Middle States Geographer, 2006, 39:69-75

CANCER CLUSTERS IN THE UNITED STATES SINCE 1995: CONSIDERING THE VALUE OF THEIR INVESTIGATION

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***ABSTRACT*:** *Cancer clusters are unusually high rates of a certain type of cancer in a town or neighborhood. They imply an environmental cause for cancer because specific local conditions could cause local concentrations of cancer. However, the study of cancer clusters is viewed with skepticism by most epidemiologists. Hundreds of studies from the 1960s through the 1990s showed no statistically significant, persuasive environmental cause for any cluster. The obvious conclusion is that clusters are simply a coincidence. In a country as large as the United States such coincidences would be expected to happen numerous times over a ten-year period. A closer look at clusters and the statistical methods used to test them, however, suggests that there may yet be value in studying cancer through clusters. There have been institutional and methodological weaknesses in previous, inconclusive studies of cancer clusters. More recently, painstaking research and more refined statistical methods have led to significant statistical links between the environment and cancer clusters in at least two notable instances. Working at fine scales with geographic information systems geographers may help to explain cancer clusters and the links between the environment and cancer.*

Keywords: *Cancer cluster, Medical geography, Epidemiology, Public health*

INTRODUCTION

Cancer clusters…the mere mention of this topic makes many epidemiologists and public health officials roll their eyes in irritation. Cancer clusters, disproportionate concentrations of a type of cancer in an area over a given time, are simply coincident clumps of the disease that are part of an overall random distribution, they say (Gawande, 1999; Thun and Sinks, 2004). It is just as if five consecutive "heads" were part of a 50-50 distribution of 100 coin flips. Clusters happen, but they do not necessarily indicate any link to the environment. The explanation goes on to say that only high-level exposures to chemicals as one might receive in an occupational setting can cause cancer. The diffuse exposure to chemicals that ordinary citizens experience in the environment is difficult to measure, and unlikely to cause cancer (ATSDR, 2002). 108 cancer cluster studies conducted by the Centers for Disease Control (CDC) between 1961 and 1982 yielded no meaningful environmental causes (Caldwell, 1990). These results have become the benchmark for cancer cluster studies in the public health community. Their message is that scarce public health resources would be better spent on broader-scale cancer studies and on teaching the benefits of positive lifestyle changes such as anti-smoking campaigns or wellness education.

Cancer clusters remain an important, contested issue, however. Over 1000 reports of cancer clusters per year come into state health agencies and the CDC from cancer sufferers, their families, friends, and doctors throughout the United States (Aldrich and Sinks, 2002). Most of these are dismissed quickly by public health officials because they include a wide range of cancers or because the cases noted are within normal cancer rates for the country. Some citizens, particularly in more significant clusters, remain convinced that there is an environmental etiology to their cancers despite officials' assertions otherwise. These people frequently organize to counter what they perceive as bureaucratic indifference, sloppy technique, and obfuscation on the part of state health departments and the CDC (FACT, 2006; Mullen, 2002). Long before Hurricane Katrina, there was little faith in public officials among those living near hazards or in cancer clusters. Activists, however, can become radicalized, developing anti-corporate or anti-government agendas that, regardless of the nobility of their cause, hurt their credibility on the specific issue of cancer.

Health officials also have credibility problems. Those who categorically state that cancer clusters are only coincidental miss the point that some clusters are likely due to behavioral or genetic factors such as uneven nutrition, smoking rates, or genetic predisposition to cancer in specific towns or neighborhoods. Also, some clusters could be due to environmental triggers. Non-workplace exposures to a carcinogen can be extremely high if it is in drinking water, in soil where children are digging and playing, or in exhaust plumes from plants funneled down small canyons or between large buildings. In addition, little is known of the thresholds between safe and unsafe exposures for children to given carcinogens. Statistical methods have not proven the link between the environment and a cluster, but where there is a cluster, they also cannot refute this link. This is particularly true in cases that satisfy an even higher confidence level than the standard 95%, and in cases of unusually high exposure to one or more mutagenic chemicals in the cluster. Perhaps the CDC's methods simply could not distinguish probable causes from confounding factors. The application of spatial statistics to cancer, in particular cluster analysis, has come far since the time of the CDC studies. Some spatial scan and global clustering methods are effective in distinguishing likely explainable clusters from random "noise" (Kulldorff et al., 2006; Gregorio et al., 2004).

Despite the fundamentally geographic nature of cancer clusters, it is an issue where few American geographers have ventured. Geographers, however, should be aware of this issue because it is so easily misunderstood and so easily dismissed by epidemiologists. More broadly, geographers may be able to help solve questions of environment and health, particularly with geospatial technology and spatial statistics methods. This paper, then, is an exploration of the past decade of cancer cluster studies and where these studies may lead, given new technologies, new techniques, and some encouraging recent results.

PUBLIC HEALTH ROLE

In 1990, the CDC turned cancer cluster studies over to the states, publishing Guidelines for Investigating Clusters of Health Events to help direct their efforts. This document emphasizes treating citizens reporting cancer clusters with respect, although the CDC appears to doubt the overall value of cluster investigations:

> From a public health perspective, the perception of a cluster in a community may be as important as, or more important than, an actual cluster. In dealing with cluster reports, the general public is not likely to be satisfied with complex epidemiologic or statistical arguments that deny the existence or importance of a cluster. Achieving rapport with a concerned community is critical to a satisfactory outcome….The unofficial consensus among workers in public health is that most reports of clusters do not lead to a meaningful outcome. Often, a "case" is not clearly defined, and the "cluster" is, in fact, a mixture of different syndromes. Frequently, no exposure or potential cause is obvious, and--to make the investigation even more difficult--there are many possible causes….Despite these impediments, reports of clusters cannot be ignored. The health agency must develop an approach that maintains community relations and that manages clusters without excessively depleting resource.

States were given the responsibility and choice to deal with cancer cluster reports however they chose. Most used the Guidelines as a framework from which to adapt their own approaches, based on an incongruous balance of political pressure and contradictory science. For instance, Minnesota did many small-scale cluster studies during the 1980s and early 1990s but has since turned to discouraging cluster reports through a public education campaign stressing the futility of cancer cluster investigations (Fagin, 2002).

Most states follow a kind of "triage" approach, weeding out 80% of cluster reports at first contact with the person filing the report. (1) Suspected Cluster - A return telephone call usually reveals that only two or three cases of a cancer in a town are in the cluster, or that different cancers are included in the cluster, or that the cluster includes relatives or friends living in other parts of the state, any of which invalidates the cluster. (2) Statistical Cluster - Those that pass the initial contact are then verified by checking against the state's cancer registry, at which point even verified clusters are usually filed away on the assumption that they are simply random concentrations. (3) Meaningful Cluster - Only clusters that are both statistically significant and likely to have an obvious cause, such as a confirmed occupational or environmental exposure, are fully investigated (Connecticut Dept of Public Health, 1999). In fact, pressure from influential political figures or from media may lead to full investigations, as well. The CDC and ATSDR (Agency for Toxic Substances and Disease Registry) offer to help if invited by the health department of a particular state, but they do not encourage such invitations. Finally, the vigor of state responses to cancer clusters correlates closely to the resources the states provide, with most states relegating cancer cluster response to part of one employee's duties (Trumbo, 2000). The result is that, of over 1000 cancer cluster reports per year throughout the United States, only a tiny fraction rise to the level of a major investigation.

Perhaps the most significant outcome of the restructuring of cancer cluster research in the early 1990s is The Cancer Registries Amendment Act of

1992, which mandated each state to establish a cancer registry with common variables and a common data structure. For each case of cancer, the state reports at least the following: demographic data on each case, industrial or occupational background of each person with cancer, date of diagnosis and source; type, site, and stage of cancer, and treatment (Public Law 102-515, 2). The registry was projected to be used to find patterns in cancer occurrence. Nevertheless, subsequent cancer cluster reports have virtually all been initiated by the public, not by the state departments of health. Many states have enhanced their cancer registries by geocoding every case as it is recorded in the registry, and some have even begun to spatially model cancer occurrences using GIS (Florida DOH, 2005).

MAJOR CANCER CLUSTERS IN THE UNITED STATES SINCE 1995

Figure 1 shows meaningful cancer clusters that have been investigated by state health departments, and/or the ATSDR since 1995. Of the thousands of cancer clusters reported to health departments around the country during the past two decades, these stand out because they are statistically significant, and they have at least a hypothetical cause such as: a heavy occupational carcinogen exposure, a leaching landfill nearby, contaminated drinking water, or they are in the plume of an incinerator, etc. Of the 49 clusters shown, 10 are well accepted as occupational or school exposures, from brain cancer among scientists at a refinery in Naperville, IL to testicular cancer among students at a high school in Elmira, NY. Only two, Tom's River, NJ and Ashland, MA, have been convincingly proven to be caused by chemical exposure in the environment. These conclusive results, having come in the past three years, represent a breakthrough for some epidemiologists, and a challenge to others who remain skeptical of the results. The remaining 37 clusters have likely causes (or they would not have been studied at all), but no statistically significant link has been drawn from the cancer to the cause.

Even the clusters made famous in the movies "A Civil Action" (Woburn, MA) and "Erin Brockovich" (Hinkley, CA) were never found by their state health departments to have a statistically significant environmental cause (Alexander and Boyle, 2000; Endean, 2001). The burden of proof for a civil jury or for corporate lawyers is typically less than for statistical tests.

The distribution of clusters is not uniform for a number of well understood reasons. First, the Northeast is densely populated and has been heavily industrialized, leading in part to a denser concentration of clusters there. The decision to investigate a cluster, however, depends on the political leadership of a given state, with some far more aggressive than others. For instance, Massachusetts' concentration of cluster investigations, including the successful Ashland study, is due to a combination of a proactive department of public health and a group of local universities which are leading in innovative analytical techniques (Ozonoff et al., 2005). Also, a disproportionate number of investigations in the Northeast are in suburban, politically active neighborhoods and towns. Most environmental health studies in Massachusetts are designated by elected officials, not by professionals in the health department (Daley, 2005). Similar neighborhoods in the South and West are newer, more transient, and with less of a tradition of environmental activism, thus fewer clusters. One wonders about the lack of inner-city neighborhoods among the cancer clusters shown. Research has shown that the American poor shoulder a relatively heavier cancer burden than the general population, particularly in cancer mortality (Haynes and Smedley, 1999). Surely they are not less susceptible to cancer clusters, simply less able to push them before local officials and the health department.

Some large states such as Texas, Colorado, and Oregon have had no major clusters confirmed since 1995. This is a function of both randomness and conscious efforts to discourage major investigations. Texas conducts cluster analyses by county from its cancer registry each year (Texas DOH, 2006), but they leave studies of the links between the environment and cancer to localities, or to university researchers (Horswell, 2006). The Colorado Department of Public Health and Environment has studied the population around an antenna farm near Golden over the past 10 years, but it has not found even a statistically significant cancer cluster there (CDPHE, 2004).

Another odd result on the map is the lack of a cancer cluster in "Cancer Alley," the infamous stretch of petrochemical plants and refineries along the Mississippi River from just north of New Orleans to Baton Rouge, Louisiana. Currently, operating and abandoned industrial sites along the river, coupled with lax environmental enforcement from Louisiana authorities has made this small region perhaps the most polluted in the United States. Nevertheless, Louisiana's Tumor Registry states that, for all cancers, white males in this region were only slightly above national averages for the period 1998-2002,

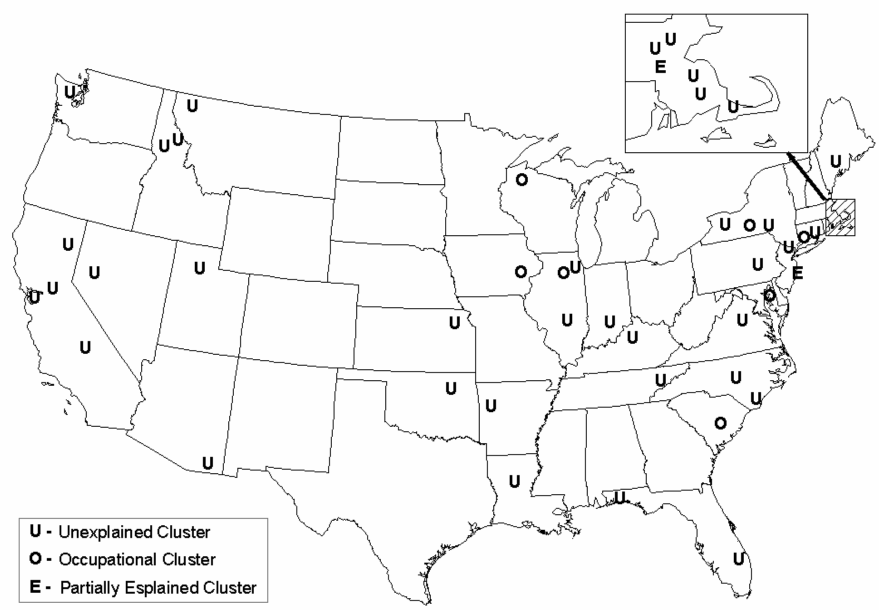

Figure 1. Major cancer cluster investigations in the United States since 1995.

while black males, black females, and white females were below national rates (LTR, 2005). The absence of a cluster in this region may be because the scale of data is too coarse to detect the effect of a single facility on surrounding residents, and the background incidence of cancer may be so high as to make “clusters” undetectable. I should note that the state’s methods, biases, and competence in dealing with all aspects of “Cancer Alley” have been effectively questioned and critiqued (Allen, 2003).

The most disproportionate cancer cluster in the US is in Fallon, Churchill County, NV (2000 pop. - 23,982), northeast of Reno, where 17 children have developed leukemia since 1997. First the CDC, invited by the Nevada State Health Division, then the ATSDR studied the cluster, concluding that they could find no environmental link to the cancers (CDC, 2003; ATSDR, 2003). They found elevated levels of arsenic and uranium in well water, and high levels of tungsten in tested soil, none of which pointed definitively toward the acute lymphocytic leukemia (ALL) which has afflicted the children. Another object of interest was the jet fuel pipeline that runs through town to the naval air station on the northeastern outskirts, but it was also cleared by ATSDR after a brief investigation. The seemingly incongruous findings of the reports, high levels of contaminants but no link to cancer, while statistically valid, have created a great deal of distrust in Fallon. In fact, with 16 cases of cancer, traditional statistical methods dictate that correlation to any cause must be overwhelming to be considered significant. Moreover, with entities like the Department of Defense or large corporations potentially at fault if strong environment-cancer cluster links are established, a cynical public may feel that skeptical officials have an agenda to protect powerful interests.

An important aside to the Fallon cluster is the work of two University of Arizona researchers, one a pediatric research professor, one a tree-ring researcher, and collaborators from around the country. They, too, feel that government epidemiologists are missing some important clues in the Fallon case. Moreover, they have found a smaller cluster of ALL in Sierra Vista, AZ, southeast of Tucson. Like Fallon, Sierra Vista has a military air base nearby using the same type of fuel as at Fallon. Also, the climate is similarly dry and dusty, and tungsten dust is blowing around as it does in Fallon. Using a combination of analyzing tree rings for chemicals in the environment, and clinical and field research on such substances as tungsten in both clusters, these researchers hope to find the right combination of factors to explain the reasons why Fallon, Sierra Vista, and other like towns are suffering high rates of childhood leukemia (Pearson, 2003; Downing, 2004).

MODEST SUCCESS

Two cancer clusters stand out from the others because they have been convincingly, though modestly, linked to environmental causes. Tom’s River, NJ and Ashland, MA are the only cancer clusters in the United States to have shown a statistically significant (95% C.I.) relationship to a likely environmental trigger. Published in 2003 and 2006, respectively, these studies may prove to be building blocks with techniques that future researchers can replicate and adapt in their studies.

Tom's River, Dover Township, NJ drew attention in the middle 1990s when it was realized that 90 cases of cancer had been diagnosed in Dover Township children under 15 years old (2000 pop. - 89,706) in the period from 1979 until 1995, 23 more than would be expected (*New York Times*, 1998). Motivated, organized parents, a key location near the lucrative tourist mecca of the Jersey Shore, and the sheer number of childhood cancer cases led local congressional leaders to push for a major effort in Dover Township with the state working with the ATSDR. They developed a strong hypothesis through detailed testing of water, air, and soil around the township, pinpointing two Superfund sites as likely sources of exposure. They then did a standard case-control study comparing cancer patients with non-cancer patients in the township, but they did it both for the cases under 20 years old, and for the cases under 5 years old at diagnosis. They also did in-depth interviews with children and their parents to build a database of contacts and exposures. This is much easier to do with children than with adults who typically have been to many more places in their lives, with poorer recollection of the details. Finally, birth records for children born in Dover Township were also examined to consider prenatal exposure to the chemicals present in the area (NJDHSS, 2003).

The result of the Dover Township study was that two environmental factors appear to have contributed to leukemia in female children under 5 years old: (1) Prenatal exposure to drinking water from the Parkway well field, which had been contaminated by trichloroethylene and tetrachloroethylene, and (2) prenatal exposure to air emissions from the Ciba-Geigy chemical/dye plant (NJDHSS, 2003). The two extra steps (i.e. including data on prenatal exposure and breaking the population into those younger than 5) were the keys to finding meaningful links between the environment and disease in this study. In the population up to age 20, leukemia occurred at a significantly elevated rate, but no significant correlation to environmental exposure was found. These results suggest that carefully thought-out investigations and finely crafted hypotheses have a greater chance of finding significant results than simply following a formula assuming that everyone in a town or city is equally at risk, a method that has consistently failed.

Ashland, MA also has a history of dye and chemical manufacturing in proximity to residential areas and resulting widespread contamination of soil and water. In 1998, after hearing from Ashland residents about an unusual number of cancers among young people in the community, the Massachusetts Department of Public Health (MDPH) found that Ashland residents under 40 years old had a significantly higher overall cancer rate than expected (MDPH, 2006). MDPH then proposed the hypothesis that exposure to the Nyanza chemical site increased cancer risk among young Ashland residents. This meant children 10-18 years old in the years 1965-1985. The MDPH used school rosters to compile a population of over 2600 subjects and then went to great lengths to contact and interview them about their circulation patterns within Ashland at that time, as well as about any cancer diagnoses received in the years since. The report asserts that the combination of substantial contact with water on or around the Nyanza site and a family history of cancer makes one significantly more likely to develop any type of cancer, as well as rarer, soft-tissue cancers (MDPH, 2006). Again, we see that a particularly well done study with a clearly defined at-risk population yields a statistically significant relationship between the environment and disease. The message appears to be that cancer cluster studies, if done correctly, are difficult, time-consuming and expensive. However, they may help to explain the relationship between environment and disease. Note: The MDPH Ashland Final Report is an excellent example of clear, direct technical writing that could be used as a teaching tool in an advanced geostatistics class.

CONCLUSION AND FUTURE DIRECTIONS

Cancer clusters are deceiving. Many occur due to random chance, but a tantalizing few are detected in the presence of chemicals or radiation that could be causing them. Studies of these clusters usually result in inconclusive results due to a complex array of confounding factors, the high statistical threshold needed for small samples, or poor understanding of at-risk populations. Careful hypothesis building and specific population definitions for the statistical methods to be used can lead to precise results that are the potential strength of cancer cluster research. Precise statistical results in a particular location can help us to decide who is getting cancer and what is causing it. Furthermore, this kind of result can help to determine how best to protect at-risk populations.

Geographers can improve cancer cluster studies through a greater use of GIS and a more refined sense of space. Cancer registries are just beginning to geocode individual cases of cancer. Geographers can contribute through spatial modeling that is outside the realm of many epidemiologists' training. In particular, spatial scan models show promise.

Modeling can go well beyond the simple zip code or census tract cluster analyses that are done by many health departments. It should extend to exposure, using finer-scale hydrologic and atmospheric models to define exposure in contaminated areas as precisely as possible. With precise data, micro-scale GIS could help geographers build space-time paths for individuals, showing where and when they intersect with carcinogen exposure, and how they differ from others. This approach could be particularly effective in a longitudinal study following some who develop and others who do not develop cancer.

Another aspect of geography that can enhance studies of any human environment interaction, but particularly the interaction of disease and the environment in a cancer cluster is visualization (Meliker et al., 2005). Epidemiologists tend not to believe their eyes as readily as geographers, but data visualization can offer insight into process and relationships that may be missed in static cartography or traditional statistical methods (Robinson et al., 2005; MacEachren and Kraak, 2001).

Cancer cluster studies are not the only way to study links between the environment and cancer; they may not even be the best way to study these links. However, a significant cluster in the presence of exposure to carcinogens offers a chance to understand on a fine scale how the environment can help to cause disease. The key is to continue to develop more refined techniques that can capture key relationships and guide researchers to conclusions that inform policy. Geographers can play a part in this development by simply applying and cultivating the spatial awareness we use in research and teaching.

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