Investigating Cancer Clusters: New Guidelines and Innovative Approaches

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Goals of This Presentation

• **What is a cluster and why do they occur?**
  – Some examples of clusters and their frequency
  – Why are clusters difficult to study?
    • Privacy concerns; adequacy of relevant data; many etiologies
  – Why can we learn by studying clusters?
    • Identify, evaluate (etiology), remediate

• **How have health departments responded?**
  – Respond to reported anomalies
    • How have traditional approaches worked?
      – In terms of epidemiologic goals?
      – In terms of addressing community concerns?

• **What are some newer approaches?**
  Proactive investigation—Surveillance
  Better data, more accurate exposures, biomonitoring
The Concept of a Cluster is very Broad
Cases DO Cluster! Some Examples

<table>
<thead>
<tr>
<th>CANCER CLUSTERS</th>
<th>DISEASE CLUSTERS</th>
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<tbody>
<tr>
<td>• Childhood Leukemia (several dozen studies since the 1950s)</td>
<td>• DBCP and male infertility (1977)</td>
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<td>• DES and vaginal cancer (1971)</td>
<td>• Kepone and neurotoxicity, infertility (1978)</td>
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<td>• Lymphoma (1970s)</td>
<td>• HIV/AIDS (1981)</td>
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<td>• BSME and lung cancer (1973)</td>
<td>• Thalidomide and phocomelia (1960s)</td>
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<td>• <strong>Vinyl chloride monomer and liver cancer (1974)</strong></td>
<td>• football players (1987)</td>
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<td>• Leukemia on Meadow St., CT (emfs--1980s)</td>
<td>• Legionnaires Disease and pneumonia (1976)</td>
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<tr>
<td>• Leukemia near Seascale Nuclear Facility (1980s)</td>
<td>• Minimata Disease (1950s)</td>
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<tr>
<td>• Cancer in NY Giants</td>
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What is a Disease (cancer) Cluster?

• Many definitions; for example:
  – “two or more cases occurring close together”
  – “5 cases representing at least a 5-fold increase in risk...seen by a single physician over a short period of time”
  – “occurrence of a greater than expected number of cases within a small geographic area and/or within a short period of time (i.e., 3-5 years)”

• Result: confusion and inconsistency!
A Typical Community Cluster Report

- A few to several dozen reported cases
- Cases aggregated, e.g., in space, time...
- No identified exposures
- No delineation of population at risk
- Limited demographic information of cases
- No residence history information
- No or limited surveillance data available
What Risk Factors Are Associated with Clusters?

• Common demographics (age, race, genetic)
  – genetic examples emerging (breast cancer)
• Common behavior (e.g., smoking, drinking)
• Common biological contact
  – several validated examples (Legionella, HIV)
• Common chemical exposures
  – workplace: several examples (VC, DBCP)
  – pharmaceuticals: few examples (DES, thalidomide)
  – “environment”: controversial
Woburn, MA: “A Civil Action”

- State Study (Parker and Rosen 1981)
  - 12 childhood cancers observed, 5.3 expected, \( p=0.008 \)
- Harvard study positive (1984)—controversial
  - 12 childhood leukemia cases where 5.3 expected
- New cases found after wells closed
  - MADPH study finds prenatal water exposure a risk (1996)

From DiPerna

As described in a book and A Major Motion Picture
Toms River, NJ: Reported CNS Cluster

- 1995-1996 Concern about cancer excess raised by nurse at CHOP
- Associations of prenatal exposure of female childhood leukemia with:
  - Drinking water, proximity to effluent pipeline, industrial air contaminants

From Asbury Park Press
Toms River, NJ: Investigation Details

- July 1997 State and Federal scientists begin $10 million study
- Results
  - No single risk factor identified as responsible
  - Associations of prenatal exposure with female childhood leukemia:
    - Parkway well field water: OR=5.0; 95% CI 0.8-31.2 (n=4: exp cases)
    - Ciba-Geigy ambient air: OR=6.4; 95% CI 1.1-37.8 (n=6)
    - Distance to Ciba-Geigy pipeline: OR=2.6; 95% CI 1.0-6.7 (n=11)
    - Some CNS elevations but few cases (unstable risk est.)
An Unreported Cluster
Manville, NJ

- Manville, NJ—excluding asbestos workers (Berry 1997)
  • 10-fold elevation of asbestosis in men (16 cases)
  • 20-fold elevation of asbestosis in women (8 cases)
  • UNREPORTED by community, physicians,…
What’s the Message

• Most clusters are identified by residents or physicians
• Health departments often are reluctant to investigate because of:
  – Resources required
  – Difficulty of determining etiology
  – Limited remediation possibilities
• Some likely never are reported
Why are Clusters Controversial?

Different Views of Clusters—1

Public—very concerned
  – personal tragedy
  – possible sentinel, possible prevention

Media—very newsworthy
  – human interest and tragedy
  – possible blame, politics
Why are Clusters Controversial?

Different Views of Clusters—2

Scientists—very uncertain
  - validity of etiologic inference
  - validity of statistical inference
  - reluctant to accept (study) unless certain

Government—need to be responsive
  - resource drain
  - opportunity for community education
Three modes of Cluster Response
Quataert (1999)

• **Public Health Action**
  – Reactive, empathetic, management

• **Monitoring**
  – Surveillance, early warning

• **Research Etiology**
  – Hypothesis driven, naive assumptions, seeks fundamental understanding
Responding to Cancer Cluster Reports in the US

- 1,100 to 1,650 per year
  - (Aldrich et al. 1991; Greenberg and Wartenberg 1991; Trumbo 2000)
  - Childhood leukemia is most frequent
  - Major come directly from the public
  - Reports likely biased (not data-based)

- Typical response is **FIND OUT WHY**
  - Few, if any, result in etiologic association
  - Huge drain of resources for health departments
  - Often result in much animosity from community

- Are there more effective response strategies?
  - Active surveillance → Public Health Action?
RESPONDING TO CLUSTER REPORTS

When Should We Investigate?

- Situation—among the worst
  - Region has “unusual” incidence
  - Pattern is persistent
  - Possible source of risk identified

When have we investigated clusters?

- Situation generates attention and pressure
  - Persistent residents
  - Media coverage
  - Political pressure

Is it surprising that many clusters do not provide convincing etiologic data?
Why Do I Believe It Is Important to Study Clusters?

IT IS GOOD PUBLIC HEALTH PRACTICE

• Address public concern—A Local Disease Excess
  – Clarify misconceptions—Allay unfounded concerns
  – Initiate study when concerns are well founded

• Encourage Remediation—Disease Prevention
  – Determine if situation is a sentinel of a larger problem
  – Identify unknown exposure situations

• Facilitate Scientific Discovery—Etiology
  – Identify new exposure-disease link
  – Identify new carcinogens
Revised CDC/CSTE Cluster Investigation Guidelines

• Greater recognition of community role and partnership
• More sensitive analytic tools
• Appreciation of role of surveillance/active investigation
• Greater emphasis on disease excess (SIR) rather than statistical p-value (sample size)
Revised CDC/CSTE Cluster Investigation Guidelines

• Basic 4 Step Process
  – Initial contact and response
  – Assessment
  – Determine feasibility of Conducting an epidemiologic study
  – Conduct epidemiologic study

• Ongoing communication and collaboration with community is essential
Realistic Methodologic Goals

**Approach:** DATA DRIVEN rather than anecdotal
- Identify high exposure/risk situations needing intervention/remediation/education
  - Changes the nature of the epidemiologic question
  - Responsive to public concerns
- For example, prioritize for epidemiologic follow up
  - Focus specific exposure-disease hypotheses
  - Identify regions most likely to yield useful and interpretable results from further study
  - Target data collection effort

"The payoff from clustering research comes from the specific hypotheses that emerge to explain the observed pattern of excess occurrence." --- Rothman (1990)
Controversy over Active Cluster Surveillance

• **Against**
  – Will identify many situations requiring investigation
  – Will not result in etiologic associations
  – Will be large drain on health department resources

• **In Favor**
  – Will identify very few situations requiring investigation
  – Will focus on most serious (unusual) situations rather than current, highly-biased “community report” approach
    • Could require presence of risk factor to trigger investigation
  – Will increase likelihood of finding etiologic association
  – By being proactive, could improve community relations

• **The Controversial Issue**
  – *How many clusters identified through surveillance would require in depth investigation?*
What Issues Would Active Surveillance Address?

Consider Childhood Cancers

• General Question:
  – *Where and in whom do childhood cancers occur?*
  
  *Do the cases form any clusters?*

• Scientific Issue:
  – *What are the major risk factors for childhood cancer?*
  
  *Are cluster(s) associated with environmental risks?*

• Policy Consideration:
  – *Would routine assessment for childhood cancer clusters be meaningful scientifically and helpful for community communication/collaboration?*

  *Should we consider Active Surveillance?*
Using New Opportunities: Surveillance

• Frequent evaluation of a large database
  – Evaluate locally
  – Look for changes in space, time, space-time
  – Assess persistence of pattern over time
• Combine disease data with other information
• Requires new methods
  • Cusum (Rogerson)
  • Scan (Kulldorff)
  • Others
• Prioritize and Validate

Proposal: Research Evaluation of GIS-Based Surveillance Program

It may not work, but WE NEED TO LOOK
Improved Exposure Information

- Better lab tools available all the time
- More sensitive epidemiologic tools
- Biomonitoring may offer opportunities
Some References for Clusters

Another Cluster: Fallon, NV

• **Large excess (RR~35)**
  – Summer 2000—5 cases of childhood ALL
  – By end of 2001, 15 diagnosed
  – 0.2 per year expected (population 8,300)

• **Home of Navy’s “Top Gun” Training**

• **Ideas Under Investigation**
  – Airborne jet fuel release; jet fuel pipeline leaks
  – Population mixing hypothesis (50,000 transients/year)
  – Arsenic in drinking water
  – Tungsten in the environment, cases, controls