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Breast Cancer Clusters in the Northeast United States: A Geographic Analysis

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High breast cancer mortality rates have been reported in the northeastern part of the United States, with recent attention focused on Long Island, New York. In this study, the authors investigate whether the high breast cancer mortality is evenly spread over the Northeast, in the sense that any observed clusters of deaths can be explained by chance alone, or whether there are clusters of statistical significance. Demographic data and age-specific breast cancer mortality rates for women were obtained for all 244 counties in 11 northeastern states and for the District of Columbia for 1988–1992. A recently developed spatial scan statistic is used, which searches for clusters of cases without specifying their size or location ahead of time, and which tests for their statistical significance while adjusting for the multiple testing inherent in such a procedure. The basic analysis is adjusted for age, with further analyses examining how the results are affected by incorporating race, urbanicity, and parity as confounding variables. There is a statistically significant and geographically broad cluster of breast cancer deaths in the New York City-Philadelphia, Pennsylvania, metropolitan area (p = 0.0001), which has a 7.4% higher mortality rate than the rest of the Northeast. The cluster remains significant when race, urbanicity, and/or parity are included as confounding variables. Four smaller subclusters within this area are also significant on their own strength: Philadelphia with suburbs (p = 0.0001), Long Island (p = 0.0001), central New Jersey (p = 0.0001), and northeastern New Jersey (p = 0.0001). The elevated breast cancer mortality on Long Island might be viewed less as a unique local phenomenon and more as part of a more general situation involving large parts of the New York City-Philadelphia metropolitan area. The several known and hypothesized risk factors for which we could not adjust and that may explain the detected cluster are most notably age at first birth, age at menarche, age at menopause, breastfeeding, genetic mutations, and environmental factors. *Am J Epidemiol* 1997;146:161–70.

breast neoplasms; cluster analysis; confounding; epidemiologic methods; geography; parity; statistics

It is well known that breast cancer mortality is higher in the northeastern part of the United States compared with the rest of the country (1–3). During 1988–1992, the 11 most northeastern states and the District of Columbia had a mortality rate 15.6 percent higher than the remaining 39 states. When ranking the 50 states and the District of Columbia, the top eight were in the Northeast, with Maryland, Vermont, Connecticut, and Maine ranked 11, 14, 20, and 22, respectively (1). There have also been reports of more localized clusters of the disease, most notably on Long Island, New York (4–6).

The high mortality rates from breast cancer on Long Island, as well as public concern about the environment, prompted the US Congress to mandate an investigation by the National Cancer Institute. The investigation is to include Long Island as well as the two northeastern counties with the highest mortality rates during 1983–1987 and at least 30 cases (Tolland County in Connecticut and Schoharie County in upstate New York) (7).

Typically with reported clusters, a statistical test is performed to assess whether the number of cases is significantly greater than what would be expected. This is often done for the cases in one specific area (e.g., Long Island); however, if that area is chosen because it has many cases, then this approach introduces preselection bias, since the same cases are used to define the hypothesis as well as to test it.

To evaluate an area with an apparently increased disease incidence or mortality rate, a more appropriate statistical approach is to use the spatial scan statistic (8–10). The method scans a larger encompassing area for possible disease clusters without a priori specification of their location or size; it identifies the approx-

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imate location of clusters, and it performs a significance test for each cluster in a way that compensates for the multiple testing inherent in such a procedure.

If we detect significant clusters using this method, a logical next step is to see whether they can be explained by known or suspected risk factors. There are a number of such risk factors for breast cancer (11, 12); and within the limit imposed by the availability of population-based data, we can adjust for these factors to see whether they explain the detected clusters. In this study we report, in addition to age, adjustments for parity (13), race (1), and urbanicity (14, 15).

MATERIALS AND METHODS

Geographic, population, and mortality data

The geographic area under study consists of Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Pennsylvania, Delaware, Maryland, and the District of Columbia. Herein, we refer to this collection of states as the Northeast. The analysis is based on the 245 counties and county equivalents in this area (16). The statistical method requires that we specify the geographic position of each county, and we used the latitude and longitude of the county centroid as specified by the 1990 Census (17). For three counties, the census centroids were replaced by visual estimation to better reflect the geographic and population-weighted centroid, since the former had been greatly influenced by a small outlying island (e.g., Block Island in Washington County, Rhode Island).

We used mortality data from publicly available computer tapes provided by the National Center for Health Statistics. During 1988–1992, there were a total of 58,943 deaths from breast cancer among women in the Northeast. Of these, 7,076 were younger than 50 years. For each death, we have data on the county of residence, age at death, and race.

Demographic data were obtained from the 1994 census revision, taking the average July 1 population estimates for 1988–1992. For each county, we obtained the total female population subdivided by age group (5-year intervals) and by race (white, black, other). The numbers are not adjusted for the census undercount. The average total population was 29,535,210 women.

Statistical methodology

To test for the presence of disease clusters and to identify their approximate location, we used a spatial scan statistic (8–10). We assumed the number of deaths in each county to be Poisson distributed. The method tests the null hypothesis that within any age group, the risk of death from breast cancer is the same in all counties. This means that the expected age-adjusted mortality rate is constant over the whole area.

The method imposes a circular window on the map and allows its center to move over the area so that at any given position, the window includes different sets of neighboring counties. If the window contains the centroid of a county, then that whole county is included in the window. For practical reasons, the center of the window is positioned only at the 245 county centroids; and at each position, the radius of the circular window is varied continuously from zero up to a maximum radius so that the window never includes more than 50 percent of the total population. In this way, the circular window is flexible both in location and size. In total, the method creates a very large number of distinct circular windows, each with a different set of neighboring counties within it, and each a possible candidate for containing a cluster of breast cancer deaths. For each window, the method tests the null hypothesis against the alternative hypothesis that there is an elevated risk of breast cancer mortality within, compared with outside, the window.

Under the Poisson assumption, the likelihood function for a specific window is proportional to

$$\left(\frac{n}{\mu}\right)^{n}\left(\frac{N-n}{N-\mu}\right)^{N-n} I(n > \mu),$$

where N is the total number of deaths over the whole area, n is the number of deaths within the window, and μ is the indirectly age-adjusted expected number of deaths within the window under the null-hypothesis. I is an indicator function that is equal to 1 when the window has more deaths than expected under the null hypothesis, and 0 otherwise. Note that n/μ and $(N - n)/(N - \mu)$ are proportional to the age-standardized mortality ratios within and outside the window, respectively. For fixed N and μ, the likelihood increases with the number of deaths, n, in the window.

This likelihood is maximized over all the windows, identifying the window that constitutes the most likely disease cluster. The likelihood ratio for this window is noted and constitutes the maximum likelihood ratio test statistic. Its distribution under the null hypothesis and its corresponding simulated p value is obtained by repeating the same analytic exercise on a large number (we chose 9,999) of random replications of the data set generated under the null hypothesis in a Monte Carlo simulation (18). The calculations were performed using the program SaTScan (19), designed specifically to implement the spatial scan statistic.

Compared with other statistical methods for spatial epidemiology (20–22), the spatial scan statistic has the following features that make it particularly suitable as a

screening tool for evaluating reported disease clusters:

1) It adjusts both for the inhomogeneous population density and for any number of confounding variables (in the description above, we used the term "age-adjusted expected ratio," but this can be extended to include adjusting for other confounders as explained subsequently.
2) By searching for clusters without specifying their size or location, the method ameliorates the problem of preselection bias.
3) The likelihood ratio-based test statistic takes multiple testing into account and delivers a single p value for the test of the null hypothesis.
4) If the null hypothesis is rejected, we can specify the approximate location of the cluster that caused the rejection.

In addition to the most likely cluster, the method identifies secondary clusters in the data set and can order them according to their likelihood ratio. There will always be sets of counties that overlap in part with the most likely cluster and that have a likelihood almost as high, since adding or subtracting a few counties does not normally change the likelihood greatly. We do not report on all clusters of this type since most of them provide little additional information; however, their existence means that although we can pinpoint the general location of a cluster, its exact boundaries must remain uncertain. Thus we always refer to the "approximate location" of a cluster. Sometimes it is of interest to see whether a significant cluster can be decomposed into two nonoverlapping subclusters, each of which would allow rejection of the null hypothesis on its own strength. One way to do this, which we have adopted, is to continuously limit the maximum cluster size in a sequential manner until no additional partitions can be made.

There also may be secondary clusters that do not overlap the most likely cluster. We report secondary clusters of this type if the likelihood ratio is larger than the likelihood ratio for the most likely cluster for at least one data set simulated under the null hypothesis (i.e., $p < 1.0$). It can be shown that the simulated p values for secondary clusters are conservative, i.e., they overestimate their true values (9).

Confounding variables

To adjust the analysis for any number of confounding variables, we used indirect standardization. The mortality rates for each cross-classification of the confounding variables were pooled across the entire Northeast and served as our standard. These rates were then applied to the appropriate population in each county to obtain confounder-adjusted expected counts.

To incorporate urbanicity, we classified each county as either urban or rural; and by knowing the county of residence for each individual, we could then proceed with indirect standardization. For the classification, we first selected all counties that are located within a metropolitan statistical area, a consolidated metropolitan statistical area, or a New England county metropolitan area with a total population of 500,000 or more according to the 1990 Census (17). We then used a concept of the US Department of Agriculture whereby metropolitan counties are divided into central and fringe metropolitan counties (23). Only the former were classified as urban, and they are marked on the map in figure 1.

In one analysis, we adjusted for parity, the number of live births that a woman has had during her lifetime. Because information on parity was not available from death certificates or for the general population, we estimated mortality rates as a function of parity using the relative risks for breast cancer incidence calculated by Layde et al. (13) from the Cancer and Steroid Hormone study. These risks are given in figure 2 and were adjusted for age, history of surgically confirmed benign breast disease, family history of breast cancer, menopausal status, irregular menses as a teenager, and adiposity.

From the 1990 Census, data are available on the average number of children born to the women in each county in each of five age groups. Under an assumption that each additional child lowers the risk of breast cancer by the same number of percentage points, we calculated the parity-adjusted expected number of deaths based on the estimated relative risks. This assumption cannot hold throughout the entire range of parity since this would mean that women with many children would have a negative risk; however, as can be seen in figure 2, it gives a reasonable approximation for the range of no children to six children where the vast majority of women fall. By fitting a linear regression line, we estimated a risk reduction of 8.8 percent per child.

It has been suggested that breast cancer may have a different etiology among pre- and postmenopausal women. For this reason, we also conducted separate analyses for women older and younger than 50 years.

RESULTS

In figure 3, we show the indirectly age-adjusted mortality rates for each county, depicting the percentage above or below the Northeast average. The results of applying the age-adjusted scan statistic to these data are shown in figure 4 and table 1, part A. The method found the most likely cluster in a region encompassing the New York City-Philadelphia metropolitan area (figure 4), with a mortality rate 7.4 percent higher than in the rest of the Northeast. This cluster was significant at the level $p = 0.0001$.

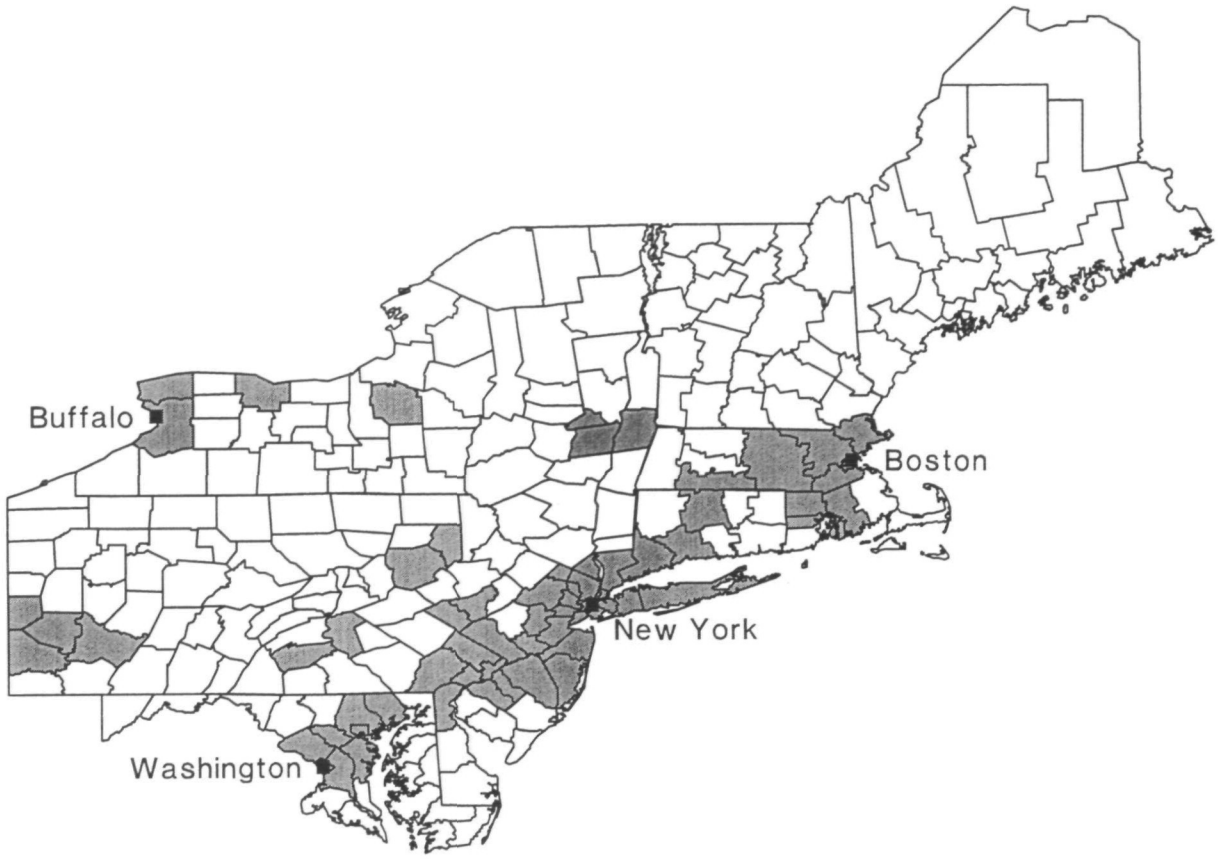

FIGURE 1. Counties classified as urban in the Northeast United States.

Additional areas in the Northeast that had higher than average mortality rates during 1988–1992 were Buffalo, the District of Columbia, Boston with suburbs, and eastern Maine. However, none of these had a statistically significant excess.

As mentioned in Materials and Methods, there are often many windows that overlap with the most likely cluster and that have only slightly lower likelihood values. Thus the exact borders of the cluster must remain uncertain. For example, in the age-adjusted analysis, with a log likelihood ratio of 34.4, the Philadelphia-New Jersey cluster was almost as strong as the larger Philadelphia-New York City cluster. This means that moving just a handful of cases could have changed the specific borders of the most likely cluster. Moreover, there are some counties within the most likely cluster with mortality rates considerably below the Northeast average, as well as counties just outside the cluster with a considerably higher rate (figures 3 and 4). The correct interpretation of the analysis is as follows: First, within the northeast United States, there is strong evidence for the existence of at least one disease cluster. Second, this cluster appears to include, but is not confined to, Long Island.

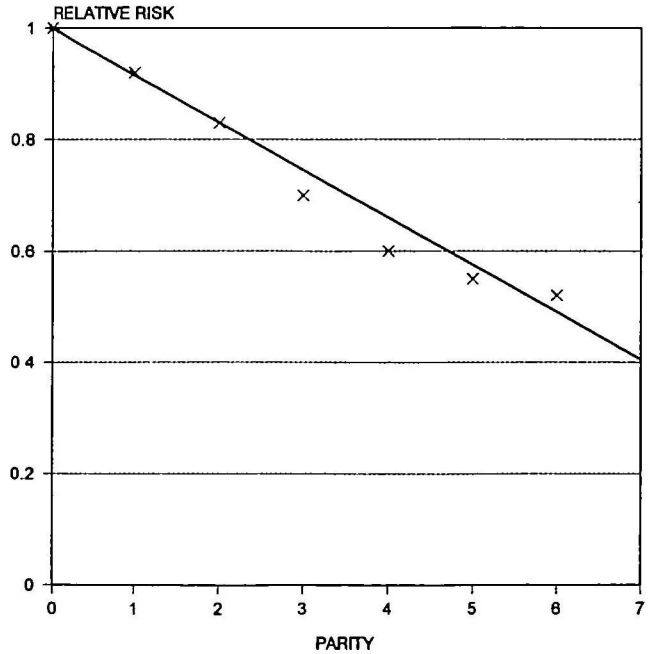

FIGURE 2. The relative risk of breast cancer incidence among women in relation to parity, as estimated by Layde et al. (13), and a linear least square fit to that data.

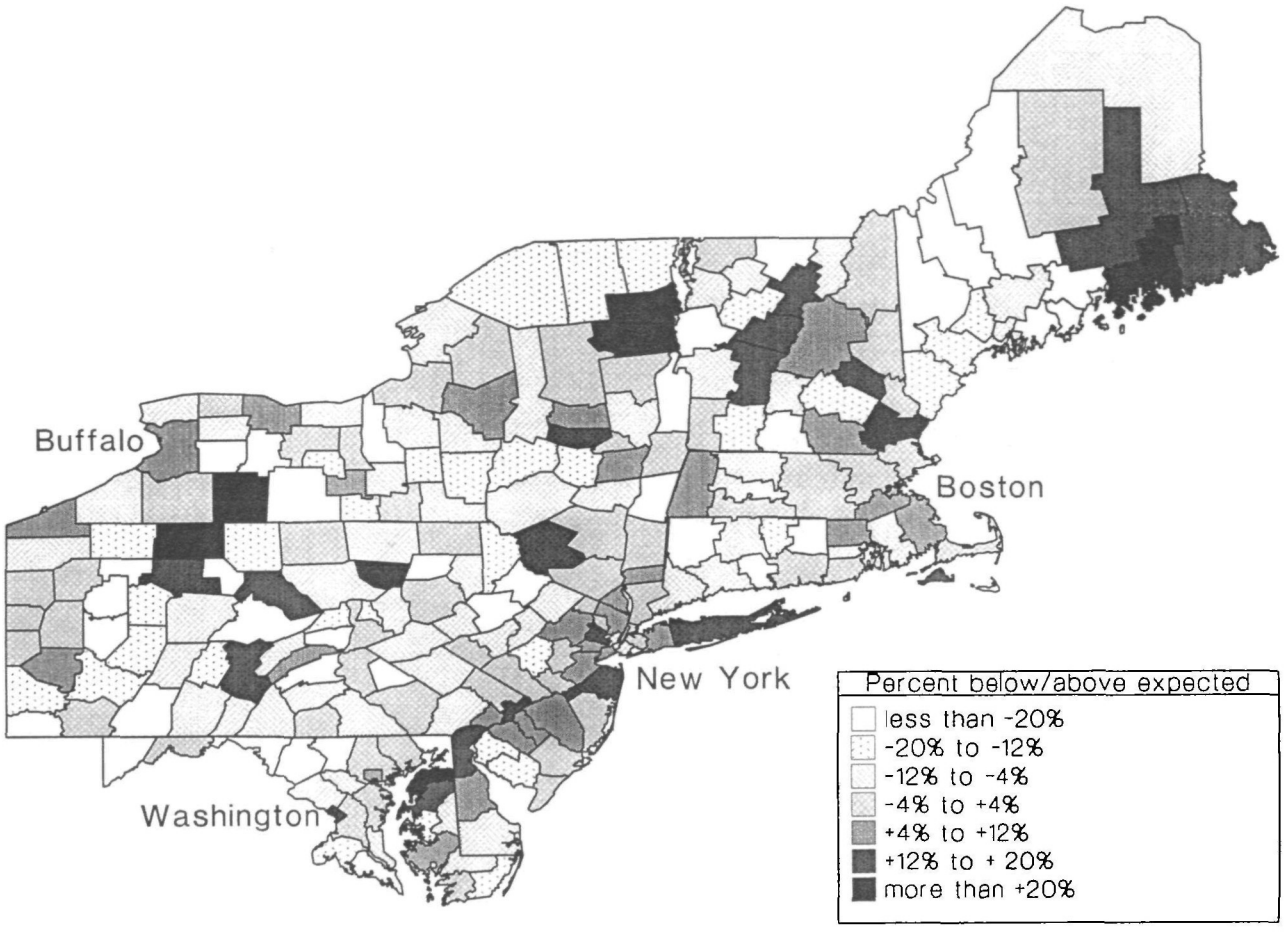

FIGURE 3. Age-adjusted breast cancer mortality rates among women in the Northeast United States, 1988–1992.

We further examined the most likely cluster by determining which smaller subclusters were strong enough, by themselves, to reject the null hypothesis. Using the sequential procedure previously described, four such subclusters emerge: Long Island, northeast New Jersey, Philadelphia, and central New Jersey. These are presented in figure 5 and table 1, part A.

Schoharie and Tolland counties were not identified as either a primary or a secondary cluster because the number of cases were 19.8 and 16.3 percent less than those expected, respectively. Hence, the excess number of deaths that were seen in these counties in 1983–1987, and on which the congressional selection criteria were applied, were not repeated during 1988–1992. If the same criteria for selecting two counties had been used during this latter period, then Essex County in New York (with Lake Placid) and Hancock County in Maine (containing Acadia National Park) would have been selected, with 27.3 and 26.3 percent more cases than expected, respectively. However, as can be seen in table 1, part A, neither of these was statistically significant.

When incorporating race as a confounding variable in addition to age, we found the same most likely cluster with a slightly higher likelihood value (table 1, part B). Adjusting for age and parity yielded a most likely cluster that was smaller in size but in the same general location. The likelihood ratio decreased from 35.7 to 28.2, indicating that parity may explain some of the excess in the New York-Philadelphia area; however, the cluster was still significant ($p = 0.0001$). The cluster was limited to Philadelphia, central New Jersey, and Staten Island (figure 4). The two counties on Long Island, Nassau and Suffolk, formed a secondary cluster that was also significant ($p = 0.0001$) (table 1, part B).

After adjusting for urbanicity, the strength of the most likely cluster decreased. This is not surprising since the area contains about half the urban population in the Northeast and only a few rural counties. As with the adjustment for age and parity, the most likely cluster was limited to Philadelphia, central New Jersey, and Staten Island, with Long Island forming a separate cluster (table 1, part B, and figure 4). Both clusters were significant ($p = 0.0001$ and 0.0017, respectively). Thus, our classification of urbanicity did not explain the excess of cases observed in the New York City-Philadelphia metropolitan area. Simulta-

FIGURE 4. The most likely cluster of breast cancer among woman for the period 1988–1992, occurring around New York, New York, and Philadelphia, Pennsylvania, as well as four secondary clusters.

neous adjustment for age, race, parity, and urbanicity gave a similar result (not shown).

Women aged 50 years and older represented 86 percent of the total number of breast cancer deaths. In this age group, the result was essentially the same as for the entire age range (table 1, part C). The most likely cluster was the same, and the excess of deaths was still 7.4 percent, whereas the likelihood ratio was slightly lower because of the smaller number of deaths involved.

For women younger than 50, however, the most likely cluster changed to the District of Columbia ($p = 0.0002$) (table 1, part C). After adjusting for race, the result was no longer significant ($p = 0.207$).

The New York City-Philadelphia metropolitan area had an excess of deaths among younger women at 6.9 percent compared with an excess of 7.4 percent in the older group. Because of the smaller number of deaths, however, the power of the test was lower. The five Philadelphia counties (figure 5) appeared as a secondary cluster for this age group, with $p = 0.016$. After adjusting for race, this cluster was no longer significant (table 1, part C).

DISCUSSION

When apparent disease clusters are first reported, they cause considerable alarm among the population and are accompanied by demand for immediate action. In such an atmosphere, it becomes difficult to dispassionately assess the strength of evidence for the existence of the hypothesized cluster. This difficulty has been compounded by lack of available statistical methods for assessing the evidence in a manner that adjusts for the preselection bias and multiple testing effects accompanying disease cluster reports. In this paper, we have presented a new method, the spatial scan statistic, which provides such an adjustment and appropriately assigns a level of significance to any detected cluster. We have illustrated the use of the method by applying it to breast cancer mortality in the Northeast United States, in light of the reported Long Island cluster. Our method reveals that the increased breast cancer mortality on Long Island is statistically significant and suggests that the increase is not confined to this area but extends down to parts of New Jersey and Philadelphia.

TABLE 1. Breast cancer mortality analysis for women in the Northeast United States, 1988–1992, using the spatial scan statistic

Analysis			Cluster						
	Age (years)	Confounders	Type	Location	Cases	Expected	RR*	LLR*	*p* value
A	All	Age	M*	New York, NY-Philadelphia, PA	24,044	23,040	1.074	35.7	0.0001
			S*	Buffalo, NY	1,416	1,280	1.109	7.1	0.122
			S	Washington, DC	712	618	1.154	6.9	0.147
			S	Boston, MA	5,966	5,726	1.047	5.5	0.398
			S	Eastern Maine	267	229	1.166	3.0	0.994
			SO*	Philadelphia, PA	3,815	3,441	1.116	20.8	0.0001
			SO	Long Island, NY	2,935	2,620	1.127	19.2	0.0001
			SO	Central New Jersey	3,784	3,437	1.108	18.0	0.0001
			SO	Northeast New Jersey	2,738	2,467	1.115	15.0	0.0001
			S	Essex, NY	51	40	1.273	1.4	1
			SO	Hancock, ME	67	53	1.263	1.7	1
B	All	Age, race	M	New York, NY-Philadelphia, PA	24,044	22,973	1.079	40.7	0.0001
	All	Age, parity	M	New Jersey-Philadelphia, PA†	9,873	9,205	1.087	28.2	0.0001
			S	Long Island, NY	2,935	2,604	1.134	21.2	0.0001
	All	Age, urban	M	New Jersey-Philadelphia, PA†	9,873	9,339	1.069	17.8	0.0001
			S	Long Island, NY	2,935	2,684	1.098	11.9	0.0017
C	≥50	Age	M	New York, NY-Philadelphia, PA	20,737	19,862	1.074	31.4	0.0001
	<50	Age	M	Washington, DC	144	87	1.670	15.8	0.0002
			S	Philadelphia, PA	525	435	1.223	9.4	0.017
	<50	Age, race	M	Washington DC	144	106	1.369	6.3	0.207
			S	Philadelphia, PA‡	753	673	1.132	5.1	0.508

* M, most likely; S, secondary; SO, secondary that overlaps with other more likely cluster; RR, relative risk within the cluster compared with the rest of the Northeast; LLR, log likelihood ratio.

† Includes Staten Island, as well as the same Pennsylvania and New Jersey counties as the larger New York City-Philadelphia cluster (figure 5), with the exception of Northampton, Sussex, Passaic, Bergen, Atlantic, and Gloucester.

‡ In addition to the five Philadelphia counties shown in figure 5, this area also includes Ocean, Mercer, Atlantic, and Monmouth counties.

When a cluster of deaths cannot be dismissed as a chance occurrence, we need to ask what may be the underlying causal mechanisms. It is most natural to look first at some of the known or hypothesized risk factors. In this study, we were able to adjust for four such factors: age, race, urbanicity, and parity. The age and race information was available for each individual. However, urbanicity was available only at the county level, so everyone in the county is classified in the same category. For parity, we had only the average for each county, and the relative risks were obtained from an unrelated case-control study (13). Hence, the adjustment for these factors in our analysis is necessarily imprecise.

How robust is the analysis to the estimation of the effect of parity on breast cancer mortality? As can be seen from table 1, part B, the likelihood ratio for the Long Island cluster is actually higher when taking parity into account, due to a higher level of parity there. This means that no matter how much parity reduces the risk of breast cancer, it cannot explain the excess of breast cancer mortality on Long Island. In the New Jersey-Philadelphia cluster, parity explains about one tenth of the excess in our model. Even if our estimate of the protective effect of parity is only half the true reduction in risk (e.g., 17–18 percent reduction per child), then parity would still account for less than 20 percent of the mortality excess, and the cluster would still be significant.

There are many other known or hypothesized risk factors for breast cancer that we were unable to include in this population-based analysis. These include age at menarche, age at menopause, age at first birth, breastfeeding, country of birth, genetic disposition/family history, alcohol consumption, access to health care, and various environmental factors. For these to explain the existence of a cluster, they not only must be true risk factors, but the population at higher risk also must be proportionally more abundant where the cluster is detected.

Old age at menarche and young age at menopause have been shown to reduce the risk of breast cancer (24). Although there are some regional differences within the United States, they do not contribute to an explanation of why rates are high in the Northeast compared with the rest of the country (25). Since we do not know the regional variation within the Northeast, however, we cannot tell whether they might partly explain the observed cluster.

Young age at first full-term pregnancy has also been shown to have a protective effect (24). Since this factor is correlated with parity (13), some of its effect

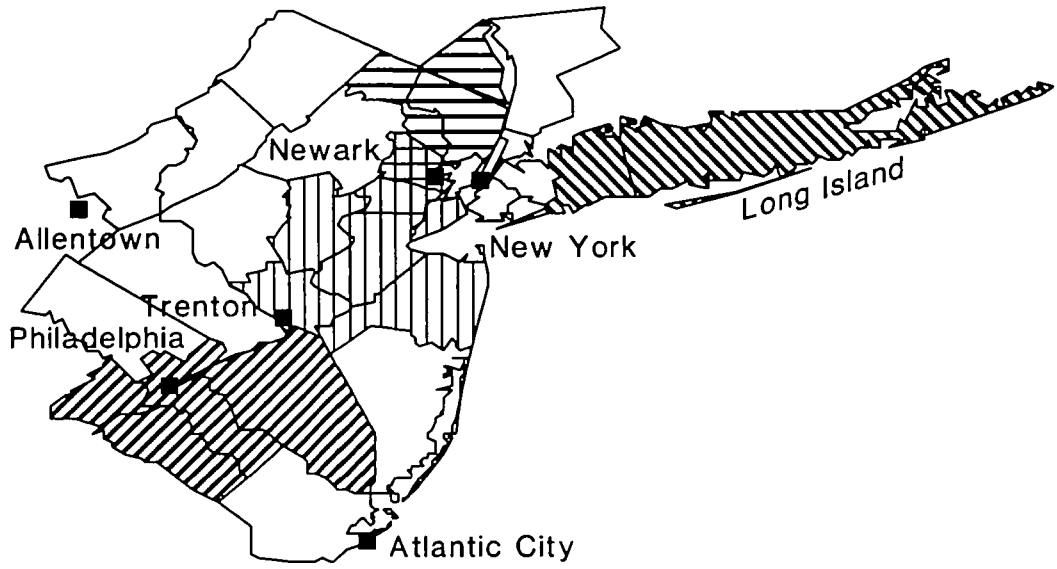

FIGURE 5. A close-up of the most likely cluster for breast cancer among women in the Northeast United States during 1988–1992, with four subclusters that are significant on their own strength. Two of the latter are overlapping, with Essex, New Jersey, as a common county.

was probably accounted for in the parity-adjusted analysis. However, young age at first full-term pregnancy also exhibits an independent effect (13) for which we could not adjust. Others have reported that age at first full-term pregnancy is greater in the Northeast than in the rest of the country and that this may explain some of the Northeast mortality excess (14, 25). We do not know its more local distribution and hence, whether it would also explain some of the excess in the New York-Philadelphia area.

Studies have reported that breastfeeding children reduces a woman's risk of breast cancer (24, 26) and that this is an independent effect after adjusting for parity (13). Breastfeeding rates are known to vary between countries (26–28), but we have no information regarding local variation of breastfeeding practices in the Northeast.

In a global comparison, breast cancer incidence is high in North America and northern Europe, medium in southern Europe and Latin America, and low in Africa and Asia (29–31). It has been shown that women migrating from Asia or Latin America bring with them some of their lower risk of breast cancer when they move to the United States (32–34). The fact that Queens (New York), Kings (Brooklyn, New York), and Hudson (New Jersey) counties have the largest percentage of foreign-born persons in the Northeast, between 29 and 36 percent (16), might explain why these counties have a lower breast cancer mortality than the surrounding suburbs. At the same time, immigration from other countries probably does not explain the general excess in the New York City-Philadelphia metropolitan area, since most of those counties have a larger percentage of foreign-born individuals than the Northeast average (16).

About 0.5 percent of US women are estimated to have a genetic mutation, increasing their risk of breast cancer and causing approximately 5 percent of all cases (35). Such mutations might be more common in the area of the most likely cluster, especially considering that occurrence of one of the specific mutations has been observed mostly in Ashkenazi Jews (36), who reside relatively frequently in and around New York City.

The relation between alcohol consumption and breast cancer is at most modest (37–40). Comparing per capita alcohol consumption between states, we find that Pennsylvania and New York are the lowest in the Northeast and that New Jersey is seventh of 12 (41). In a study of alcohol-related admissions during 1989 among Medicare patients aged 65 years and older, Pennsylvania, New York, and New Jersey all had lower rates than any of the other northeastern states (41). These factors combined do not make alcohol a strong potential candidate for explaining the observed excess of mortality in the New York City-Philadelphia area.

Access to health care, both in terms of mammography and treatment, is a factor that may influence breast cancer survival and hence breast cancer mortality. This is a potential explanation for why blacks have a higher mortality rate, especially in light of the evidence that incidence rates are about the same (for ages <50 years) or lower (for ages ≥ 50 years) among black than white women (1). Hence, this is one possible explanation for some of the excess breast cancer mortality among young women in the District of Columbia. However, substantial parts of the New York City-

Philadelphia cluster consist of affluent urban suburbs with good access to health care (16).

A number of environmental factors have been proposed as possible causes of increased risk for breast cancer. These include ionizing radiation (42), organochlorines such as dichloro-diphenyl-trichloro ethane (DDT), 1,1-dichloro-2,2-bis (*p*-chlorophenyl) ethylene (DDE), and polychlorinated biphenyls (PCBs) (43, 44), electromagnetic fields (45–47), polycyclic aromatic hydrocarbons (PAHs) (43, 48), excessive exposure to light (47, 49), lack of solar radiation (50, 51), and hair dyes (42). Only ionizing radiation is generally considered an established risk factor. The rest are uncertain, with inconclusive evidence from studies undertaken so far. Since many of these environmental factors are likely to have an uneven spatial distribution, we cannot exclude them as possible explanations for the detected cluster, although we do not know that any are excessively common in the New York City-Philadelphia metropolitan area.

It is important to put the magnitude of the excess risks observed in this study into perspective. The New York City-Philadelphia metropolitan area has a 7.4 percent excess (odds ratio 1.074) compared with the rest of the Northeast, which in turn has a 12.4 percent excess compared with the rest of the country. This means an excess of 20.6 percent when comparing the cluster area to the rest of the United States outside the Northeast.

The significant cluster among women younger than 50 years in the District of Columbia disappears after adjusting for the fact that it has a large black population and that breast cancer mortality is relatively high among young black women. Hence, the important problem to focus on might not be why the rates are so high in the District, but rather why there is an excess of mortality among young black women. With the exception of the District of Columbia, there is no evidence of different clusters in the two different age groups.

A few statistical points merit special mention. The analysis should be seen in the context of the whole area under study. It makes no sense to ascribe a *p* value to a specific cluster without relating it to the size of the area under study, in our case the Northeast.

The fact that we are dealing with data aggregated to the county level means that we do not have enough resolution to efficiently detect clusters affecting only a small part of a county. This could be overcome by conducting the analysis on a census tract or block group level, again applying the spatial scan statistic. Although it would be cumbersome to obtain such data for the whole of the Northeast, it might be of interest to conduct such an analysis for parts of the New York City-Philadelphia metropolitan area.

Concerning a secondary cluster that is not significant, it is important to keep in mind that lack of significance could be because the result has occurred truly by chance because the test is conservative or because the increased risk as well as the power of the test is too low to detect it. For example, in Buffalo, New York, with 1,280 expected cases, there is 80 percent power to detect an excess risk of 14 percent. For a smaller area like Hancock County, Maine, with 53 expected cases, an excess risk of 76 percent is needed to obtain the same power.

Our geographic analysis is based on mortality data and residence at time of death. Mortality can be influenced by access to primary and secondary medical care, quality of treatment, and posttreatment surveillance. Differences in mortality rates in different areas can result from differences in the geographic distribution of these clinical variables as well as from differences in risk factors for disease incidence. In addition, there is a considerable time lag between exposure to many of these risk factors and time of death, when a substantial proportion of individuals may have migrated to another geographic area. Therefore great caution should be exercised in interpreting the results of geographic mortality studies, and in particular, efforts to ascribe the cause of a mortality cluster to some local environmental exposure should be placed under rigorous scrutiny.

In summary, we have identified a statistically significant excess of breast cancer mortality in the New York-Philadelphia metropolitan area, including Long Island. We have accounted for some of the known and hypothesized risk factors for breast cancer mortality. Some were found to be unlikely explanations for the excess, and data were unavailable to evaluate others. The latter group includes most notably age at first birth, age at menarche, age at menopause, access to clinical care, breastfeeding, genetic mutations, and environmental factors.

More generally, we found the spatial scan statistic to perform a useful function in this analysis, enabling us to evaluate more reliably the strength of evidence for the reported Long Island cluster. The method should prove extremely helpful when confronting new reports of disease clusters.

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REFERENCES

1. Miller BA, Gloeckler Ries LA, Hankey BF, et al, eds. SEER cancer statistics review, 1973–1990. Bethesda, MD: National Institutes of Health, 1993. (NIH publication no. 93–2789).
2. Pickle LW, Mason TJ, Howard N, et al. Atlas of US cancer mortality among whites: 1950–1980. Washington, DC: Department of Health and Human Services, 1987. (DHHS publication no. (NIH) 87–2900).
3. Riggan WB, Van Bruggen J, Acquavella JF, et al. US mortality rates and trends, 1950–1979. Washington, DC: National Cancer Institute/Environmental Protection Agency, 1983. (EPA publication no. 600/1–833–015a).
4. Jenks S. Researchers to comb Long Island for potential cancer factors. J Natl Cancer Inst 1994;86:88–9.
5. Lewis-Michi EL, Melius JM, Kallenbach LR, et al. Breast cancer risk and residence near industry or traffic in Nassau and Suffolk counties, Long Island, New York. Arch Environ Health 1996;51:255–65.
6. Wittenberg C. Long Island breast cancer studies move forward. J Natl Cancer Inst 1994;86:1501–3.
7. US Congress. Public law 103–43. June 10, 1993.
8. Hjalmars U, Kulldorff M, Gustafsson G, et al. Childhood leukemia in Sweden: using GIS and a spatial scan statistic for cluster detection. Stat Med 1995;15:707–15.
9. Kulldorff M. A spatial scan statistic. Communicat Stat Theory Methods (In press).
10. Kulldorff M, Nagarwalla N. Spatial disease clusters: detection and inference. Stat Med 1995;14:799–810.
11. Gail M, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989; 81:1879–86.
12. Kelsey JL, ed. Breast cancer. Epidemiol Rev 1993;15:1–263.
13. Layde PM, Webster LA, Baughman AL. The independent associations of parity, age at first full time pregnancy, and duration of breastfeeding with the risk of breast cancer. J Clin Epidemiol 1989;42:963–73.
14. Blot WJ, Fraumeni JF, Stone BJ. Geographic patterns of breast cancer in the United States. J Natl Cancer Inst 1977; 59:1407–11.
15. Nacsa PC, Burnett WS, Greenwald P, et al. Population density as an indicator of urban-rural differences in cancer incidence, upstate New York, 1968–1972. Am J Epidemiol 1980;112: 362–75.
16. Slater CM, Hall GE, eds. 1993 county and city extra: annual metro, city and county data book. Lanham, MD: Berman Press, 1992.
17. US Bureau of the Census. Statistical abstracts of the United States. 111th ed. Washington, DC: GPO, 1991.
18. Dwass M. Modified randomization tests for nonparametric hypotheses. Ann Math Stat 1957;28:181–7.
19. Kulldorff M, Rand K, Williams G. SaTScan, version 1.0, program for the space and time scan statistic. Bethesda, MD: National Cancer Institute, 1996.
20. Proceedings of the National Conference on Clustering of Health Events. Am J Epidemiol 1990;132:S1–202.
22. Lawson A, Waller L, Biggeri A, eds. Spatial disease patterns. Stat Med 1995;14:2289–501.
22. Jacquez GH, ed. Conference on Statistics and Computing in Disease Clustering, British Columbia, Canada, July 21–22, 1994. Stat Med 1996;15:681–952.
23. Butler MA, Beale CL. Rural-urban continuum codes for metro and non-metro counties. Washington, DC: Economic Research Service, US Department of Agriculture, 1993. (AGES publication no. 9425).
24. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47.
25. Sturgeon SR, Schairer C, Gail M, et al. Geographic variation in mortality from breast cancer among white women in the United States. J Natl Cancer Inst 1996;87:1846–53.
26. UK National Case-Control Study Group. Breast feeding and risk of breast cancer in young women. Br Med J 1993;307: 17–20.
27. Ekbom A, Hsieh CC, Ltichopoulos D, et al. Breast-feeding and breast cancer in the offspring. Br J Cancer 1993;67:842–5.
28. Ereudenheim JL, Marshall JR. Re: Exposure to breastmilk and risk of breast cancer, authors reply. (Letter). Epidemiology 1995;6:199–200.
29. Kelsey JL. Breast cancer: magnitude of the problem and descriptive epidemiology. Epidemiol Rev 1993;15:7–16.
30. Kurihara M. Cancer mortality statistics in the world, 1950–1985. Nagoya: University of Nagoya Press, 1989.
31. Parkin DM, Muir CS, Whelan SL, et al, eds. Cancer incidence in five continents, vol 6. Lyon: IARC, 1992. (IARC scientific publication no. 15).
32. Rosenwaike I. Cancer mortality among Puerto Rican-born residents in New York City. Am J Epidemiol 1984;119:177–85.
33. Thomas DB, Karagas MR. Cancer in first and second generation Americans. Cancer Res 1987;47:5771–6.
34. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 1993;85:1819–27.
35. Baker SG, Freedman LS. Potential impact of genetic testing on cancer prevention trials, using breast cancer as an example. J Natl Cancer Inst 1995;87:1137–44.
36. Struewing JP, Abeliovich D, Peretz T, et al. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nature Genet 1995;11:198–200.
37. Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. Cancer Causes Control 1994;5:73–82.
38. Rosenberg L, Metzger LS, Palmer JR. Alcohol consumption and risk of breast cancer: a review of the epidemiologic evidence. Epidemiol Rev 1993;15:133–44.
39. Roth HD, Levy PS, Shi L, et al. Alcoholic beverages and breast cancer: some observations on published case-control studies. J Clin Epidemiol 1994;47:207–16.
40. Schatzkin A, Longnecker MP. Alcohol and breast cancer. Cancer 1994;74:1101–10.
41. Adams WL, Yuan Z, Barboriak JJ, et al. Alcohol-related hospitalizations of elderly people: prevalence and geographic variation in the United States. JAMA 1993;270:1222–5.
42. John EM, Kelsey JL. Radiation and other environmental exposures and breast cancer. Epidemiol Rev 1993;15:157–62.
43. Davis DL, Bradlow HL, Wolff M, et al. Medical hypothesis: xenoestrogens as preventable causes of cancer. Environment Health Perspect 1993;101:372–7.
44. Key T, Reeves G. Organochlorines in the environment and breast cancer. Br Med J 1994;308:1520–1.
45. Cantor KP, Dosemeci M, Brinton LA, et al. Re: Breast cancer mortality among female electrical workers in the United States. (Letter). J Natl Cancer Inst 1995;87:227–8.
46. Loomis DP, Savitz DA, Ananth CV. Breast cancer mortality among female electrical workers in the United States. J Natl Cancer Inst 1994;86:921–5.
47. Stevens RG. Electric power use and breast cancer: a hypothesis. Am J Epidemiol 1987;125:556–61.
48. Morris JJ, Seifter E. The role of aromatic hydrocarbons in the genesis of breast cancer. Med Hypotheses 1992;38: 177–84.
49. Hahn RA. Profound bilateral blindness and the incidence of breast cancer. Epidemiology 1991;2:208–10.
50. Garland FC, Garland CF, Gorham ED, et al. Geographic variation in breast cancer mortality in the United States. Prevent Med 1990;19:614–22.
51. Gorham ED, Garland FC, Garland CF. Sunlight and breast cancer incidence in the USSR. Int J Epidemiol 1990;19:820–4.