the U.S. [17]. Increasing age, African American race, family history of prostate cancer, and genetic variations and mutations are established risk factors for prostate cancer, although the etiology is largely unknown despite an extensive effort to identify causes of this malignancy [16, 17]. The role of lifestyle and dietary factors are thought to play a role in prostate cancer risk, as past research has identified obesity, physical inactivity, and smoking as significant modifiable risk factors for this malignancy [18-21]. Our cancer assessment is ecologic in nature, thus, aside from age, sex, and race, we could not model or adjust for factors such as physical activity, family history of disease, or body mass index that may have influenced the results. Based on a review of the literature and

statements by prominent cancer organizations [16, 17], no manufactured gas plant by-product compound has been clearly or consistently associated with prostate cancer risk.

Perhaps the most likely reason for the elevation in prostate cancer incidence during 1991-2010 is the increased rate of prostate-specific antigen (PSA) screening in Champaign County versus the comparison counties. Indeed, based on the Behavioral Risk Factor Surveillance System (BRFSS) survey from the Centers for Disease Control and Prevention (CDC) and administered by the Illinois Department of Public Health [9], the percent of men who underwent PSA screening was higher in Champaign County than Sangamon, Macon, and Winnebago counties (as a composite percentage) during the study period. Furthermore, composite rates of PSA screening were higher in Champaign County than the counties without former gas plants. It is well-established and well-publicized that screening for prostate cancer results in an increase in incidence rates, whereas a proportion of prostate cancers may otherwise go undetected without screening [22-24]. In a sentinel review paper on the epidemiologic impact of screening on the incidence and mortality of prostate cancer in the U.S., it was suggested that PSA testing was the likely cause of the dramatic increase in prostate cancer incidence during the 1990s [23]. Although PSA testing is useful for early diagnosis, its value as a screening tool has been under scrutiny because the theoretical benefit on mortality is questionable [24]. According to a recent study from the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized screening trial, men who underwent annual prostate cancer screening with PSA testing and digital rectal examination had a 12 percent higher incidence rate of prostate cancer compared with men in the control group (who did not undergo PSA testing) [25]. However, approximately the same rate of death from prostate cancer was observed between groups, and no evidence of a mortality benefit was found in age or pre-trial PSA testing strata [25]. In our assessment, we observed a statistically

significant increase in prostate cancer incidence in Champaign County (where a greater proportion of individuals underwent PSA testing) but no statistically significant difference in prostate cancer mortality versus the comparison counties.

Melanoma was also associated with a statistically significant positive association (incidence only). Cancer incidence data for melanoma were not available at the zip code level, thus, it is uncertain if melanoma occurrence was higher in the areas directly circumscribing the abandoned plant. Approximately 21.3 out of 100,000 men and women are diagnosed annually with melanoma, and it is about twenty times more common in whites than blacks [17]. The major risk factor for melanoma is exposure to ultraviolet (UV) rays (sunlight is the primary source of UV rays), particularly among persons with fair skin. Other risk factors include having a large number of moles, having one or more first-degree relatives who have had melanoma, and being immunosuppressed [16]. It has been hypothesized that malignant melanoma may occur as a result of exposure to occupational or environmental chemicals (e.g., vinyl chloride, arsenic, polychlorinated biphenyls, petrochemicals, pesticides), particularly because malignancy can develop in cutaneous areas that have not been exposed to sunlight [26]. However, the epidemiologic evidence relating chemical exposures to melanoma risk is inconsistent. Thus, it is unclear whether the positive incidence rate ratio in Champaign County is the result of an artifactual finding from multiple comparisons, or has been confounded by sun exposure or other factors, such as immunosuppression. Moreover, general health concerns that the local population may have about living next to a former gas manufacturing site may lead to surveillance bias due to increased screening. Furthermore, a statistically significant deficit of melanoma was observed in Champaign County based on SIR analyses, and no statistically significant associations for melanoma were found based on comparisons with counties that did not have a former gas plant.

Finally, esophageal cancer incidence was elevated when Champaign County was compared with the non-gas plant counties in our sensitivity analysis of cancer incidence, but this observation was not substantiated by the main analyses, the sensitivity analysis of cancer mortality, or by the SIR analysis.

Alternatively, an unknown manufactured gas product compound may have produced the slight elevations in prostate cancer and/or melanoma incidence in the main analyses. This scenario is unlikely, however, given the plausible explanations listed above and because reduced rates were observed for cancers with known environmental or chemical relationships. That is, no "indicator" cancer types with established environmental or chemical etiology were observed in excess. For example, IARC has classified "coke production" as carcinogenic to humans (Group 1) for lung cancer because of exposure to PAHs in the industry (although associations from the occupational studies are somewhat tenuous) [27-29]. In a quantitative review of occupational exposures to PAHs, lung cancer and bladder cancer risk was elevated significantly among workers in the coal gasification industry [30]. However, ~~I~~in our assessment, we observed statistically significant reduced mortality and incidence rates of 15% and 17%, respectively, for lung & bronchus cancers, and no associations for urinary system and bladder cancers. Moreover, our analyses were based on rates of cancer at the community level, not among workers likely exposed to much higher concentrations of possible chemical exposures.

It is unclear as to why there was a preponderance of inverse associations in Champaign County and the study zip codes versus the comparison counties. *A priori*, we developed a systematic protocol for identifying comparable counties. We identified counties based on residential status (urban/rural) and similar demographic and socioeconomic characteristics, and our analyses were adjusted for age, sex, and race (at the county level). Based on the 2000 census

information, there were approximately 7% fewer 'ever' smokers in Champaign County versus the comparison counties. This may explain, in part, the observation of lower cancer rates, particularly for lung & bronchus, in Champaign County. In addition, the prevalence of other potentially important factors, such as alcohol consumption or obesity, in these counties may have confounded the observed associations. However, relatively similar patterns of associations were observed in sensitivity analyses comparing Champaign County and the study zip codes with counties that did not have a former gas plant, and based on SIR analyses using nationally representative cancer data from the SEER program.

Most of the literature on manufactured gas plants focuses on the environmental and ecological impacts of the gas process residues and waste products. As such, considerable literature exists on the methodological, toxicological, elemental chemistry, and extracting techniques involving remediation and compound evaluations from abandoned sites [31-34]. While potentially hazardous compounds may have been produced as part of the gas manufacturing process, the extent and level to which compound residues persist at the sites is unclear. In certain cases, potential hazards may be overestimated as samples in some studies have been consistent with background levels or below the assumed level [1, 35]. As mentioned previously, the literature on direct or indirect human health risks from an epidemiologic standpoint, is sparse. DeHate et al. [1] investigated soil vapor intrusion at 10 commercial buildings and 26 single family and multi-family residential properties overlying and/or adjacent to three former manufactured gas plant sites. Soil vapor samples and indoor/outdoor air were analyzed for VOCs, and comparative risks were evaluated based on maximum and mean concentrations for BTEX relative to background levels. All hazard indices were less than one or were comparable to mean and maximum background levels, and there was no evidence of

manufactured gas plant-related soil vapor intrusion from any of the 36 sites. Based on these findings, the authors reported that no increased public health risks were associated with occupied residential or commercial properties overlying or surrounding former manufactured gas plant facilities [1]. Occupational epidemiologic studies involving postulated gas plant exposures, such as PAHs [27, 30], BTEX [36-38], and coal tar [30, 39-41], are extensive but none have evaluated potential disease outcomes resulting from residing in a community that includes a former manufactured gas plant site.

Our historical cancer assessment has limitations that are commonplace with analyzing population-level data. Prime among the limitations is that we did not have individual-level information on lifestyle, dietary, medical, or occupational factors. In addition, we did not have personal information regarding potential exposures (e.g., to soil, groundwater, or air) from the manufactured gas process. We were, however, able to adjust cancer estimates for age, sex, and race. Because of the complete, systematic, and statewide registry in Illinois, data for persons diagnosed with cancer were assembled in an unbiased fashion. Identification and reporting of cancer cases in the ISCR is mandated by state law. The population sizes (i.e., the denominator for estimating cancer rates) for the study periods were based on the 1990 and 2000 census information. If there was considerable in- or out-migration of the population over time, the estimated RRs may have been affected. The gas plant ceased operations in 1953, and although immediate release of potential compounds may have diminished at that time, concern about the persistence of compounds over time in the vicinity has been raised. Our analyses were conducted on the basis of publically available aggregate-level data. We began our analytical period at the earliest time point possible that enabled us to merge cancer data and census data. Given our analytical periods, there is sufficient latency to observe a carcinogenic effect, if one exists.

However, we were not able to capture cases that occurred in earlier time periods, with possible greater exposures. It may be possible that our analyses are not sensitive enough to identify small effects of plant exposures because of the nature of residential exposure classification. Despite these limitations, we found no clear or consistent evidence of an increase in cancer occurrence among residents in a community circumscribing a former manufactured gas plant. ~~Furthermore,~~

T~~t~~he validity of our results is enhanced by the utilization of three comparison populations: 1) counties very well-matched demographically that had former gas plants, 2) comparison counties without former gas plants, and 3) nationally representative cancer data from the SEER program. These three types of analyses serve as complementary comparisons to examine the consistency of findings across different population metrics. We implemented an objective methodological approach to identify counties in the state of Illinois that were the most closely matched (demographically) to the analytical zones. By using this approach, we were able to account for some prominent confounding factors at the aggregate level. However, the most closely matched comparison areas also had former gas plants. Therefore, we conducted a second analysis by matching demographic factors that was restricted to counties without former gas plants. Finally, we conducted analyses using nationally standardized rates of cancer. Despite the variation in analytical approaches, results were consistent between techniques.

We conducted a community cancer assessment for the purpose of appraising the public health regarding the occurrence of cancer among residents in a community with a former manufactured gas plant. Although this study did not include individual-level information, rates of total cancer and most cancer sites in the Champaign County area and zip codes circumscribing the abandoned facility were lower versus similar comparison areas, and based on nationally standardized rates of cancer. The primary exception is for prostate cancer, although there may be

relevant explanations for the higher rates aside from potential exposure emanating from the former manufactured gas plant site, such as an incidence spike due to higher PSA testing rates in Champaign County, a statistical artifact based on multiple comparisons, or confounding by unmeasured factors. Furthermore, a review of the literature did not reveal any known relation between the potential gas plant compounds and prostate cancer risk. Interpretation of results from our analyses should be made in the context of the many limitations of ecological-based study designs. However, ~~In conclusion,~~ the results from this retrospective cancer mortality and incidence assessment do not support an increase in cancer occurrence in communities surrounding a former manufactured gas plant in Champaign, IL.

AUTHOR CONTRIBUTION: DDA, DHG, and JPF were responsible for conception and design of the research. Statistical analyses were carried out by XJ. DDA, XJ, LCB, DHG, SRI, and JPF were responsible for development of the manuscript, critical revision and intellectual content.

FUNDING: This work was supported by Ameren Corporation.

COMPETING INTERESTS: DHG has served as an expert witness on behalf of Ameren in litigation related to manufactured gas plants. DDA, XJ, LCB, DHG, SRI, and JPF are employed by EpidStat Institute, all of whom were contracted by Ameren Corporation to support the study.

DATA SHARING STATEMENT: The full data set is available by emailing the corresponding author of the study.

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