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Over the past several years, there has been considerable concern and controversy about a potential brain cancer cluster in a Stillwater neighborhood. This concern was elevated to a larger scale when a WCCO Dimension report entitled, "Neighborhood Killer" aired on November 4, 1994.

Over the last decade, the Minnesota Department of Health (MDH) has dealt with nearly 1,100 similar concerns. During the course of these interactions, we have learned much about the relative importance of the technical and psychosocial components of these concerns. Our experience indicates that technical responses to these mostly non technical concerns are often not well received. However, we continue to pursue analytic perspectives on these concerns in the hope that they may assist in determining their public health significance.

The concern that was highlighted by the Dimension report involved the occurrence of ten brain cancers during a ten-year period in a population of approximately 6,000 people. The report quantified this rate as approximately three times the national average. The level of this reported risk, coupled with the fact that several of the brain cancers had occurred in children, exacerbated fears among persons in the Stillwater community. However, the estimate of risk was not meaningful; in fact, it was misleading and was generated by the investigators succumbing to the well-documented but, nonetheless, seductive pitfalls of cancer cluster statistics.

The major methodologic error incorporated into the above analyses is referred to as the "Texas Sharpshooter Syndrome." The Texas sharpshooter fires bullets into a barn wall and then draws his target around the bullet holes. The analogy to disease occurrence is observing a number of like conditions in an artificially circumscribed area and then asking, is this occurrence unusual? The approximation of risk using existing morbidity or mortality data assumes that the index population is drawn at random from the overall population from which the rates were derived. Applying standard statistical procedures to populations known a priori to be unusual invalidates the laws of probability and renders resultant estimates of risk as misleading. This approach is almost equivalent to selecting one's lottery numbers after the lottery is completed. That is, chance or probability has little to do with the outcome.

Table 1 contains data that illustrate this concept. This table contains indirectly standardized brain cancer rates - referred to as standardized morbidity ratios (SMRs) for various populations in the Stillwater region. The SMR is calculated using age-specific brain cancer incidence rates for the state (1988-1992) derived from the Minnesota Cancer Surveillance System (MCSS). For the entire county, there is a 20% deficit of brain cancer compared to the state. As the index population becomes more circumscribed, the SMR increases. The city of Stillwater, which contains the neighborhood of 6,000 people where the perceived excess

Table 1. Effect of Decreasing Index Population on Indirectly Standardized Brain Cancer Rate (Males and Females Combined)

Population	SMR*
Washington County; 5 years, all ages	0.8
Stillwater Zip Code; 5 years, all ages	1.3
City of Stillwater; 5 years, all ages	1.6
Index Neighborhood; 7 Years, All Age Groups	3.4
Index Neighborhood; 4 Years and 6 Age Groups in which Cases Occurred	14.8

*Standardized Morbidity Ratio (vs. State of Minnesota)

occurred, had a 60% increased risk. Considering just the 6,000 person neighborhood for all age groups and the complete seven-year period (corresponding to available MCSS data), the SMR was 3.4; very similar to the Dimension report's finding. However, if we shrink the target population to include only those age groups and years for which brain cancers occurred in the 6,000 person neighborhood, the SMR becomes 14.8. Therefore, depending on how tightly the (index) population is circumscribed, the risk ranges from a 20% deficit to a 1,380% excess.

This range of brain cancer risk exemplifies another aspect of cancer cluster statistics. In addition to the nonrandom nature of the reports of cancer clusters, one must also account for the inherently large variability of the incidence of relatively rare cancers. To obtain an insight into the extent of the variability, consider the age-standardized data in Figure 1 on brain cancer incidence for 1988-1992 based on female rates for Minnesota counties. Similar distributions are seen for males. Over the five-year period, no brain cancers were diagnosed in female residents of Grant, Isanti, Lake of the Woods, Mahnomen, Pipestone, and Traverse counties; yet a total of 8.6 was expected based on statewide MCSS data. Scott County had nearly an 85% deficit and Red Lake a 350% excess. No county had exactly the "average" amount of brain cancer, and one is struck by the fact that the concept of the "normal" amount of brain cancer must be approached cautiously.

Another perspective on the variability of the incidence of relatively rare cancers is given in Table 2. According to data from the MCSS, the SMRs for brain cancer in the city of Stillwater males and females compared to the state are 1.47 and 1.84, respectively. There are 14 counties where the male SMR exceeded 1.47 and nine counties where the female SMR for brain cancer exceeded Stillwater's female rate. Thus, over the five-year period, 1988-1992, 23 county rates exceeded the Stillwater rates. The frequency with which large SMRs occurs is informative and assists in understanding that on a population basis, "excess risks" of this magnitude occur frequently. It also is interesting to note that in the counties where the male rates were large, the female brain cancer rate was nominal, and in the counties where the female rates were high, the male brain cancer rate was identical to the overall state average. This observation reinforces an important aspect of cancer cluster statistics; on a population basis, the finding of "unusually" high rates is to be expected and by itself is not a cause for concern.

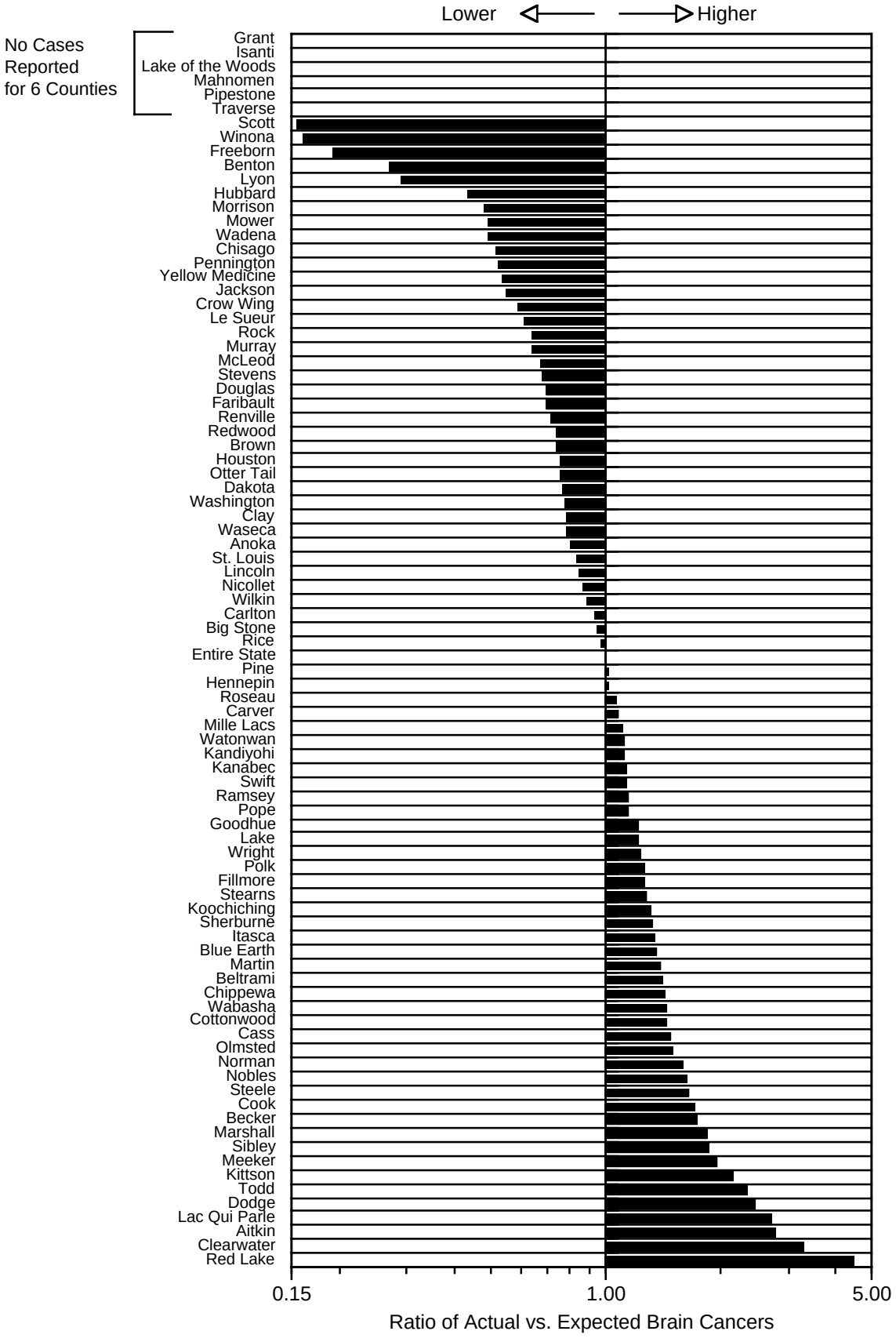
The calculation of a meaningful probability requires a population-based statistic that accounts for the variability and nonrandom nature of the observation. In the statistical literature, this is referred to as controlling for multiple comparisons. For example, if 100 comparisons are being made using $p < 0.05$ as the definition of "statistically significant," one should expect five of the comparisons to be statistically significant by chance alone. The same concept applies to cluster analyses where the entire population is implicitly at risk. Therefore, the question becomes how many 6,000 person "communities" in Minnesota would experience ten or more brain cancers in any ten-year period? For simplicity, let's consider the Minnesota population of 4.3 million

Table 2. 1988-1992 County Populations with Indirectly Standardized Brain Cancer Rates Exceeding Stillwater's Males (1.47) and Females (1.84)

Males			Females		
County	N	SMR	County	N	SMR
McLeod	9	1.52	Sibley	4	1.86
Beltrami	9	1.53	Meeker	6	1.95
Clay	13	1.53	Kittson	2	2.15
Goodhue	12	1.56	Todd	8	2.35
Koochiching	6	1.78	Dodge	5	2.44
Nicollet	9	1.88	LacQuiParle	4	2.72
Pipestone	4	1.88	Aitkin	6	2.77
LacQuiParle	4	1.98	Clearwater	4	3.28
Benton	10	2.00	Red Lake	3	4.47
Dodge	6	2.11			
Pope	5	2.11			
Norman	5	2.79			
Red Lake	3	3.14			
Grant	5	3.58			
*Total**	100	1.84	*Total*+	42	2.45

*SMR for females = 1.09
+SMR for males = 1.00

BRAIN CANCER RATES BY COUNTY COMPARED TO STATE: FEMALES, 1988-1992



partitioned into non-overlapping groupings of 6,000 each. There would be 729 such groups of 6,000 people. Using MCSS data to estimate a statewide rate and the Poisson probability model yields a probability of 0.0041 that any single 6,000 person community would experience ten or more brain cancers in a ten-year period. Therefore, in any ten-year period, three Minnesota communities of 6,000 people (729 x .0041) would expect ten or more brain cancers. Thus, an incidence of brain cancer at the level that Stillwater has experienced is expected several times each decade in the state. In reality, there are almost a limitless number of aggregations or groups of 6,000 people that we could define based on residence, workplace, church group, school affiliation, etc. Thus, the number of potential clusters of this magnitude that could come to recognition is substantially larger than this.

An additional concern expressed in Stillwater was the occurrence of brain cancer in a married couple. Again, this appears to be an extremely improbable event. Data from the MCSS provide a different perspective. The lifetime risk of developing a brain cancer after age 20 is greater than 1 percent (1.06%). This estimate of lifetime risk incorporates the current age-specific brain cancer incidence rates for the state as well as the age-specific life expectancy of Minnesotans. If the probability that a single individual will develop a brain cancer after age 20 is 1/100, then the probability that any two individuals will both develop brain cancer in their lifetimes is 1/10,000. An often quoted statistic is that the probability of a home being hit by lightening is 1/100,000, approximately ten times less likely than a married couple both developing brain cancer. From a purely analytic point of view, the occurrence of two brain cancers during the lifetime of a household is not that unusual.

Collateral analyses demonstrated that the distribution of histologies (astrocytoma, glioma, meningioma, and neurilemmoma) was statistically indistinguishable between cancers occurring in the Stillwater area and the state as a whole. A difference in cell type would have increased suspicions about the possibility of a common etiologic experience, while not finding a difference should have been reassuring.

A final statement on the statistical realities of dealing with cancer clusters addresses the usefulness of in-depth studies involving a small number of subjects. Statistical power is the probability that if a risk exists at a certain level, the study would be able to detect it. For the situation with 10 cases and 40 controls (considered the optimal case/control mix), a case-control study would be able to detect relative risks greater than 15-fold less than 80% of the time for any reasonable postulated population level of exposure to the risk factor. This level of risk exceeds that of smoking and lung cancer or benzene and leukemia, for example. Although there are few established risk factors for brain cancers, the magnitude of the suspected risks based on large studies are in the range of 1.5-fold to 2-fold; less than one-tenth of what could be detected with the limited data based on 10 cases and 40 controls. It is through the conduct of large, well designed studies that we will learn more about the etiology of brain cancer.

On the basis of the statistical and epidemiologic evidence, the MDH attempted, but did not succeed, in reassuring some citizens of Stillwater and their civic leaders that nothing unusual was going on and that additional study was not needed. As the debate and controversy continued, substantial concerns were expressed about a number of environmental quality issues. Whenever concerns about environmental exposures are elevated either in a workplace or a community, it is important to review existing regulatory data to reassure, if possible, the concerned population that their current environmental quality is protective of their health. Findings from this review cannot exonerate or implicate any reasons for the cancer occurrence. But, abstract and impersonal statistical analyses are not satisfying, and the community concern must be dealt with as an issue unto itself. For further questions on this situation or other cancer clusters, please contact the Minnesota Cancer Surveillance System at (612) 623-5216.