Investigating Cancer Clusters: New Guidelines and Innovative Approaches

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RESEARCH • TREATMENT PREVENTION • EDUCATION

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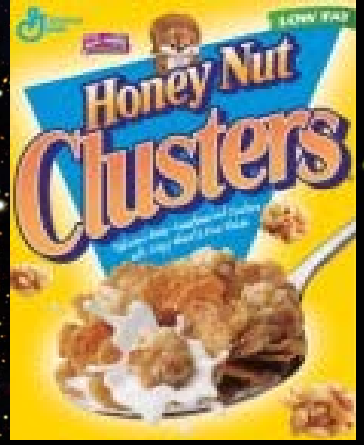
Goals of This Presentation

- **What is a cluster and why do the 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

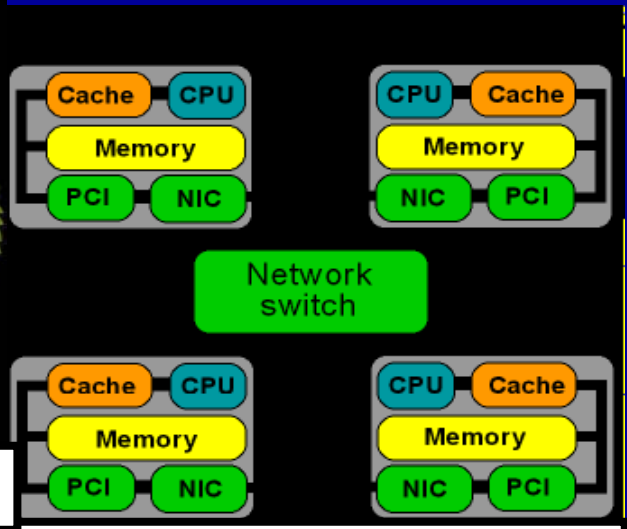
  Better data, more accurate exposures, biomonitoring

Star Cluster



Cluster Cereal

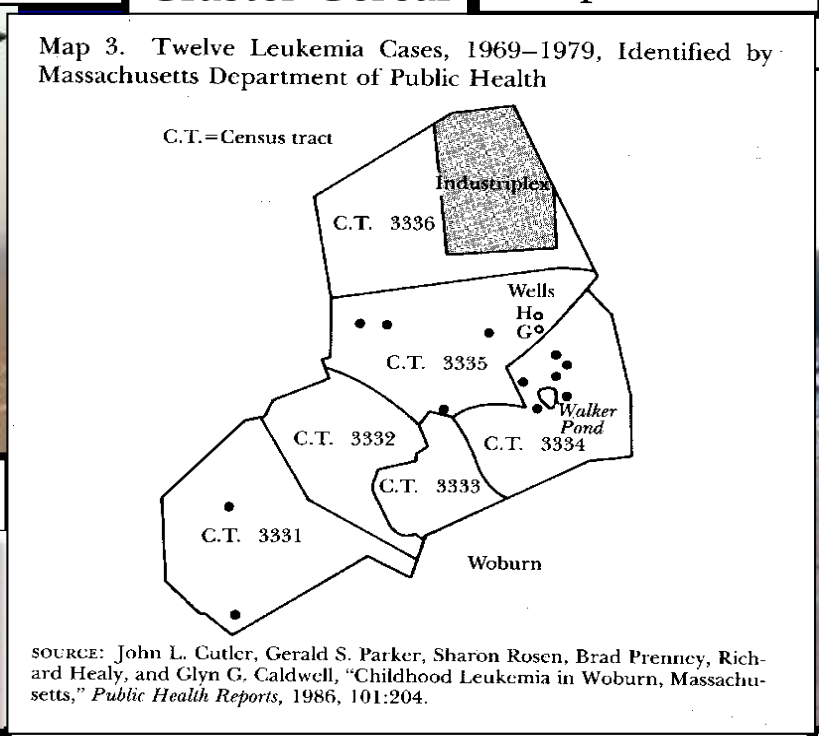
Grape Cluster



4 node PC workstation cluster

Cluster Bombs

Cluster Headache



Childhood Leukemia cluster

Cluster of Cars

The Concept of a Cluster is very Broad

Cases DO Cluster! Some Examples

CANCER CLUSTERS

- Childhood Leukemia (several dozen studies since the 1950s)
- DES and vaginal cancer (1971)
- Lymphoma (1970s)
- BSME and lung cancer (1973)
- **Vinyl chloride monomer and liver cancer (1974)**
- Leukemia on Meadow St., CT (emfs--1980s)
- Leukemia near Seascale Nuclear Facility (1980s)
- Cancer in NY Giants

DISEASE CLUSTERS

- **DBCP and male infertility (1977)**
- Kepone and neurotoxicity, infertility (1978)
- HIV/AIDS (1981)
- **Thalidomide and phocomelia (1960s)**
- football players (1987)
- Legionnaires Disease and pneumonia (1976)
- Minimata Disease (1950s)

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

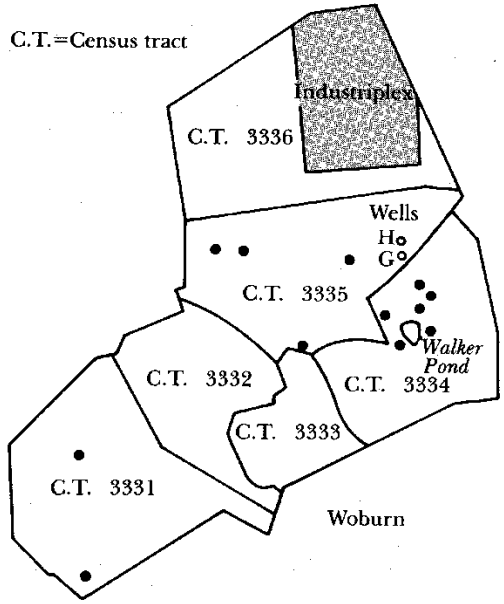
- A few to several dozen reported cases
- Cases aggregated, e.g., in space, time…
- No identified exposures
- No delineation of population at risk
- Limited demographic information of cases
- No residence history information
- No or limited surveillance data available

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"*

Map 3. Twelve Leukemia Cases, 1969–1979, Identified by Massachusetts Department of Public Health



SOURCE: John L. Cutler, Gerald S. Parker, Sharon Rosen, Brad Prenney, Richard Healy, and Glyn G. Caldwell, "Childhood Leukemia in Woburn, Massachusetts," *Public Health Reports*, 1986, 101:204.

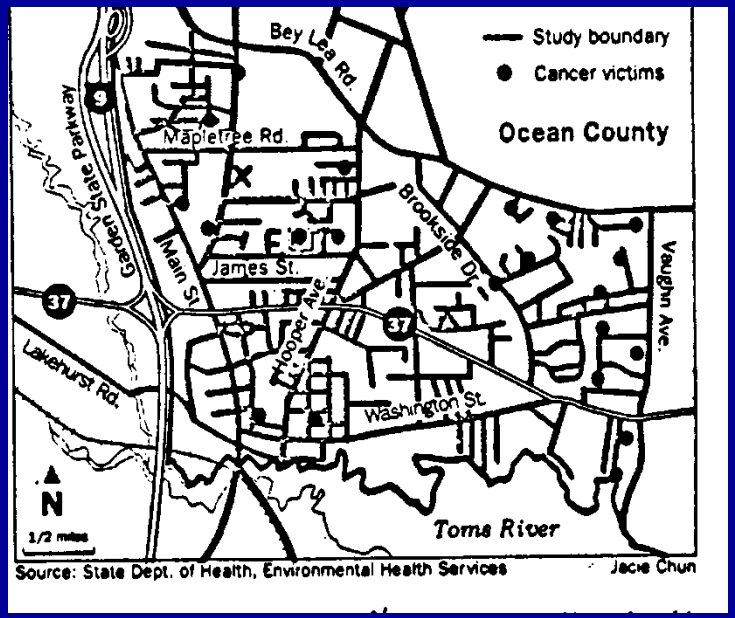
- State Study (Parker and Rosen 1981)
  - 12 childhood cancers observed, 5.3 expected, p=0.008
- Harvard study positive (1984)—controversial
  - 12 childhood leukemia cases where 5.3 expected
- New cases found after wells closed
  - MADPH study finds ***prenatal water exposure*** a risk (1996)

From DiPerna

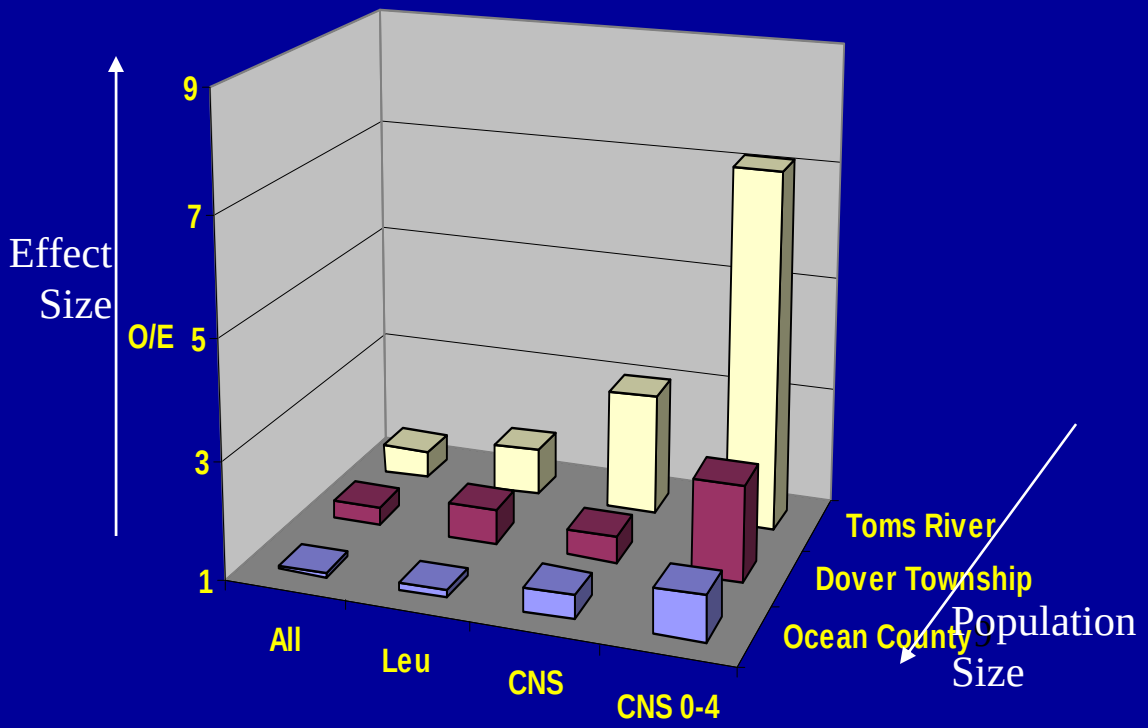
As described in a book and A Major Motion Picture

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 of 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)

How do we identify appropriate areas?... **SURVEILLANCE**

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

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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