Health Consultation

Review of Bladder Cancer Data

RAYMARK INDUSTRIES
(a/k/a RAYMARK INDUSTRIES, INCORPORATED)

STRATFORD, FAIRFIELD COUNTY, CONNECTICUT

EPA FACILITY ID: CTD001186618

MAY 14, 2001

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333

Health Consultation: A Note of Explanation

An ATSDR health consultation is a verbal or written response from ATSDR to a specific request for information about health risks related to a specific site, a chemical release, or the presence of hazardous material. In order to prevent or mitigate exposures, a consultation may lead to specific actions, such as restricting use of or replacing water supplies; intensifying environmental sampling; restricting site access; or removing the contaminated material.

In addition, consultations may recommend additional public health actions, such as conducting health surveillance activities to evaluate exposure or trends in adverse health outcomes; conducting biological indicators of exposure studies to assess exposure; and providing health education for health care providers and community members. This concludes the health consultation process for this site, unless additional information is obtained by ATSDR which, in the Agency's opinion, indicates a need to revise or append the conclusions previously issued.

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Prepared by:

Connecticut Department of Public Health
Under a Cooperative Agreement with the
Agency for Toxic Substances and Disease Registry

Summary

During environmental investigation in 1993, residential, recreational, commercial, and industrial properties in Stratford, Connecticut, were identified as posing health threats to the surrounding community. These sites were contaminated with lead, asbestos, and polychlorinated biphenyls owing to the waste disposal practices of Raymark Industries, a facility on the Environmental Protection Agency's National Priorities List.

This report is a follow-up to the November 1998 study titled *Cancer Incidence and Birthweight in Relation to Exposure to Raymark Waste*. Bladder cancer data from the original report was re-analyzed utilizing improvements in the methodologies. An additional five years of bladder cancer data was also added and analyzed by means of detailed surface models created in Geographic Information Systems software (GIS). The surface models are presented as maps of male and female bladder cancer in six different time periods.

In Stratford, waste was distributed at many locations. In this report, three distance-based exposure models, developed for the original health study, are applied to bladder cancer data from the Connecticut Tumor Registry: (1) buffer zones, (2) distance from the nearest site, and (3) a cumulative exposure model.

After controlling for age and gender and assigning geographic coordinates to case residential address at diagnosis, the association between exposure and bladder cancer was modeled using logistic regression. An innovative approach to estimate the referent population was the use of the Census Referent Population Methodology.

Female bladder cancer odds ratios continued to be slightly elevated, similar to the original health study results. However, the follow-up and original analyses were not conducted as time-series analyses. The elevated odds ratios may be due to treating 1968 - 1991 as a single period of time. A new methodology was developed which allowed the creation of surface models of bladder cancer rate ratios. Six maps of male and female bladder cancer in six different time periods were created. This provided a useful time-series analysis of the distribution of bladder cancer in Stratford, Connecticut.

The conclusions are that while elevated odds ratios for female bladder cancer did exist near the waste sites, the time-series spatial analysis maps show that female bladder cancer is not consistently elevated near the waste sites over time. Additionally, in the most recent time period, female bladder cancer is almost non-existent. For male bladder cancer, the odds ratios were elevated but not significant. The only odds ratio that was significant for males was the distance category furthest away from the waste sites. The time series spatial analysis maps show that male bladder cancer is not consistently elevated near the waste sites over time. However, when compared to the Connecticut male bladder cancer rates, there is an increase over time within the town of Stratford.

Background

In November 1998, the Connecticut Department of Public Health (CT DPH) under a Cooperative Agreement with the Agency for Toxic Substances and Disease Registry (ATSDR), published a study titled *"Cancer Incidence and Birthweight in Relation to Exposure to Raymark Waste, Stratford, Connecticut"*[1]. This health consultation serves as a follow-up to that original cancer study.

On May 26, 1993 the Agency for Toxic Substances and Disease Registry (ATSDR) issued a Public Health Advisory to alert government agencies and the public of an imminent public health hazard in Stratford, Connecticut. This hazard was associated with past, present, and potential future exposures to waste from past operations and disposal practices of Raymark Industries, Inc. The primary contaminants of health concern included asbestos, lead, and polychlorinated biphenyls (PCBs).

Raymark Industries, Inc. operated a facility on 75 East Main Street in Stratford from 1919 until September 1989 when operations ceased. The Raymark Industries site covers approximately 33.4 acres. The facility produced brakes, clutch parts, and other friction based products. During the manufacturing process, wastes generated included ignitable and corrosive waste, solvents, liquid adhesives, phenolic resins, alcohol, caustic, phenolic mixtures, lead, asbestos, PCBs, and dioxins/furans[2]. A map of the waste sites can be found in figure 1.

Raymark routinely disposed of its waste on the facility property and at other locations in Stratford. From 1919 to July 1984, Raymark used a system of lagoons in an attempt to capture the waste lead and asbestos. Over this 65-year period, these lagoon systems were located throughout the western and central portions of the Raymark site. As the lagoons filled up with sludge, they were often dredged and the material was used as fill in locations around Stratford. At several locations, the fill was evident in surface soil by the presence of brake parts and friable asbestos.

Following the release of the Public Health Advisory, the Environmental Protection Agency (EPA), ATSDR, the Connecticut Department of Environmental Protection (DEP), the Connecticut Department of Public Health (DPH) and the local health department initiated a number of activities to identify additional waste areas, reduce or eliminate exposure to known sites and address public health questions. These activities included extensive surface soil and depth sampling, review of environmental data, development of health consultations, voluntary blood lead screening, and preliminary health statistics reviews. A Public Health Assessment has been completed for Raymark and provides details on the history of the site, and pathways of exposure.

Previous Heath Study Summary: Cancer Incidence and Birthweight in Relation to Exposure to Raymark Waste

The original cancer study focused on two analyses. The first analysis compared the town rates to the State of Connecticut rates (comparative morbidity figure) over time. This was done to assess the trend of disease. The second analysis compared the odds of disease and exposure to Raymark waste. Exposure classification was based on several exposure models.

Four tumor types, bladder and testicular cancer, mesothelioma, and any site in individuals under age 25 (early onset cancer [EOC]) were reviewed in the original study. Due to the original finding and the availability of data, this follow-up focuses on male and female bladder cancer.

Epidemiological studies have shown that exposure to asbestos is a risk factor for mesothelioma and exposure to solvents is a risk factor for bladder cancer. Asbestos and solvents are components of Raymark waste. Testicular cancer was also included in this study because of concerns raised by the citizens of Stratford. Citizens expressed concerns regarding cancer among persons less than 25 years of age and testicular cancer because some of the Raymark waste was used as fill at recreational areas at Short Beach Park and Wooster Middle School. It was felt by the citizens that younger persons would have had the potential for more exposure to contaminants at these recreational areas and may have been at greater risk of developing cancer from that exposure.

Comparative morbidity figures were used to compare the incidence of the cancers in Stratford versus the State of Connecticut and to assess trends in cancer incidence for four categories of cancers: bladder cancer, mesothelioma, testicular cancer, cancers at any site in individuals under age 25 (early-onset cancer [EOC]). All cancers had been diagnosed between 1968 and 1991. No trend could be found for testicular cancer, mesothelioma, or EOC. However, bladder cancer among males and males and females combined increased during the study period as compared to state rates.

After controlling for age and gender and assigning geographic coordinates to case residential address at diagnosis, the association between exposure and the cancers was modeled using logistic regression. Exposure models were developed that were based on proximity to the waste. Census records were used to estimate the referent population. Crude incidence rates by block group were calculated to assist in the interpretation of the spatial analysis of cancer incidence.

No evidence of an association between exposure and mesothelioma was found. Evidence of an association between bladder cancer, testicular cancer, EOC and exposures was limited and inconsistent. The overall bladder cancer incidence among males and females combined was not elevated, however, the bladder cancer incidence among women was slightly elevated among those who lived closer to the Raymark waste sites.

Available Data and Information

Cancer data for the original health study and the follow-up analyses were obtained from the Connecticut Tumor Registry (CTR). Tumors were extracted from the CTR if they were diagnosed between January 1, 1968 and December 31, 1991 (original study) or, between January 1, 1968 – December 31, 1996 (follow-up study). At the time the data were collected for the follow-up study, 1996 was the last complete year of tumor data available. Population data were obtained from the 1990 US Census. Spatial data were obtained from the Connecticut Department of Environmental Protection and the Environmental Protection Agency, Region I.

Methodological Improvements

The original cancer study raised questions with regard to female bladder cancer. There were elevated odds ratios for female bladder cancer with the block group (OR = 1.96 [1.21, 3.17]) and distance to the nearest site exposure model (OR = 1.61 [1.12, 2.32]). Upon further research, it was determined that a better way to spatially examine cancer data was needed to conduct any additional analyses on female bladder cancer. This led to the development of the Census Referent Population Methodology (CRPM). This methodology modeled the location of the general population using the addresses from a digital phone book, the 1990 U.S. Census population data, and a series of sophisticated computer programs. The CRPM allowed researchers to reanalyze the original study data, taking advantage of all the proximity exposure models developed for the original study. A full description of the CRPM can be found in Appendix B.

The CRPM provided us with a referent population data set that is based on the distribution of people within a block group as opposed to the entire population residing at the block group centroid (geographic center of the block group). This enhancement eliminated the differential misclassification that existed in the original cancer analysis. The CRPM was used in the re-analysis of the original health study data (1968 - 1991). While the results from the re-analysis are not profoundly different than the original study results, they are believed to be more accurate.

The CRPM also allowed a more detailed spatial analysis to be accomplished. This analysis builds surface models of disease within Stratford. The maps that are created from the spatial model building process provide an overview of bladder cancer in Stratford over time.

Statement of Issues

During the public presentation of the original cancer report, citizens were concerned about an elevated odds ratio for female bladder cancer. This concern was the basis for the CT DPH to conduct additional analyses to further enhance our understanding of female bladder cancer in Stratford.

There were several methodological limitations that limited the original cancer analyses. Since it's release, the CT DPH has developed new techniques to estimate the distribution of the population that allow for improved statistical precision in comparison to the original study. More advanced disease mapping methodologies have also been developed. These methods allow for the visualization of disease patterns within small areas.

Methods

Follow-up Bladder Cancer Analyses

This health consultation presents the results of two analyses. The first analysis presents the original health study data (1968 – 1991) re-analyzed using the methodological enhancements presented in Appendix B. The second analysis presents the follow-up analyses using the original data plus five additional years (1968 – 1996).

A. Analysis: The application of the CRPM to the existing data set (1968 – 1991) for female bladder cancer.

Cases of bladder cancer in Stratford, identified by the CTR, were included in the study if they were diagnosed between 1968 and 1991 and if the patients reported a residence in Stratford at the time of diagnosis.

Age and gender were tested for inclusion as control variables in logistic regression models used to predict the odds of developing bladder cancer. The results indicated that including age and gender did help predict the odds of developing bladder cancer. Because variables other than age and gender had not been systematically recorded in the 1968-1991 CTR or on the medical records, only age and gender were sufficiently complete and accurate to be included.

Since the CTR only collects information on people who develop a tumor, the 1990 Census was used for the referent population. The census records the number of people of each gender within 31 age ranges. To model age as a continuous variable, individuals in each age category were assigned the midpoint of the range. For example, if there were 21 females and 11 males in age category 22 - 24 years within a given block group, each of these individuals would be assigned an age of 23 years.

To test for a linear trend with age, four age categories were constructed: < 45, 45-64, 65-74, and >74 years. If age was included in a model, a comparison was made between age as a categorical variable and age as a continuous variable. The test statistic was calculated by subtracting the scaled deviance associated with the restricted model (without age and/or gender) from the scaled deviance associated with the full model (with age and/or gender included). Age was categorized in four age groupings owing to evidence of a significant departure from linear trend. Race was considered for the analysis of bladder cancer but was not included in the final models because most of the subjects were white

(98%). Gender was also available for all cases and was used as a control variable for the bladder cancer analysis. Gender significantly improved the fit for models predicting bladder cancer. Analyses stratified by gender were also conducted.

Exposure Models: Based on Distance from Waste Sites

Three different exposure models were utilized in the analyses (buffer zones, distance from the nearest site, and the cumulative exposure model. Each exposure model was based on the distance each case/non-case was from one of the numerous Raymark waste sites in Stratford. A detailed description of the exposure models can be found in the original health study. A summary of the exposure models follows.

Buffer Zones

Distance was also modeled as a categorical variable (buffer zones). An exposure radius was selected arbitrarily (1/4 mile buffers). Residences within a quarter mile of the nearest waste site were considered "exposed". This analysis was then repeated for residences from 1/4 to 1/2 mile, 1/2 to 3/4 mile, and 3/4 to 1 mile. Residences more than 1 mile from the nearest waste site were considered "unexposed" and comprised the comparison population for the four buffer zones. These exposure classification schemes are shown in Figure 3. If distance of residence does correlate with exposure and exposure is associated with the disease under investigation, one might expect decreasing odds of disease in concentric rings further from the waste sites.

Distance from the Nearest Site

The distance from each individual to the perimeter of the waste sites was calculated. Distance from the nearest waste site was modeled as a continuous variable. The continuous variable was used to model the odds associated with living each mile closer to the nearest site, assuming that the relationship between distance and the odds of cancer is linear (Figure 3).

Cumulative Exposure Model

This model attempts to estimate the potential exposure by adding the probability of being exposed to each of the 39 Raymark waste sites. The model incorporated the distance to each waste site, the area of each waste site, and the type of waste site. Assuming that distance from waste sites is correlated with exposure, this model describes the relationship between distance and the probability of exposure to waste contaminants. This model incorporates the measured distance from each case residence to all the waste sites and includes terms for relating probability of visiting a waste site to exposure. To relate the combined distance of each residence to the cumulative probability of spending a unit of time at any of the 39 waste sites, the area of each waste site is considered (Figure 3).

B. Analysis: Calculation of the Comparative Morbidity Figure in five year increments 1968 – 1996)

A limitation of the previous health study work in Stratford has been the time period studied. The original health study examined data from 1968 – 1991 as one point in time. The number of cases increased with each year, while the number of non-cases remained the same. This can give the appearance of a relationship between space and time that does not really exist.

For example, if five cases of bladder cancer were to occur on a street, they may appear related because they occurred to people living on the same street. However, without knowing when the cases occurred, there is an assumption made that the cases are related in time and in space. If these cases occurred to a different individual, one every five years, the relationship between them becomes less obvious. In this example, the cases would be related in space, but not in time.

In the analyses described in the previous section, increasing odds ratios for female bladder cancer as you get closer to the Raymark Waste appears to be a positive finding. This finding led the CT DPH to examine what could be the driving force behind the results. One issue was the effect of treating 24 years as one point in time. The data were re-analyzed with time being considered. The analyses were conducted spatially. Maps were produced that presented the bladder cancer incidence in five year groupings. As stated earlier, this required the use of CRPM to model the location of the census referent population.

Age adjusted incidence rates for male and female bladder cancer for Stratford in comparison to the State of Connecticut were computed. The age adjusted incidence rates were computed for six time periods beginning in 1968 through 1996 for 1146 locations or points (X & Y coordinate pairs) within Stratford, spaced 1/8 mile apart. The time periods consisted of five-year time periods and one four-year time period. The four-year time period was used because 1996 was the last full year of data available from CTR when the study began.

The direct method of standardization was utilized. Summary age and gender adjusted incidence rates for each of the seven time periods were compared to each other. The rates were standardized to a standard population to control for the effects of population changes and age distributions over time[3]. The U.S. 1990 Standard Million was used as the reference population for the direct standardization analysis. Breslow and Day recommend utilizing a published set of weights for direct standardization as it promotes comparability between series[4]. This enabled the analysis of trends in cancer incidence over time.

The tumor data were stratified into four age groups, <45, 45-64, 65-74, >74. Incidence rates computed using a direct method as described above are inappropriate to use when the cell numbers are small[5]. By using only four age groupings, this problem was addressed in advance. The direct standardized incidence rates for the State of Connecticut and for the town of Stratford were compared by means of a comparative morbidity figure (CMF).

The comparative morbidity figure (CMF) is used as a comparative measure of incidence. In this study it provides a measure of the ratio of Stratford rates to Connecticut rates after they have been adjusted to control for the effects of age. The CMF was derived by dividing the age standardized incidence rate for Stratford by the age standardized incidence rate for Connecticut. Age was aggregated into four stratums. The formula for the CMF is

$$CMF = \frac{\sum_{j=1}^{4} w_j s_j / p_j}{\sum_{j=1}^{4} w_j c_j / t_j},$$

where w_j is the stratum specific population distribution weight from the 1990 U.S. Standard Million; s_j is the number of tumors in Stratford within the stratum; p_j is the Stratford population total for the stratum; c_j is the number of tumors in Connecticut within the stratum; t_j is the Connecticut population total for the stratum.

Confidence intervals were also constructed around the CMF from the standard error. Breslow and Day suggest transforming to the log scale to correct for skewness in the distribution of the CMF. The formula for the confidence interval is

$$_{e}(\ln(CMF) \pm 1.96(SE(\ln(CMF)))),$$

where;

$$SE(\ln(CMF)) = \frac{SE(CMF)}{CMF}.$$

The Census Referent Population Methodology (CRPM) was used to represent the population of Stratford. The 1990 US Census was used with the CRPM. Because address data from a digital phone for each of the time periods was not available, the 1990 Census data was also used as the denominator for each of the six time periods.

While the population numbers for Stratford has been stable over time, the population as a whole has aged. Using the 1990 Census as the referent population will have an effect on the CMF's. The actual population in Stratford in the late 1960's was younger then in 1990. The older 1990 population would over estimate the expected number of tumors and therefore, lower the standardized incidence rate. This situation is unavoidable. Blockgroup level Census data is simply not available for the 1960 census.

The CMF's give an indication of what is happening in Stratford as compared to Connecticut over time. This type of analysis does not evaluate exposure to the waste.

When examining CMF's it is important to remember that the number does not relate to actual incidence of disease. The CMF is the ratio between the age adjusted direct standardized incidence rates for Stratford and Connecticut.

A lattice or grid of 1146 points spaced 1/8 of a mile apart was generated in Stratford. For each lattice point, a CMF was calculated. The CMF was based on all tumor and CRPM data within 1/8 of a mile from each lattice point. Rushton and Lolonis developed this method of exploratory spatial analysis for use with birth data[6]. However, the CRPM provides us the ability to use tumor data for similar analyses.

Once the CMF was created for all 1146 lattice points, a surface model of the CMF across the study area was developed utilizing Geographic Information System (GIS) software.

Results

A. Results: The application of the CRPM to the existing data set (1968 – 1991) for female bladder cancer.

A total of 307 cases of bladder cancer were recorded by the tumor registry and geocoded. Logistic regression models that estimate odds of cancer due to exposure are presented in Table 1. Bladder cancer was controlled by age and stratified by gender. The relationship between age and the odds for bladder cancer was not linear. Using the four categorical age groups significantly improved the fit compared with the models using age as a continuous variable. The results will be presented by gender and exposure model.

Female

Buffer Zone in miles

The odds ratio for female bladder cancer did increase as you moved closer to the waste sites. Even though the categories that were furthest away, ½ to ¾ and ¾ to 1-mile, were not statistically significant, OR=1.00 (95% C.I. 0.43-2.34) and OR=1.27 (95% C.I. 0.63-2.56) respectively. The categories closest to the sites, ¼ to ½ and < ¼ mile, were statistically significant, OR=2.05 (95% C.I. 1.09-3.84) and OR=2.49 (95% C.I. 1.26-4.91) respectively. What is important here is the increasing trend; as you mover closer to the waste sites, the odds ratios increase.

Distance from the nearest waste site

This model calculates the difference from each mile of distance from the nearest waste site to the cancer case residence. The results are presented as the odds ratio (the odds of disease for each mile closer to a waste site). For every mile closer to a waste site, the odds ratio for female bladder cancer is OR=1.66 (95% C.I. 1.14-2.41). This is statistically significant.

Cumulative Exposure

This model calculates the difference from each mile of distance from all the waste sites while taking into account the type of waste site and the likelihood someone would visit that site. Again, this result was significant, OR=2.61 (95% C.I. 1.22-5.58).

Male

Buffer zone in miles

The odds ratio for male bladder cancer did not increase as you moved closer to the site as it did with females. It was much more sporadic with only one zone being statistically significant (3/4 – 1 Mile, OR=1.66 [95% C.I. 1.10-2.50]).

Distance from the nearest waste site

For every mile closer to a waste site, the odds ratio for male bladder cancer is OR=1.14 (95% C.I. 0.96-1.36). This is slightly elevated but not statistically significant.

Cumulative Exposure

The odds ratio for each mile of distance from all the waste sites, while taking into account the type of waste site and the likelihood someone would visit that site for male bladder cancer is OR=1.14(95% C.I. 0.73-1.78). Again, this is slightly elevated, but not statistically significant.

B. Results: Calculation of the Comparative Morbidity Figure in five-year increments 1968 – 1996)

The results for female and male bladder cancer can be viewed in Appendix A, figures 4 and 5. The figures represents the age adjusted CMF for the six time periods by gender. None of the CMFs were statistically significant. Because of the very fine spatial resolution (1/8 mile lattice of points), and adjusting for age, many of the CMF were calculated using small numbers.

The maps in figure 4 demonstrate that female bladder cancer is not occurring in one location within the town of Stratford. With each time period one can see the pattern of female bladder cancer change. During time period 1978 – 1987, there is a greater area of elevated CMFs as compared to the first time period (1968 - 1972). However, during time period 1993 – 1996 there are very few areas with elevated CMFs. Most of the Stratford rates are at or lower than the State of Connecticut rate for that time period.

Consistent with the results of the previously published health study, the maps in figure 4 do not show an overall increase in female bladder cancer over time.

The maps in figure 5 demonstrate that male bladder cancer is also not occurring in one location. With each time period one can see the pattern of male bladder cancer change. The area of elevated CMFs increases during the time period 1988 – 1992. Throughout the entire six time periods, the CMF for male bladder cancer is generally increasing. Consistent with the results of the previously published health study, the maps in figure 5 do show an overall increase in male bladder cancer over time.

Discussion

A. Discussion: The application of the CRPM to the existing data set (1968 – 1991) for female bladder cancer.

The limitations in the original health study also apply to this analysis and are presented in Appendix C. It is important to note that the enhancements to the methodologies did not add or subtract the number of people with bladder cancer in each exposure model category. It did, however, change the number of people estimated to be in the same exposure model category that did not get bladder cancer. This in turn changed the odds ratios. For comparison purposes, the odds ratio's using the methodologies in the original health study are presented in Table 1

In Table 1, the distance from the nearest waste site model was significantly elevated for females but not for males. The 0 to 1/4-mile, 1/4- to 1/2-mile, 1/2- to 3/4-mile, and 3/4- to 1-mile buffer zones were modeled to compare each one with the area of Stratford that was more than 1 mile from the nearest waste. These four buffer zones allow for comparisons between the odds for cancer within a given buffer zone and the odds for cancer outside that zone. For females, the odds for bladder cancer were elevated in three of the four buffer zones within 1 mile of the waste site. The odds for female bladder cancer were not elevated in the ¾ to 1-mile buffer zone. The odds for female bladder cancer were significantly elevated within < ¼ and ¼ to ½ -mile buffer zones.

For males, the odds for bladder cancer were elevated within all four buffer zones. However, the odds were only statistically significant within the ¾ to 1-mile buffer zone. For the cumulative exposure model, the odds were elevated for both females and males with only females being statistically significant.

One of the forces driving the elevated female bladder cancer odds ratios near the waste sites were a few cases of female bladder cancer in the Housatonic Boat Club/Elm Street area combined with the lack of cases further away from the waste. The cases that were close to the waste sites were in an area whose population density is lower than that on the opposite side of town (near Bridgeport). This would have the effect of increasing the odds ratios.

The spatial analyses in the original health study, and in this follow-up, used one time period of 24 years (1968 – 1991). Time was not considered in the original spatial analyses. However, the original study also published the results of a trend analysis. The trend analyses compared the rate of cancer in Stratford to the State of Connecticut over seven different periods of time. This analysis demonstrated that there was not a significant increase of female bladder cancer over time. The opposite was true for male bladder cancer. The original study did find a statistically significant trend of male bladder cancer over time. However, as mentioned, the analyses utilizing exposure models present time as a single unit.

This is a potentially critical issue. The Connecticut Tumor Registry routinely publishes reports that present cancer Standardized Incidence Ratios (SIRs) in five-year increments. This provides the reader with an opportunity to examine how the SIRs change with time. By including all of the data over an extended time period, the ability to see what happens over time is lost.

Although GIS allows us to approach the analysis of disease rates with unprecedented spatial flexibility, results must be interpreted cautiously. Incomplete control of confounding using existing databases and exposure misclassification using proximity measurements limits the role of these studies to detecting patterns of disease and generating hypotheses to explain them. Detecting disease patterns and generating hypotheses are very important roles, but they should never be confused with the detection of causality.

Presenting odds ratios does give the reader the sense that the relationship between the Raymark wastes and disease rates may be causal. The true relationship will never be known. Based on citizen requests to follow-up the analyses for female bladder cancer and the potential misclassification with the exposure models, the CT DPH continued to examine bladder cancer rates in Stratford.

Also, the apparent conflict between the trend analysis and the exposure model results, lead the CT DPH to approach the issue of bladder cancer in Stratford, Connecticut in a different manner. An additional analysis was conducted that examined five additional years of data and the critical component, time.

B. Discussion: Calculation of the Comparative Morbidity Figure in five-year increments 1968 – 1996)

A limitation with the original health study was the lack of individual exposure information. Because of the lack of exposure data, surrogates were utilized. How close a citizen was to a waste site determined the exposure status. Without accurate exposure data, the study results needed to be interpreted with caution. One could not make statements that any result was due or caused by Raymark waste. That limitation still exists. This follow-up did not attempt to address the issues of ecological exposure assessment. It did however, address the issues of changes in bladder cancer incidence over time.

The six images (Figure 4) of female bladder cancer (CMF) demonstrate that female bladder cancer is not occurring in one area of town versus another. The purpose of the original health study and this follow-up was to address citizens concerns about increased cancer incidence around Raymark waste sites.

There are no locations in town that demonstrate consistent elevations in bladder cancer incidence among females. The maps show where the previously identified elevations in female bladder cancer come from. Previous work reported an elevation of female bladder cancer odds ratios as you moved closer to the Raymark waste sites. This was especially true for the Elm Street/Housatonic Boat Club area. In figure 4, time period 1978 - 1982 and 1983 - 1987, you can see pockets of elevated rates near the Elm Street/Housatonic Boat Club area. However, for time period 1988 - 1992 and 1993 - 1996, these elevated pockets are gone. While it is impossible to say why it occurred, the fact that it is no longer present indicates that it is not an ongoing problem in Stratford.

The previous study also found that female bladder cancer did not have a significant trend over time. In viewing figure 4, you can see that while the CMFs increase for time period 1978 - 1982 and 1983 - 1987, they decrease in 1988 - 1992 and 1993 - 1996. These maps support the previous trend analyses.

The six images (Figure 5) of male bladder cancer (CMF) also demonstrate that male bladder cancer is not occurring in one area of town versus another. Male bladder cancer appears and disappears throughout the town. It is also useful in understanding the previous results. The previous work did report a significant increasing trend for male bladder cancer in Stratford. The six maps in figure 5 demonstrate that clearly. What is also clear is that the locations where elevations in male bladder cancer occur appear to be random. There does not appear to be elevations only in areas where Raymark waste was located. In fact, for time period 1993 - 1996, most of the elevations are occurring in areas where there was no Raymark waste.

The previous work showed that for males, the odds ratios for bladder cancer did not increase as you moved closer to the waste sites. These images clearly show that in any given time period the male bladder CMF may or may not be elevated. There appears to be no visual relationship to the waste.

While maps in figure 5 do show an increasing trend for male bladder cancer, care should be taken when interpreting these results. The data used for the analyses did not have important information on smoking, family history, and occupational exposures to bladder carcinogens. It is quite possible that the increase in male bladder cancer can be explained by addressing these potential confounders, or it may be due to chance or random variation.

The 95% confidence interval had been calculated for each CMF. However, because none of the CMFs were statistically significant, only the CMFs were included in the surface model calculated with the GIS. The focus of this analysis was to visualize how bladder cancer developed within the town of Stratford over time, the issue of statistical significance is not very important. The study was not intended to be utilized as "cluster investigation". It only meant to display how the pattern of bladder cancer developed over time in Stratford, Connecticut.

These types of small area analysis introduce a great deal of flexibility with regards to spatial analysis. However, it comes at a cost. The small areas studied often have very small numbers with regard to cases of bladder cancer or number of non-cases . These small numbers can create unstable results. The CMFs may seem to be of concern, but when examined in more detail, it is discovered that one case in an area with low population density can drive the CMF very high. Regardless, these surface models are still useful. They give a good indication of where within a small area, like a town, that cancer is occurring. One word of caution, the maps should not be used to make links from elevated CMFs to any environmental contamination. They are not designed for that purpose.

The issue of using the 1990 Census for each time period could introduce error. The CMF is created with age adjusted State rates in the denominator. For the State rates, the appropriate population year was used for each time period. This was not available for Stratford. While the population in Stratford has aged, it has a stable total number. The affect on the results would depend whether the 1990 Census over or under estimated the earlier population totals. An over estimated population would lower rates, while an under estimated population could increase rates.

While it is impossible to make definitive statements regarding causal relationships between Raymark waste and male or female bladder cancer, it is possible to address spatial associations. One can look at each map and see the pattern of disease. If the disease is not showing up where you suspect an environmental exposure is or has occurred, then they may not be related. The reverse also holds true. If the disease is only occurring where the suspected environmental exposure is or has occurred, they may be related. Regardless, without accurate individual exposure data, these statements on disease associations with exposure are qualitative and not based on quantitative analyses.

Conclusions

Previous Work

Bladder cancer for males showed a significantly increasing trend over the study period. Bladder cancer was also slightly elevated among those who lived closer to Raymark waste. The elevation was greater and statistically significant for women.

Current Work

This report examined the incidence of bladder cancer for males and females in Stratford during the time periods 1968 – 1991 and 1968 - 1996. There were elevated odds ratios for females who lived closer to Raymark waste, however, this elevation is not consistent over the entire study period and may be due in part to not adjusting for time in the analysis.

The maps of female bladder cancer CMF demonstrate that there appears to be no evidence of an increase in the trend over time of female bladder cancer in Stratford. The maps of male bladder cancer CMF demonstrate that there appears to be evidence of an increase in the trend over time of male bladder cancer in Stratford. While there is an increased trend for male bladder cancer, care should be taken when interpreting these results. The data used for the analyses did not have important information on smoking, family history, and occupational exposures to bladder carcinogens. It is quite possible that the increase in the male bladder cancer trend can be explained by addressing these potential confounders, or it may be due to chance or random variation. The CT DPH has no definitive evidence linking female or male bladder cancer and Raymark waste.

Recommendations

When the data become available, male and female bladder cancer for the time period 1997 – 2002 should be reviewed. Additionally, the towns around Stratford should be analyzed to determine if the elevated male bladder cancer comparative morbidity figures exists in areas other than Stratford.

The Connecticut Department of Public Health should work with the Stratford Health Department and local community organizations to facilitate education regarding cancer and Raymark waste.

Public Health Action Plan

The Public Health Action Plan for the Raymark sites contains a description of the actions to be taken by the Agency for Toxic Substances and Disease Registry, and the Connecticut Department of Public Health in the vicinity of the site. Included in this plan is a commitment on the part of the Agency for Toxic Substances and Disease Registry and the Connecticut Department of Public Health to follow up on this plan to ensure that there is implementation. The public health actions to be implemented by the Agency for Toxic Substances and Disease Registry, the Connecticut Department of Public Health are as follows:

- The Connecticut Department of Public Health will review and summarize additional tumor data collected by the Connecticut Tumor Registry.

- The Connecticut Department of Public Health will provide environmental health education for local public health officials, the local medical community, and local citizens.

CERTIFICATION

The Health Consultation for Raymark Industries–Review of Bladder Cancer Data was prepared by the Connecticut Department of Public Health under a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR). It is in accordance with approved methodology and procedures existing at the time the health consultation was initiated.

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The Division of Health Assessment and Consultation (DHAC), ATSDR, has reviewed this Health Consultation and concurs with its findings.

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Table 1. Odds Ratios (OR) for Bladder Cancer Stratified by Gender and controlling for Age , 1968 – 1991, Stratford, Connecticut

		New Methodology (CRPM*)		Previous Methodology (BG Centroid)	
Gender	Exposure Model	Number of Cases and Non-Cases	OR (95% CI)	Number of Cases and Non-Cases	OR (95% CI)
Female					
	Buffer Zone (in Miles)				
	(<1/4)/(>1)	17/3393	2.49 (1.26-4.91)	17/2966	2.47 (1.26-4.87)
	(<1/4-1/2)/(>1)	24/5898	2.05 (1.09-3.84)	24/7191	1.55 (0.83-2.90)
	1/2-3/4)/(>1)	15/5762	1.27 (0.63-2.56)	15/5338	1.25 (0.62-2.51)
	(3/4-1)/(>1)	8/3734	1.00 (0.43-2.34)	8/3983	0.87 (0.37-2.02)
	>1	17/7353	-	17/6662	-
	Total:	81/26140		81/26140	
	Distance from nearest waste site	-	1.66 (1.14-2.41)	-	1.53 (1.08-2.17)
	Cumulative Exposure	-	2.61 (1.22-5.58)		-
Male					
	Buffer Zone (in Miles)				
	(<1/4)/(>1)	30/3148	1.27 (0.80-1.99)	30/2843	1.23 (0.78-1.93)
	(<1/4-1/2)/(>1)	53/5315	1.35 (0.92-1.98)	53/6281	1.03 (0.70-1.50)
	(1/2-3/4)/(>1)	44/5212	1.15 (0.77-1.72)	44/4954	1.12 (0.75-1.67)
	(3/4-1)/(>1)	43/3285	1.66 (1.10-2.50)	43/3535	1.30 (0.87-1.94)
	>1	56/6289	-	56/5636	-
	Total:	226/23249		226/23249	
	Distance from nearest waste site		1.14 (0.96-1.36)		1.10 (0.93-1.30)
	Cumulative Exposure	-	1.14 (0.73-1.78)		-

All models control for age in four age groupings.
*-Census Referent Population Methodology

Appendix A: Maps

Figure 1 Stratford Connecticut

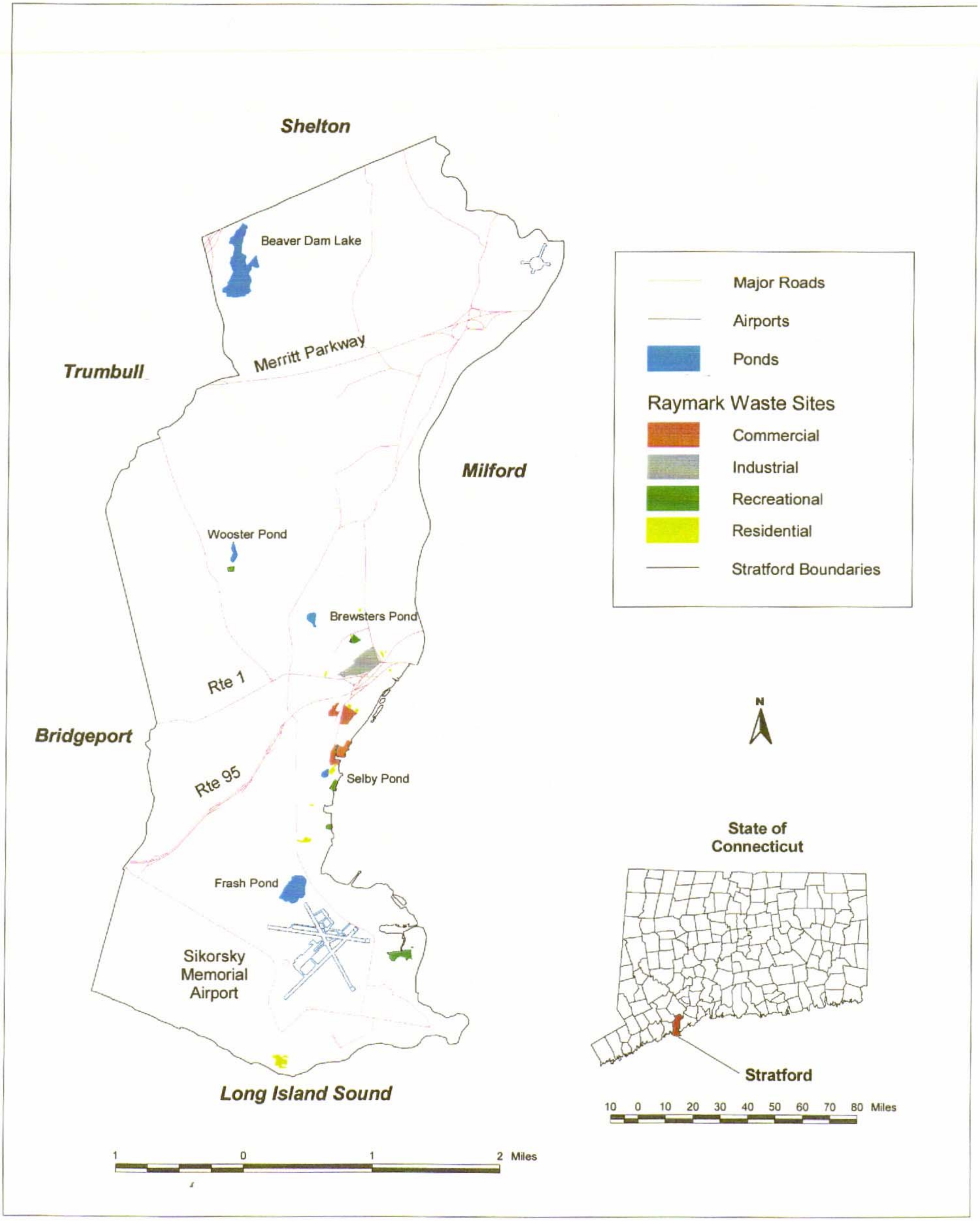


Figure 2: 1990 U.S. Census Blockgroup Boundaries, Stratford, Connecticut

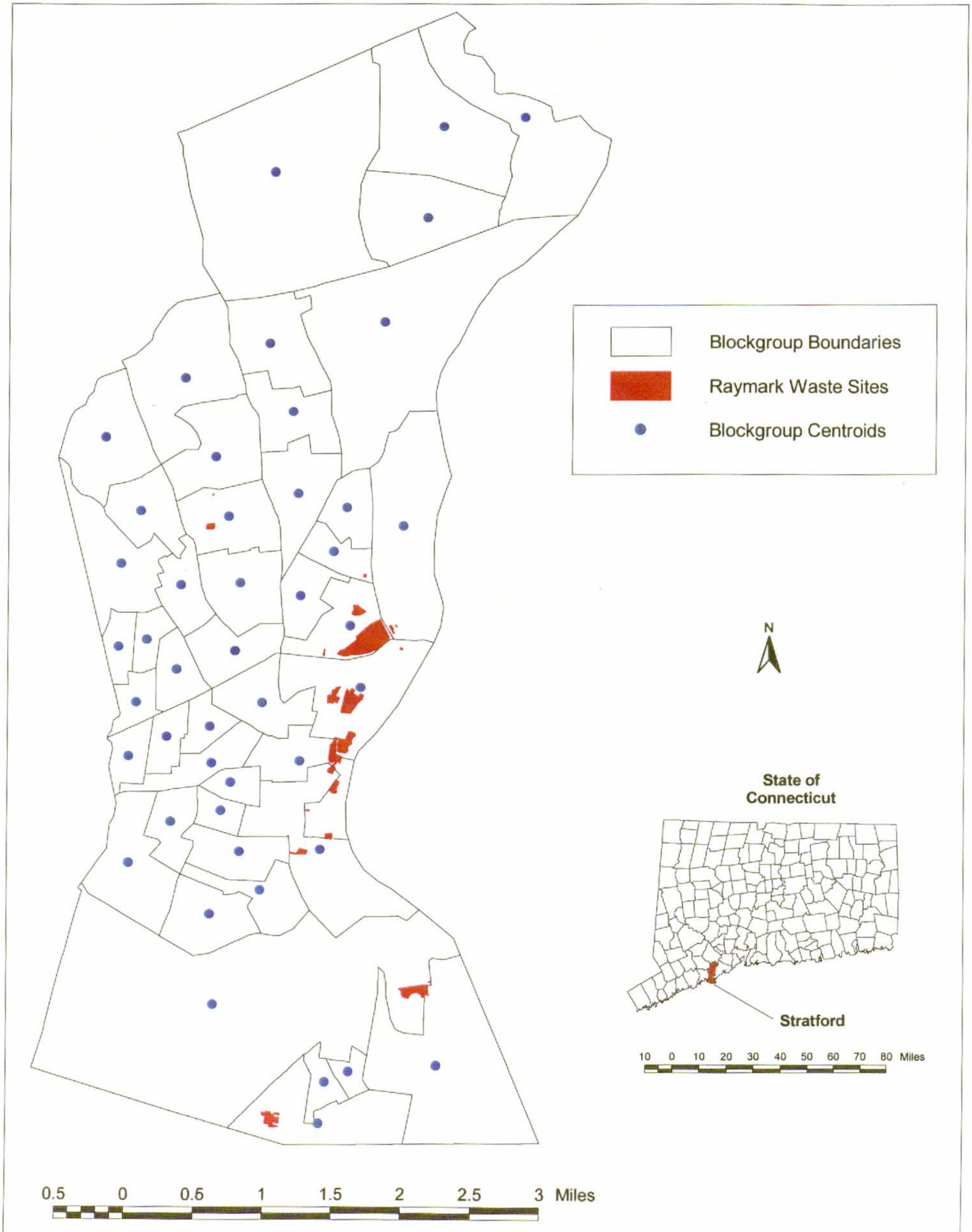


Figure 3: Three Exposure Models Utilized in the Stratford Bladder Cancer Follow-up Study, Stratford, Connecticut, 2000

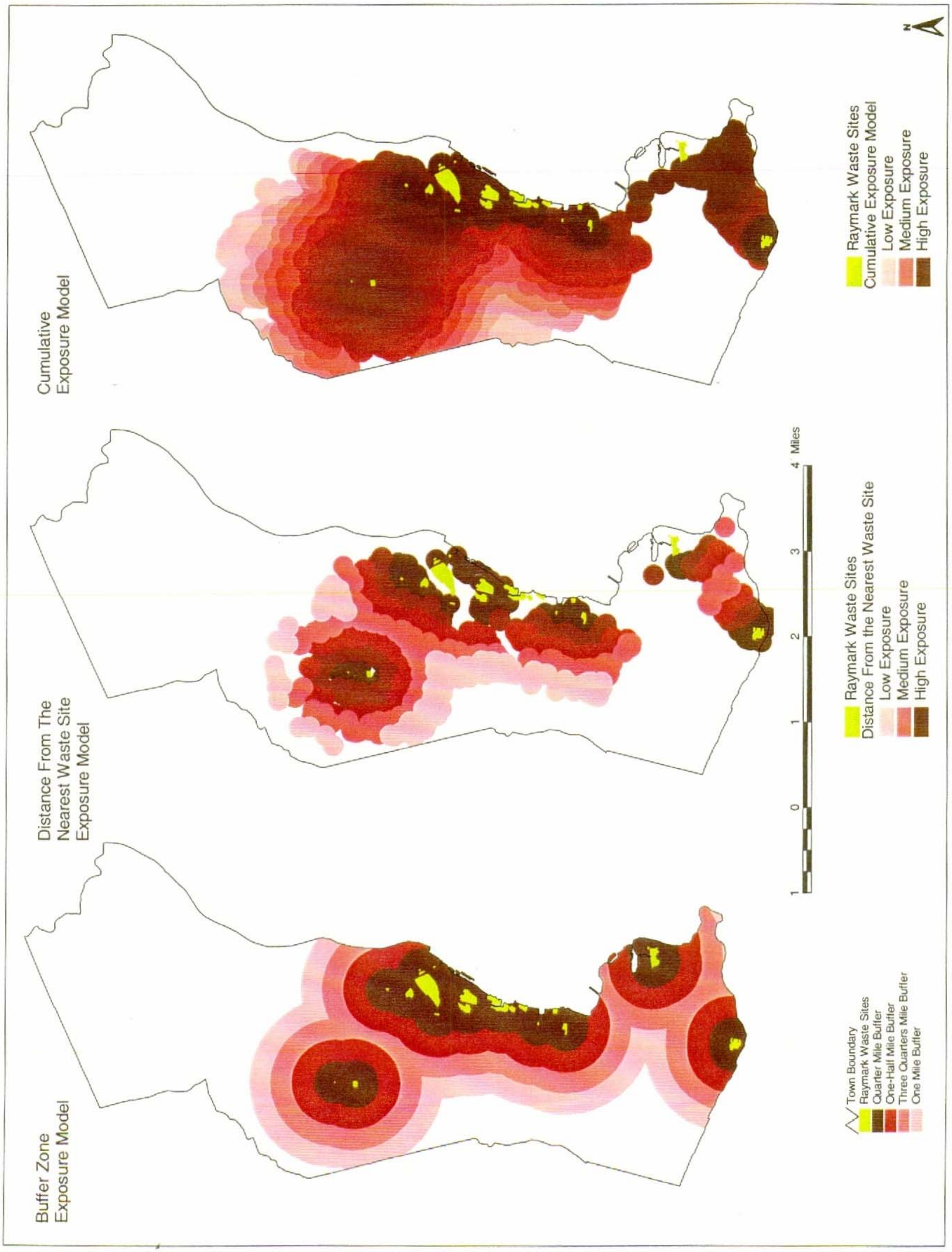
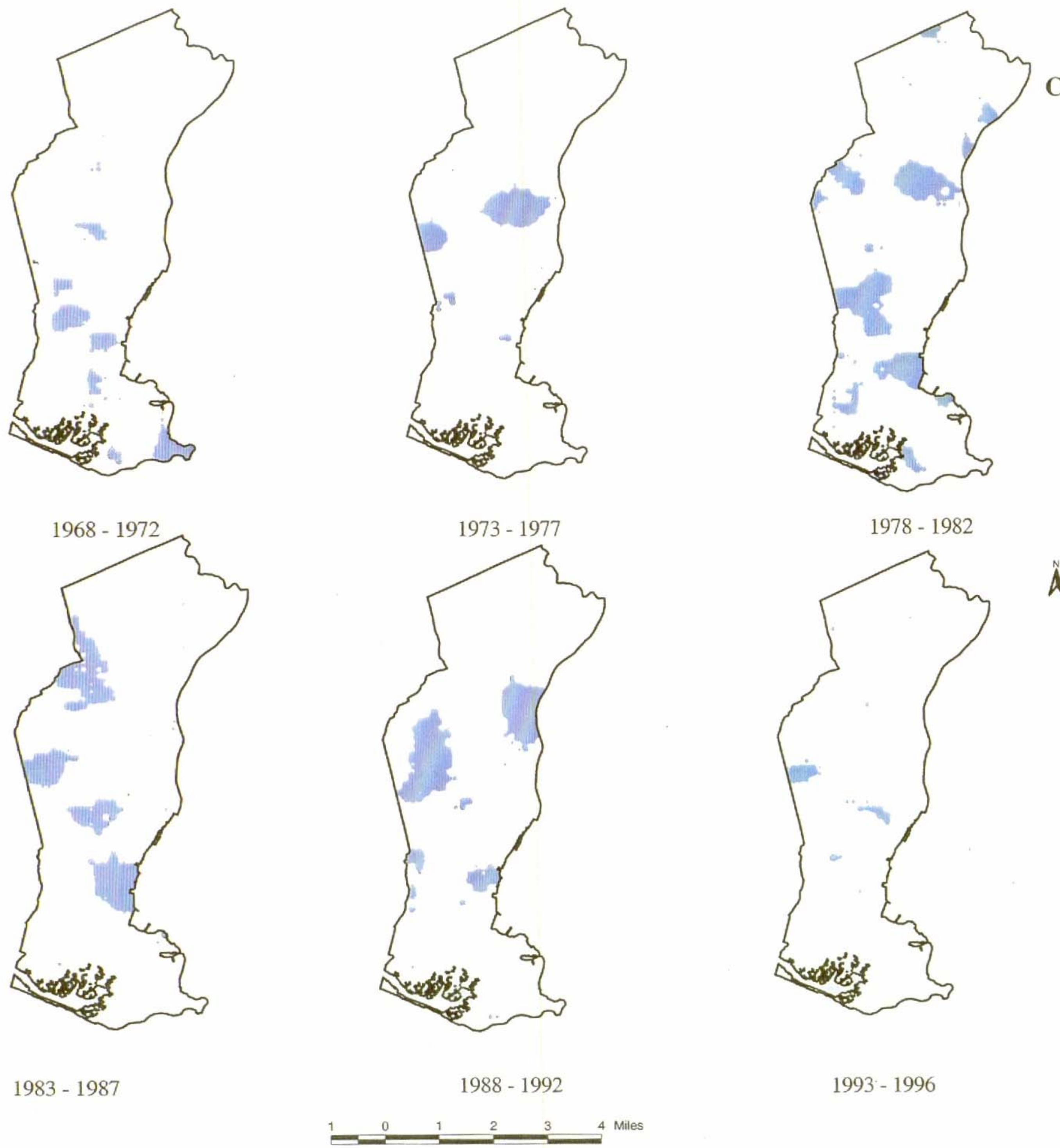


Figure 4 Female Bladder Cancer Comparative Morbidity Figure (CMF) 1968 - 1996 Stratford, Connecticut



Town Boundaries
CMF Female Bladder Cancer
Lower Then or Equal to State Rate
Greater Then State Rate

Tumor data obtained from the Connecicut Tumor Registry, Connecticut Department of Public Health. Population data obtained from the 1990 U.S. Census, STF3A.

A lattice of 1146 points spaced 1/8 of a mile apart was generated in Stratford. For each of these points, age adjusted incidence rates for female bladder cancer in comparison to the State of Connecticut was computed (comparative morbidity figure [CMF]).

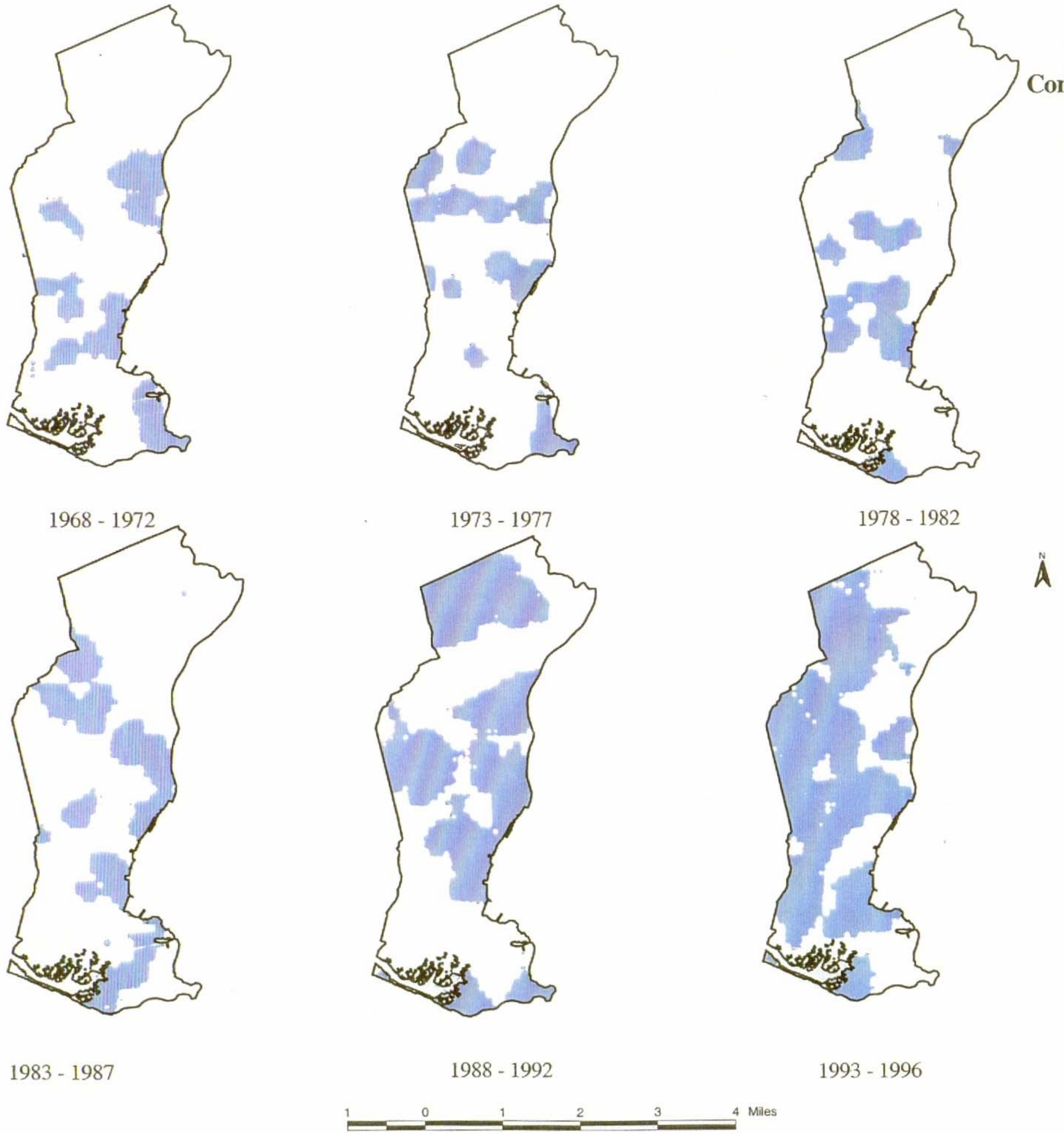
The comparative morbidity figure is used as a comparative measure of incidence. In this study it provides a measure of the ratio of Stratford rates to the State of Connecticut rates after they have been adjusted for the effects of age.

For this study, age was aggregated into four stratums (<45, 45-64, 65-74, >74).

None of the tests were statistically significant.

State of Connecticut

Figure 5 Male Bladder Cancer Comparative Morbidity Figure (CMF) 1968 - 1996 Stratford, Connecticut



Town Boundaries
CMF Male Bladder Cancer
Lower Then or Equal to State Rate
Greater Then State Rate

Tumor data obtained from the Connecicut Tumor Registry, Connecticut Department of Public Health. Population data obtained from the 1990 U.S. Census, STF3A.

A lattice of 1146 points spaced 1/8 of a mile apart was generated in Stratford. For each of these points, age adjusted incidence rates for male bladder cancer in comparison to the State of Connecticut was computed (comparative morbidity figure [CMF]).

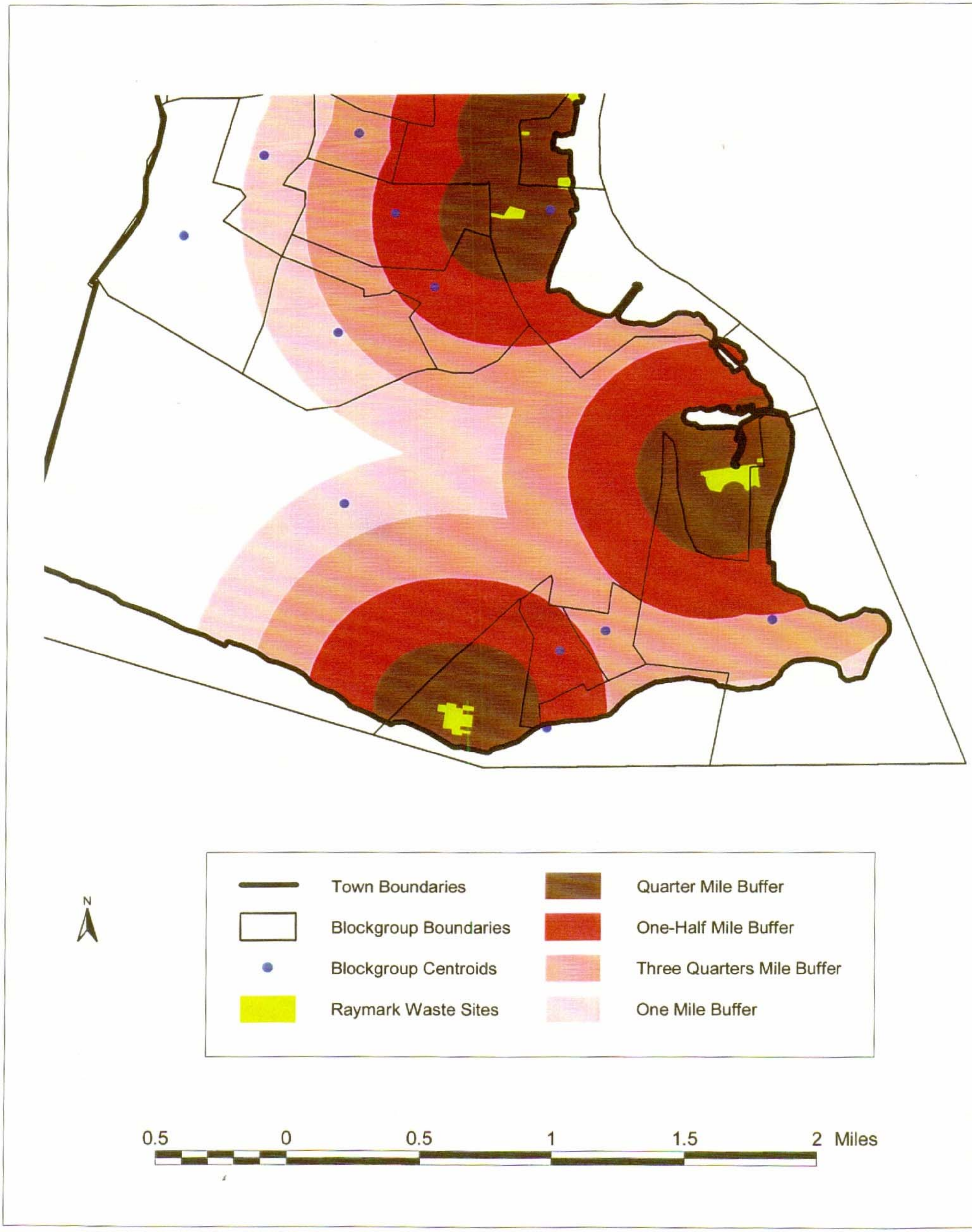
The comparative morbidity figure is used as a comparative measure of incidence. In this study it provides a measure of the ratio of Stratford rates to the State of Connecticut rates after they have been adjusted for the effects of age.

For this study, age was aggregated into four stratums (<45, 45-64, 65-74, >74).

None of the tests were statistically significant.

State of Connecticut

Figure 6 Stratford Connecticut Town and Census Blockgroup Boundaries



Appendix B: Census Referent Population Methodology (CRPM)

CRPM: Expanding the Census

The census data were expanded (disaggregated) to create a record for each person counted in the census' summary data. Census data for 1990 were obtained from the U.S. Bureau of the Census (U.S. Department of Commerce, Washington, DC) in the form of Summary Tape File (STF) 3A data files on CD-ROM. The initial work was with census variable P14: race by sex by age. P14 has five categories for race, two for gender, and 31 for age. A program was written in Visual FoxPro (Version 5.0; Microsoft Corporation, Redmond, WA) to build a new table that contained a record for every combination possible in variable P14. For example, in a block group summary record for P14 B (white women), age is represented in 31 categories. Table 1 (A) demonstrates what that might look like in aggregate form. As the census is disaggregrated (expanded), the new table (Table 1B) would end up with five records, with race classified as white, gender classified as female, age classified as age category 1, and disease status classified as non-diseased.

In Stratford, according to the 1990 U.S. Census, there are 46 block groups with 49,389 people. The initial methodology created a data set with 49,389 records. The next step was to merge the expanded census data with a geocoded digital phone directory.

Table 1. A representative sample of the P14B variable (number of white females in each of 31 age categories) in the STF3A 1990 U.S. Census in Aggregate and Expanded Form.

A. Census Aggregate					B. Expanded Version		
Block Group Id	Age Category 1	Age Category 2	...	Age Category 31	Gender	Race	Age Category
0101011	5	3		23	Female	White	1
					Female	White	1
					Female	White	1
					Female	White	1
					Female	White	1

Locational assignment of Census controls

The authors prior investigations of cancer cases extracted from the CTR were limited by the assumption that the referent population is evenly distributed throughout the census area, so that the location of residence can be approximated by the centroid (i.e. the geographic center of a polygon). All residents of a given block group were assigned the same location information, the block group centroid. This approach introduced considerable bias as seen in Figure 6, which shows the centroids for two block groups in the middle of marsh land or water that is far from most residences. Also clear are the high rates of misclassification for the zones of proximity to the waste sites.

An alternative to using centroids would be to assume a uniform population distribution. Based on the assumption that the residents are evenly distributed throughout the census area, the area is split in proportion to the area of exposure intersecting it. For example, if an exposure plume intersects 50 per cent of a census tract, then 50 per cent of the residents are assumed to be affected by the plume. However, populations are not necessarily evenly distributed within a census area, and this problem becomes particularly acute when the census area includes nonresidential sections.

To allow for these limitations that arise from assuming an even distribution of the population, we used a digital phone book directory to provide a simple and accurate source of information for simulating the distribution of residents within a census block group. This method offered the least amount of uncertainty concerning the distribution of an individual's actual place of residence. A statewide point data set simulating the location of individuals in Stratford, CT was prepared from the digital phone directory, and the demographic characteristics of individuals obtained from the U.S. Census.

The term "residential listing" will be used to represent the geocoded digital phone book. The accuracy of this methodology is limited only by the quality of the digital phone directory, the geocoding rate, and the fact that all residential dwellings do not have identical numbers of telephone numbers. The telephone database is used to establish the density and distribution of dwelling locations, and bias results from slight inaccuracies in the number of individuals assigned per dwelling. All individuals in each block group of the census are assigned a coordinate location from the phone directory, and in block groups with fewer phone lines per capita the number of individuals assigned to each coordinate would be correspondingly higher.

To simulate the location of residence for the 49,389 Stratford residents who make up the referent population, the 20,511 residential addresses contained in an electronic phone database for Stratford were geocoded. The next step was to assign the census records to the residential listing.

Randomization of census data to phone book coordinates

The expanded census data were randomized to the residential listings within each block group. A Visual FoxPro program was used to loop through each block group and execute the following tasks. The residential listings are (1) assigned a random number; (2) order the records; and (3) assigns a residential listing to the census records until all listings have been utilized. In the event that not all the census records are assigned a residential listing, the digital phone book is re-randomized, and the process is repeated until every census record in the block group has been assigned a residential listing. This process ensures that every residential listing is utilized in the final data set.

Because the analysis of interest is exploratory spatial analysis, having the best locational data possible is critical. Since the randomization occurs at the block group level, the spatial errors that might arise in assigning the census records to the residential listings are limited to the block group. If the randomization were being carried out at the tract or block level, errors would be limited to those respective census areas.

Such processing creates a large file that represents only one pseudo population makeup that has the demographic characteristics of the census block group and the residence distribution of the phonebook. However, this is only one of a large number of possible populations. Each resultant data set can then be considered a model of the population of Stratford. Because of the randomization, results will differ with each replication of the randomization process.

Once the census records had been joined to the residential listings, the locations of geocoded tumor records were merged into the final data set. These data were then exported to a format useful in a statistical software package and were ready to be analyzed. Regression models defining the possible association between exposure to Raymark waste and bladder cancer were developed, using the Connecticut Tumor Registry (CTR) for case information and the Census Referent Population Methodology (CRPM) for the comparison group.

Statistical Error

This methodology violates the assumption that the regressor variable does not have error associated with it. Each replication of the model distributes the non-diseased referent population to slightly different residential locations within the block group. For one iteration of the model , we apply the linear logistic model to obtain q, the probability that a person within group i has disease X ($X = 1$ if diseased, 0 if non-diseased)

$$\log\{\frac{\theta_i}{1-\theta_i}\} = \alpha + \sum_{i=1}^{t} \beta_i X_i$$

β_i is the log odds of disease for the ith group

$$\beta_i = \log \Omega_i$$

And Ω_i = the odds ratio of the ith iteration.
We assumed that the mean parameter estimate of the N iterations could be defined as

$$\overline{\beta_{\circ}} = \frac{\sum_i \beta_i}{N}$$

where N = the total number of iterations. The standard error of β_0 was assumed to be the sum of the error of the parameter estimate per iteration plus the error associated with drawing the sample.

This error was estimated according to the following equation:

$$Se(\overline{B_{\circ}}) = \sqrt{\frac{\sum [Se(B_i)]^2}{N} + \frac{\sum (B_i - \overline{B}_{\circ})^2}{N-1}}$$

The purpose of the new methodology describe here was to simulate the population distribution within the block group. We anticipate that factors such as unlisted numbers or residences without a phone will have little impact on our model when the spatial filter is large (i.e. statewide). Slight variability in the number of points used to simulate the population locations is not expected to alter the rates or odds ratios. Despite the limitation of assuming individuals could be assigned to 25,000 phone locations independently and at random, this is a substantial improvement for spatial analyses. The blockgroup centroid methodology made use of only 46 blockgroup centroids to assign the locations of the 49,389 individuals.

Appendix C: The Original Health Study Limitations

A.) EXPOSURE ASSESSMENT

Ecological studies often rely on population based estimates of exposure. Studies utilizing GIS sometimes compare political subdivisions (e.g. counties) or create "buffers" of geographic areas defined as exposed (e.g. within one mile of a site). This study improved upon those methods by comparing three exposure models, each refining the estimation of exposure. However, each of these models shared an important weakness by relying on the use of a single residential location and its proximity to waste in the estimate of exposure. Actual exposure to the Raymark waste is primarily dependent on physical contact with the soil. In addition, occupational exposures are not appropriately recognized or characterized based on residential location. Exposure misclassification may occur using these exposure models because proximity to waste may not provide an accurate estimate of actual exposure.

1.) Distance to Nearest Waste Site Model and Buffer Zones
This model treats all the waste sites equally with regard to area and site type. A large waste site may present a higher probability of exposure than a smaller site, however, two residences located equidistant from each of these two different sized sites would receive the same "exposure" classification. In addition, a recreational site may present a higher probability of exposure versus a commercial or industrial site but would be treated the same in the distance to nearest site model. Additionally, the buffer zones were arbitrarily determined. The buffer zone is not based on actual knowledge of chemical contaminates.

2.) Cumulative Exposure Model
In addition to producing a continuous estimate of exposure based on distance, the cumulative exposure model incorporated a number of factors that likely affect the probability of exposure. These factors included the area of each of the sites and the type of site (such as residential, recreational, or commercial property). In addition, this model is not based on the nearest site but provides a cumulative exposure "score" that includes all the sites. By incorporating these factors the probability of actually coming in contact with the waste becomes more refined. For example if a person lived equidistant from a recreational and a commercial property, they would be more likely to spend time at the recreational property. A major limitation of this approach is the lack of empirical data to support some of the assumptions used in the model. For instance, we do not know how much more appealing a recreational site is versus a commercial site. In addition, this model again relies on residential proximity and would not take into account an individual who works at a commercial property.

Modeling the risk of exposure to contamination in soil presents a number of difficulties. Unlike exposure to drinking water or ambient air, exposure to soil is contingent upon an individual's actions with respect to their interaction with the media. The models applied in this study refine the assessment of exposure to contamination in soil by incorporating factors that likely affect an individual's interaction with a site. Because the cumulative exposure model was flexible and allowed for the incorporation of various site characteristics, it could be applied to studies of health outcomes and environmental exposures, including the potential for exposure to multiple sources of environmental contaminants.

B.) USE OF EXISTING DATA SOURCES

An objective of this work was to utilize the existing data sources at the Connecticut Department of Public Health. While tumor records were complete and accurate in many respects, these data were not collected specifically for this study. Information concerning many potential risk factors for cancer was not available for analysis (including specific information on exposure to the Raymark waste).

C.) LATENCY BETWEEN EXPOSURE & DISEASE

The latency period between exposure and disease onset for the cancer cases can be ten to twenty years or longer. Because of this long latency period, issues such as estimation of exposure based on one residential address become particularly problematic.

D.) MOVEMENT OVER TIME

A major limitation of the cancer analysis is the inability to track the movement of cases over time. An assumption is made that all the cases lived in the same house for the entire study period. If a cancer patient moved prior to diagnosis, the address reported on the medical record would not reflect where the individual lived during the relevant exposure period.

As long as the movement occurs equally in both groups, exposed moving away from exposed areas and non-exposed moving into exposed areas, the bias will be non-differential. This has the effect of moving the point estimate towards the null. If movement is different between groups, more people move in than out or more people move out than in, the bias will be differential. This will have an unpredictable effect on the point estimate.

The mobility of the population over time is even more of a concern with respect to the cancer analysis due to the long latency between exposure and tumor diagnosis. The cancer study rests on the assumption that the location of the individual at the time of cancer diagnosis is the address they lived at decades earlier when relevant exposures may have occurred.

Information regarding residential history on cancer cases was not available from the CTR records. A few cases had residential information if they moved and continued to receive treatment for their cancer. However, the address change only represented the address at the time medical care was received and not when the case moved.

When the address at cancer diagnosis is used to approximate exposure, residential mobility becomes an important limitation. In future ecological studies that use existing datasets, an attempt needs to be made to obtain the information on residence history.

E.) USE OF 1990 CENSUS DATA AS CONTROLS

The Tumor Registry is a population based registry which provides demographic and disease data on the cases, but not on the comparison population. The comparison group for the cancer analysis was the 1990 census population. Since the population aged over the study period, the use of the 1990 census data could underestimate the odds ratios for the cancers that tend to occur later in life. It would also tend to overestimate the odds ratios for the cancers that tend to occur earlier in life.

OCCUPATIONAL EXPOSURE

The tumor registry database did not include the occupational history of the patient in a consistent manner for the duration of the study period, and this important confounding factor could not be controlled.

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