# Performance of Cancer Cluster Q-statistics for Case-Control Residential Histories


Jaymie R Meliker

Graduate Program in Public Health, Department of Preventive Medicine
Consortium for Inter-Disciplinary Environmental Research (CIDER)
Stony Brook University (SUNY)

Co-investigators: Chantel D. Sloan[1], Geoffrey M. Jacquez[2], Carolyn M Gallagher[1], Mary H Ward[3], Rikke Baastrup[4], Ole Raaschou-Nielsen[4]

[1]Stony Brook University (SUNY), [2]BioMedware, Inc., [3]US National Cancer Institute, [4]Danish Cancer Society



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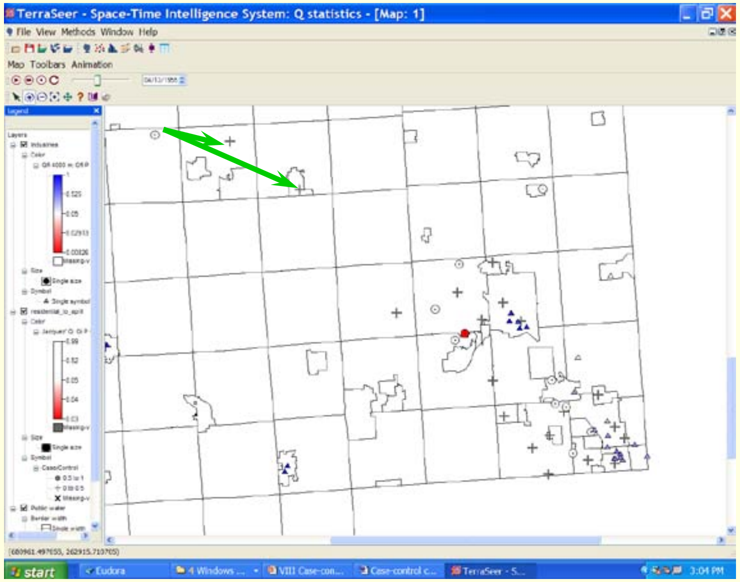
# Statement of Problem

- Goal: Use cancer clusters to generate valuable hypotheses for diseases with largely unknown etiology
  - Most cancer cluster investigations ignore disease latency, using locations at time of diagnosis or death
  - Recent statistical advances have begun to investigate clustering in mobile populations
    - Spatial generalized additive models
    - Jacquez’s Q-statistics
  - Few performance evaluations have been conducted on these new statistics
    - Multiple testing through time is a large concern

# Q-statistics for Case-Control Populations

- Rely on a matrix representation that describes how spatial nearest neighbor relationships change through time
- Space-time extension of Cuzick-Edwards' Test
- User must specify number of nearest neighbors
  - Neighbors that are cases are then counted around each case
    - Repeated every time there is a change in location



# Q-statistics cont'd

- Different versions:
  - $Q_{ikt}$: When and where is there local clustering around a case?
    - Assesses clustering around each case every time there is a change in residence
  - $Q_{kt}$: When is there global clustering of cases?
    - Assesses global clustering at each time slice
  - $Q_{ik}$: Is there clustering surrounding a case, on average, throughout his/her mobility history?
    - Assesses clustering around a person through time; Sum of $Q_{ikt}$
  - $Q_k$: Is there global clustering, overall across all cases, in the residential histories?
    - Assesses whether, in general, clustering is present

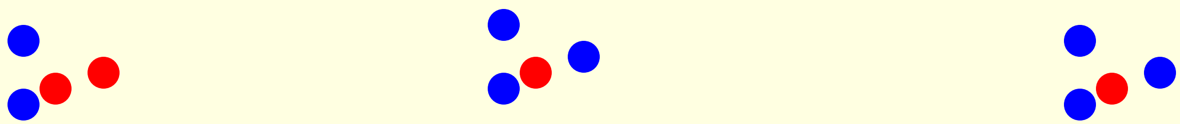
Focused versions are also available

# Procedure for Evaluating Significance

- Step 1. Calculate Q-statistic (Q*) for the observed data.
- Step 2. Reallocate the case-control identifier $c_i$ over the participants using approximate randomization, and calculate Q-statistic:
  - consistent with the desired null hypothesis
  - holding the observed number of cases fixed
  - holding the locations and attributes fixed

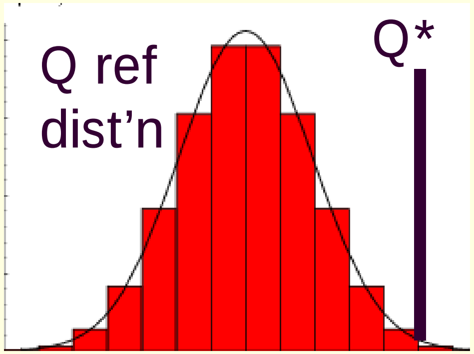
Repeat many times (e.g., 999) to create a reference distribution

● Case
● Control



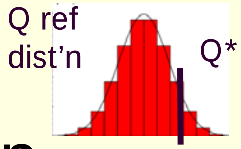
Observed | Randomization #1 | Randomization #2

- Step 3. Compare Q* to this reference distribution to evaluate the statistical probability of observing Q*.



# Comments on Q-statistics and Evaluating Significance

- Must run many randomizations to resolve small p-values




  - Time-consuming → lessens likelihood of p-value correction such as false discovery rate[1]

- Can we identify a p-value to use as a cut-off for significance (in light of multiple testing)?

- Can we determine which Q-statistic(s) to use to identify a cluster?

[1]Caldas de Castro M, Singer BH. Controlling the false discovery rate: A new application to account for multiple and dependent tests in local statistics of spatial association. Geogr Anal 2005; 38: 180-208.

# Analytic Plan

- Blank slate: many approaches could be used
- Simulated clusters were created to examine Q-statistics’ performance
  - Used actual mobility histories from studies of NHL in US, and testicular cancer in Denmark
- Examine whether Q-statistics identify simulated clusters, and differentiate them from false positives

# Simulated Clusters

- Iowa
- California
- Central Denmark

- Reflected a variety of space-time cluster characteristics

Table 1. Characteristics of the Cluster Regions

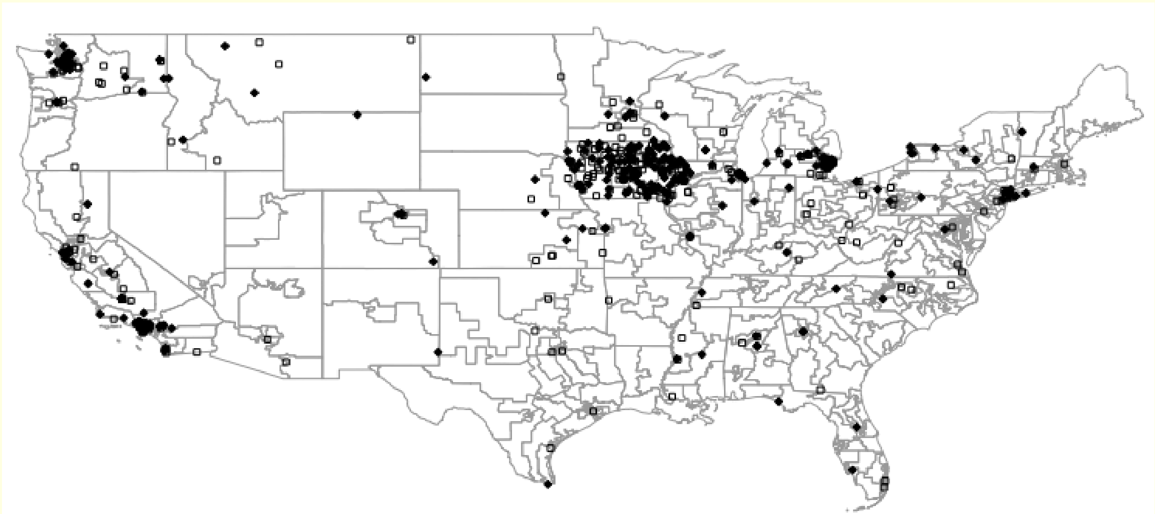
| | | Number of Cases | Cluster Size[a] | Cluster Density[b] | Case Mobility[c] |
|---|---|---|---|---|---|
| US Case-Control Dataset, Clusters Created in 1960 | 1000 residential histories | | | | |
| | | 5 | 1.0% | 100% | 99% |
| | | 12 | 2.4% | 100% | 90% |
| | Iowa | 18 | 3.6% | 95% | 83% |
| | | 27 | 5.4% | 90% | 84% |
| | California | 43 | 8.6% | 63% | 47% |
| | 2378 residential histories | | | | |
| | | 6 | 0.3% | 75% | 87% |
| | Iowa | 14 | 0.6% | 70% | 80% |
| | | 23 | 1.0% | 66% | 84% |
| | | 33 | 1.4% | 69% | 78% |
| Danish Case-Control Dataset, Clusters Created in 1971 | 6594 residential histories | | | | |
| | | 11 | 0.3% | 89% | 50% |
| | | 41 | 1.1% | 84% | 74% |
| | | 90 | 2.6% | 82% | 70% |
| | | 127 | 3.7% | 81% | 80% |

[a]Cluster Size: Percent of cases in cluster out of total number of cases in study

[b]Cluster Density: Percent of cases in cluster region out of total number of cases and controls in cluster region from 1960-1975 in US dataset, 1971-1980 in Danish dataset.

[c]Case Mobility: Percent of person-years of cases in cluster region out of maximum possible person-years from 1960-1975 in US dataset, 1971-1980 in Danish dataset

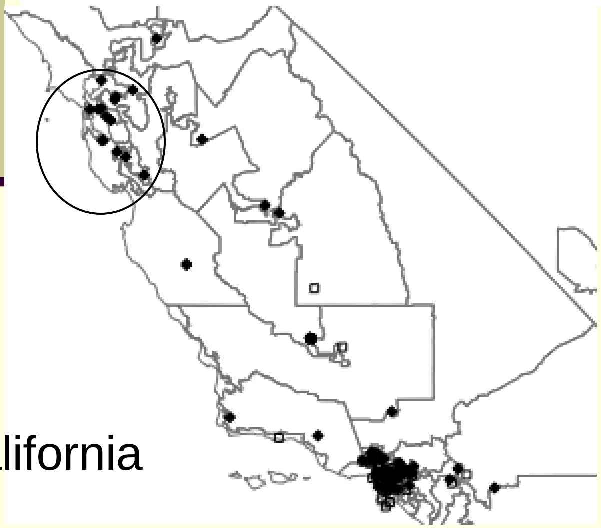
# US Cluster Regions



Case

Control

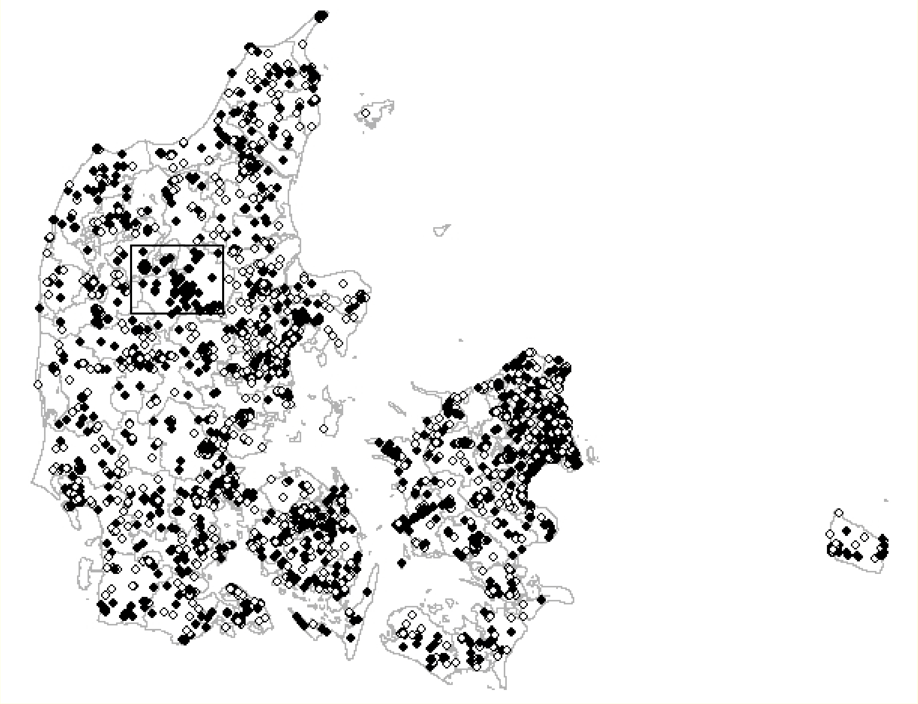
Locations in 1960



California

Iowa

# Danish Cluster Region



Locations in 1971

# Results - Summary

- Using k=5, 10, 15 (and 20)
- Global $Q_k$: significant (p=0.05) for only 1 of the 31 analyses of simulated clusters
- Local $Q_{ikt}$: significant (p=0.01 or smaller) even for very small clusters, but unable to differentiate true clusters from false positives
- Global $Q_{kt}$: time-slice global; also conservative like $Q_k$
- Local $Q_{ik}$: best able to identify true clusters and differentiate them from false positives.
- Combining $Q_{ik}$ and $Q_{ikt}$ showed best performance

# Local Clusters Significant for both $Q_{ik}$ (p=0.001) and $Q_{ikt}$ (p=0.05)

| | Cluster Region | Number of Cases in Cluster | No. of Nearest Neighbors | True Positives[a] | False Positives[b] | Max. Size of False Positive Cluster[c] |
|---|---|---|---|---|---|---|
| US Case-Control Dataset | Iowa, 500 cases, 500 controls | N=0 (purely random) | k=5 | N/A | 0 | 0 |
| | | | k=10 | N/A | 1 | 1 |
| | | | k=15 | N/A | 0 | 0 |
| | | N=5 | k=5 | 0 | 2 | 1 |
| | | | k=10 | 0 | 1 | 1 |
| | | | k=15 | 0 | 1 | 1 |
| | | N=12 | k=5 | 0 | 0 | 0 |
| | | | k=10 | 0 | 1 | 1 |
| | | | k=15 | 0 | 0 | 0 |
| | | N=18 | k=5 | 1 | 0 | 0 |
| | | | k=10 | 5 | 0 | 0 |
| | | | k=15 | 2 | 0 | 0 |
| | | N=27 | k=5 | 11 | 0 | 0 |
| | | | k=10 | 16 | 0 | 0 |
| | | | k=15 | 11 | 1 | 1 |
| | | | K=20 | 0 | 0 | 0 |
| | California, 500 cases, 500 controls | N=43 | k=5 | 0 | 0 | 0 |
| | | | k=10 | 2 | 1 | 1 |
| | | | k=15 | 0 | 0 | 0 |
| | California + Iowa, 500 cases, 500 controls | N=43 in Cal. N=27 in Iowa | k=10 | 6, in both Iowa and Cal. cluster regions | 0 | 0 |

Calif cluster:
Greater size,
lower density,
lower mobility

Each row presents results of one suite of Q-statistic analyses.

# Local Clusters Significant for both $Q_{ik}$ (p=0.001) and $Q_{ikt}$ (p=0.05) Cont'd

| Cluster Region | Number of Cases in Cluster | No. of Nearest Neighbors | True Positives[a] | False Positives[b] | Max. Size of False Positive Cluster[c] |
|---|---|---|---|---|---|
| Iowa, 1189 cases, 1189 controls | | k=5 | N/A | 2 | 1 |
| | N=0 (purely random) | k=10 | N/A | 1 | 1 |
| | | k=15 | N/A | 0 | 0 |
| | | k=5 | 0 | 3 | 2 |
| | N=5 | k=10 | 0 | 4 | 2 |
| | | k=15 | 0 | 4 | 1 |
| | | k=5 | 0 | 2 | 1 |
| | N=12 | k=10 | 0 | 2 | 1 |
| | | k=15 | 0 | 3 | 2 |
| | | k=5 | 3 | 2 | 2 |
| | N=18 | k=10 | 2 | 2 | 2 |
| | | k=15 | 1 | 3 | 2 |
| | | k=5 | 3 | 2 | 2 |
| | N=27 | k=10 | 3 | 3 | 2 |
| | | k=15 | 2 | 3 | 2 |

Did not perform as well differentiating clusters of smaller density from false positives.

Fairly consistent across choice of k-nearest neighbors.

Maximum size of false cluster never exceeds 2 individuals.

# Local Clusters Significant for both $Q_{ik}$ (p=0.001) and $Q_{ikt}$ (p=0.05) Cont'd

| | Cluster Region | Number of Cases in Cluster | No. of Nearest Neighbors | True Positives[a] | False Positives[b] | Max. Size of False Positive Cluster[c] |
|---|---|---|---|---|---|---|
| Danish Case-Control dataset | Viborg, Denmark, 3297 cases, 3297 controls | N=0 (purely random) | k=5 | N/A | 0 | 0 |
| | | | k=10 | N/A | 0 | 0 |
| | | | k=15 | N/A | 1 | 1 |
| | | | k=20 | N/A | 2 | 1 |
| | | N=11 | k=5 | 0 | 0 | 0 |
| | | | k=10 | 0 | 0 | 0 |
| | | | k=15 | 0 | 0 | 0 |
| | | | k=20 | 0 | 0 | 0 |
| | | N=41 | k=5 | 0 | 0 | 0 |
| | | | k=10 | 2 | 0 | 0 |
| | | | k=15 | 3 | 0 | 0 |
| | | | k=20 | 5 | 2 | 1 |
| | | N=90 | k=5 | 1 | 0 | 0 |
| | | | k=10 | 2 | 1 | 1 |
| | | | k=15 | 10 | 0 | 0 |
| | | | k=20 | 11 | 3 | 1 |
| | | N=127 | k=5 | 5 | 0 | 0 |
| | | | k=10 | 6 | 0 | 0 |
| | | | k=15 | 22 | 1 | 1 |
| | | | k=20 | 32 | 4 | 1 |

Performs better for larger clusters (but still not that large: size ~2-4%!).
Some differences across choice of k-nearest neighbors.

# Supplementary Analyses

- We ran FDR p-value adjustment on two of the simulated clusters (only 2 because time-consuming), using 9999 randomizations to create reference distribution

| Cluster Region | Number of Cases in Cluster | No. of Nearest Neighbors | True Positives[a] | False Positives[b] | Max. Size of False Positive Cluster[c] |
|---|---|---|---|---|---|
| Iowa, 500 cases, 500 controls | N=18 | k=10 | 5 | 0 | 0 |
| | FDR results | | 0 | 0 | 0 |
| | N=27 | k=10 | 16 | 0 | 0 |
| | FDR results | | 5 | 0 | 0 |

Suggests FDR is more conservative than combined $Q_{ik}$, $Q_{ikt}$ approach.

# Conclusions

- These are the first simulation analyses of Q-statistics and provide several insights into their performance:
  - Ability to detect cluster is sensitive to # of cases, cluster size, density, and population mobility
  - Global $Q_k$ is conservative, unable to detect localized clusters
  - Local $Q_{ik}$ and $Q_{ikt}$ were able to identify strong true clusters, occasionally without false positives, using a critical value for $Q_{ik}$ of $p=0.001$ and examining $Q_{ikt}$ ($p \leq 0.05$) only among those individual cases significant for $Q_{ik}$.
  - Choice of k not critical for these ranges of cluster characteristics

# Conclusions cont'd

- Recommendation from these limited simulations:
  - Begin analyses using k=10 or k=15 neighbors
  - A cluster of three significant ($Q_{ik}$, $Q_{ikt}$) individuals or larger can be called a true positive and is a good starting point for follow-up studies
    - Only useful for distinguishing dense, large, low mobility clusters
    - Misses smaller, lower density, less persistent clusters
    - At this stage in development of Q-statistics, we feel this is an acceptable compromise since it limits inquiry into false positives, thereby conserving limited resources for more thorough investigations of true clusters
    - Are implementing this rule set with these (non-simulated) datasets

# Future Work

- Generalizability uncertain: differences such as edge effects, population density, mobility patterns, case-control ratio, and cluster shape, size, and density
- At this juncture, we recommend user conducts similar sets of simulation analyses on each dataset to determine the best criteria (p-values, number of *k* nearest neighbors) for identifying true positive clusters
  - In time we hope a consistent rule set will emerge
  - Alternatively, could explore wide library of potential clusters, datasets, and geographies to derive more empirical rule-set(s) and sensitivity to cluster characteristics; this would take a very long time.
- Comparing results of Q-statistics with other recently developed methods for mobile populations (Sabel et al., 2009; Webster et al., 2006) is also important

# Thank you!

Contact details:
jrmeliker@gmail.com

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