Environmental Questions and Community Concerns: the Role of Public Health Research

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The Context

- Community leaders in a rural county expressed concern regarding perceived excess brain and breast cancer.
- The county is transitioning from remote and rural to mixed suburban-rural land use, and experiencing concomitant socioeconomic changes.
- West Virginia University and the West Virginia Bureau for Public Health created a multidisciplinary response team consisting of experts in cancer, cancer registry data, community health, environmental health, and survey research.

The Approach

- Meetings with key community leaders were held to better understand the concerns and associated issues
- Two interconnected activities were undertaken:
  - A community health survey
  - A systematic review of available health, environmental, demographic, and other available data

Community Questions

- Didn’t something have to cause this?
- What should we be measuring (biologic monitoring and medical surveillance) to protect ourselves from more of it?
- How do we guarantee (or increase) safety?

Epidemiologists' Questions

- Population and design
- Use of scarce resources
- Is this a true cluster?

Cluster Characteristics

- Numerator first (backwards epidemiology)
- Rearward projection of linked denominator
- Concerned population
- Astute clinician
- Rarely, a public health official on whose “turf” the question rests

Problems of Cluster Epidemiology

- "Texas sharpshooter"
  - Numerator manipulations and sliding case definitions
  - Denominator manipulations in space/time
- Biostatistics when *n* is small

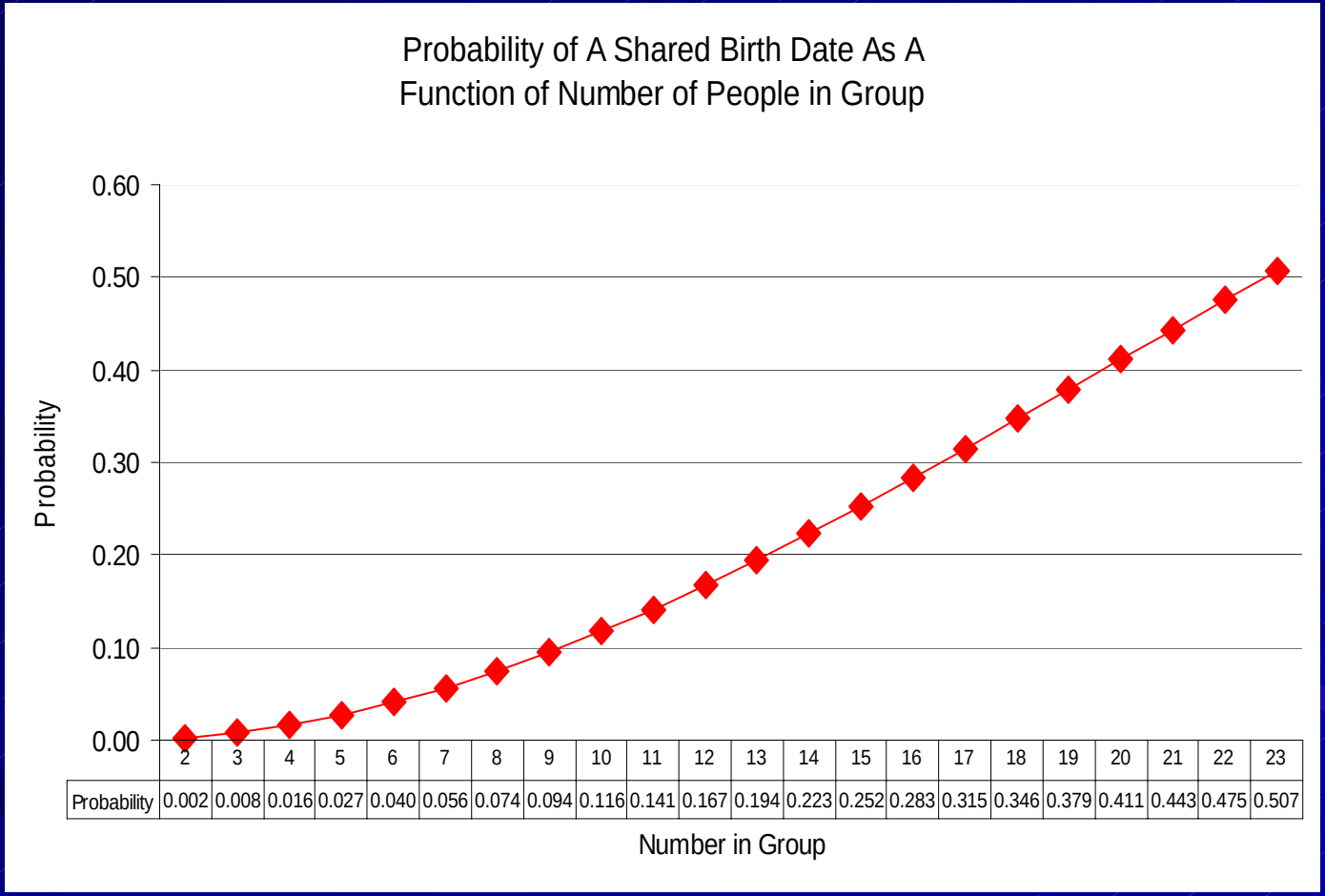
Problems of Cluster Epidemiology

- Bias: Unequal case finding in index (denominator) and control populations
- A posteriori reasoning:
  - Biostatistical testing presumes the null hypothesis, but clusters are investigated because they are unusual.
  - “If you start with a difference…”

Consider the Number of Groups to Which You "Belong"

- Family
- Neighborhood
- Work colleagues and professional groups, people you serve through your job, counterparts in other states/programs…
- Adults who have children/grandchildren at the same school/day care, on the same team, in the same band…
- People with whom you went to school, summer camp…
- Faith community and people you know from previous faith communities
- People with whom you volunteer or share hobbies, carpool, ride the bus…

Clusters “Happen”



	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Probability	0.002	0.008	0.016	0.027	0.040	0.056	0.074	0.094	0.116	0.141	0.167	0.194	0.223	0.252	0.283	0.315	0.346	0.379	0.411	0.443	0.475	0.507

Sentinel Occupational Clusters

- Important sources of understanding about (new) etiologic relationships.
- From 1775 to 1991, at least 133 etiologic discoveries derived from sentinel occupational clusters.

Community Clusters

Disease	Agent	Year
Parkinsonian Syndrome	MPTP	1979
PCP Pneumonia	HIV	1981
Eosinophilia Myalgia	“Peak E”	1989
Epilepsy	Cartoons	1997
Urothelial Cancer	Herbal Medicine	2000
Other: Epping Jaundice, Ginger Jake, Toxic Oil Yusho and Yu-Cheng		

Do We Miss Real Causes?

- YES!
- Commonly, the limits of population science (and most other scientific fields) are tested because they cannot “prove negatives.”

Community Health Survey

Methods

- Community leaders and the agricultural extension service provided preliminary information about exposure issues.
- A survey was developed by tailoring survey items with established reliability and validity to meet local needs.
- The *Moorefield Examiner* graciously agreed to distribute the survey.
  - Additional copies of the survey were distributed at key community locations.

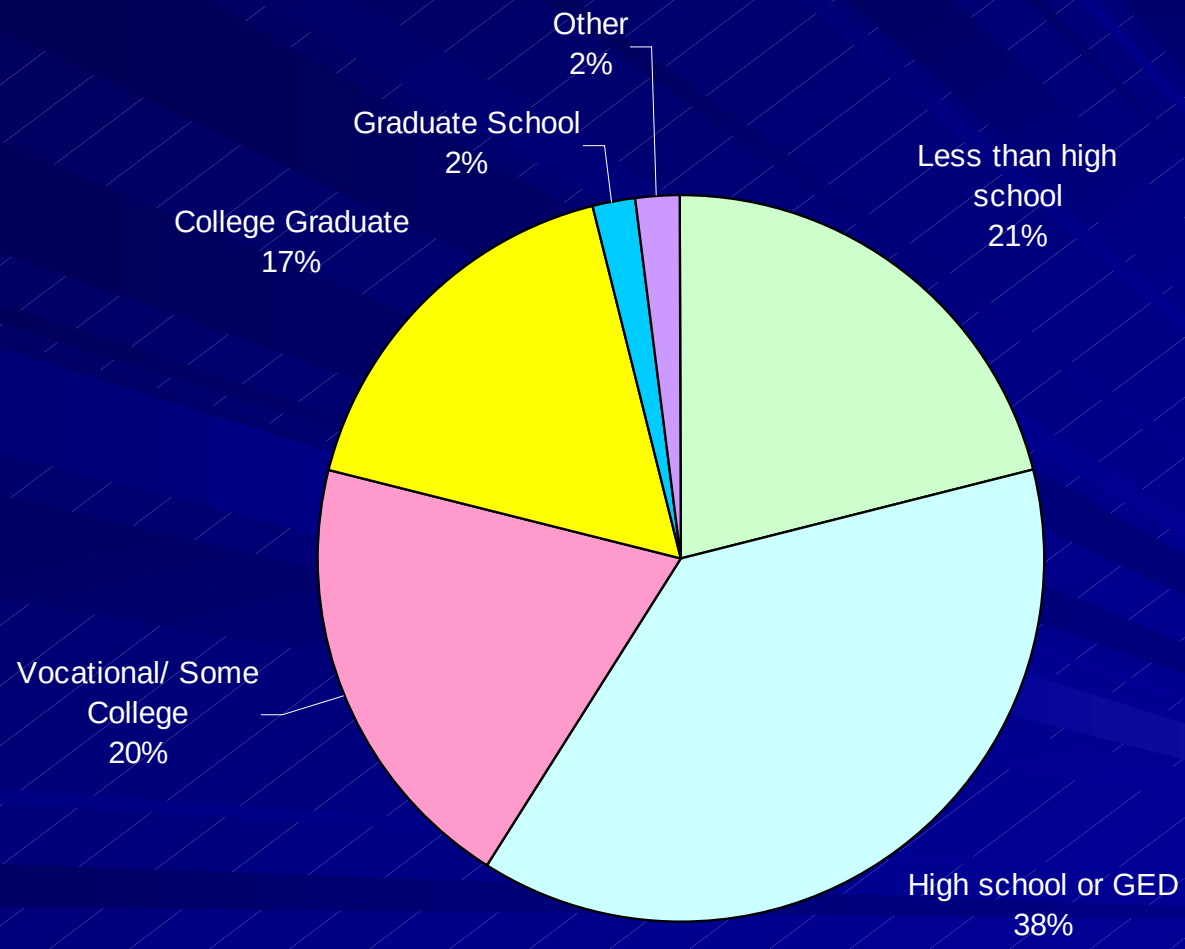
Results

- Very good response rate:
  - 2,097 anonymous surveys were returned from a county with an estimated 5,200 households
- Respondents were in a position to understand community health issues:
  - More than half (58%) grew up in the county
  - The mean length of county residence was 19.9 years.

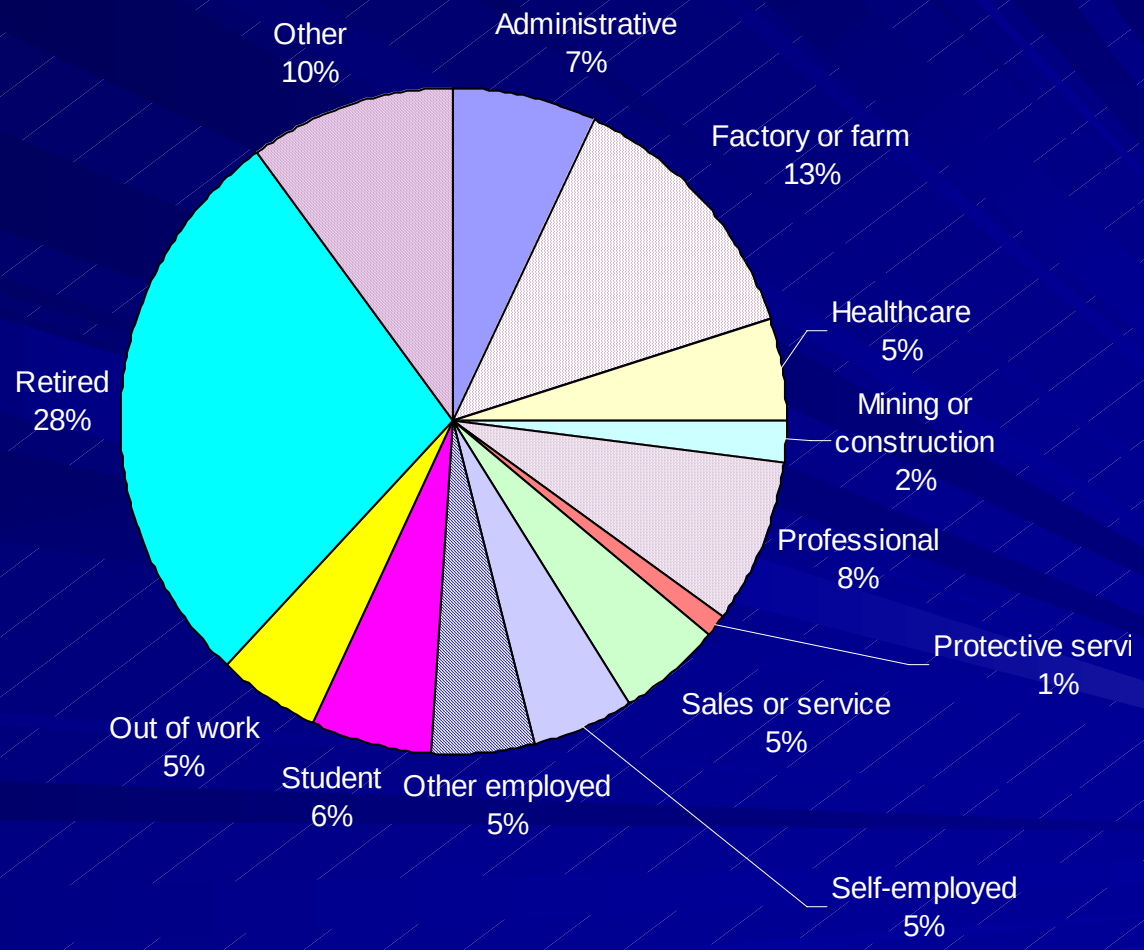
Demographics

	Hardy County 2000 Census	Survey Respondents
Median Age	38.9	50.4
% Female	51	62
% White	98	96

Educational Attainment

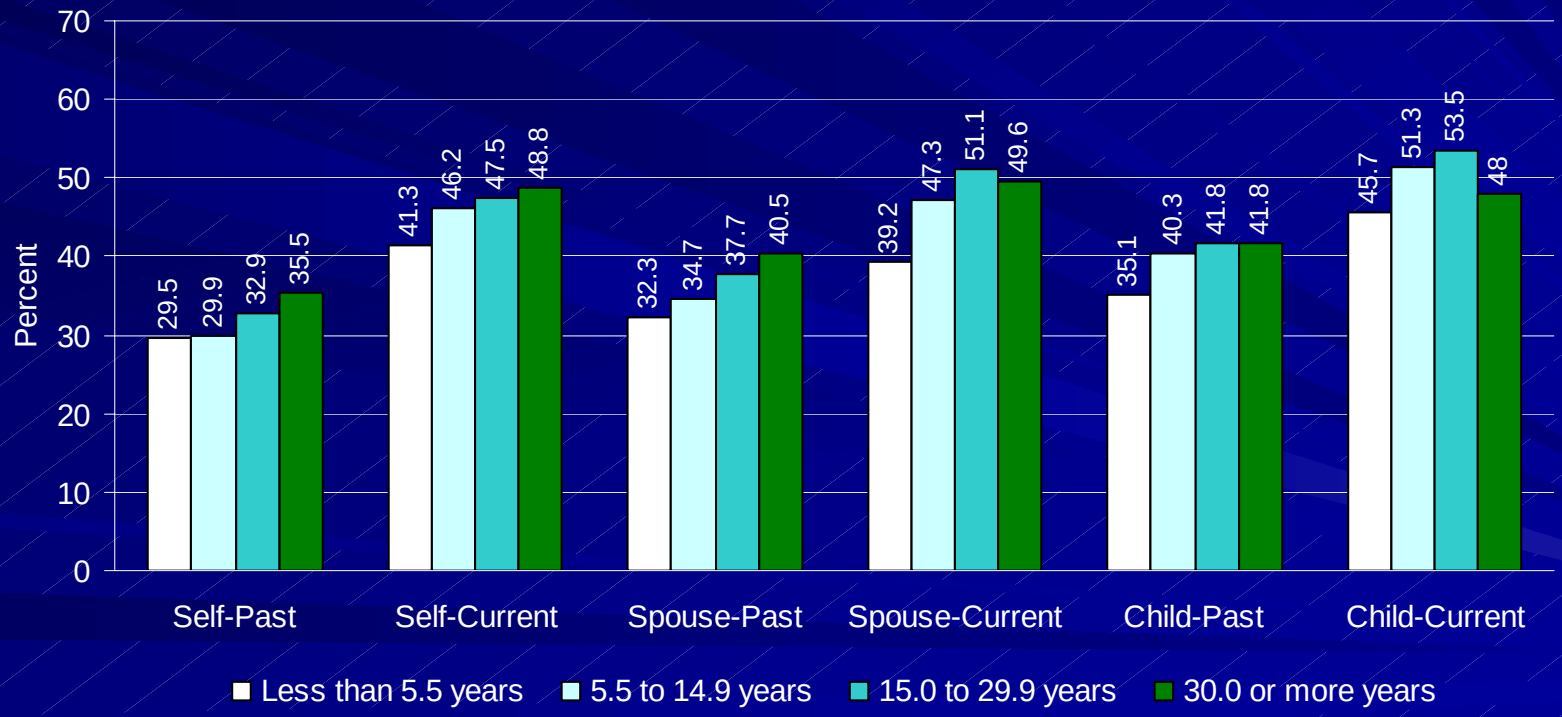


Employment Status

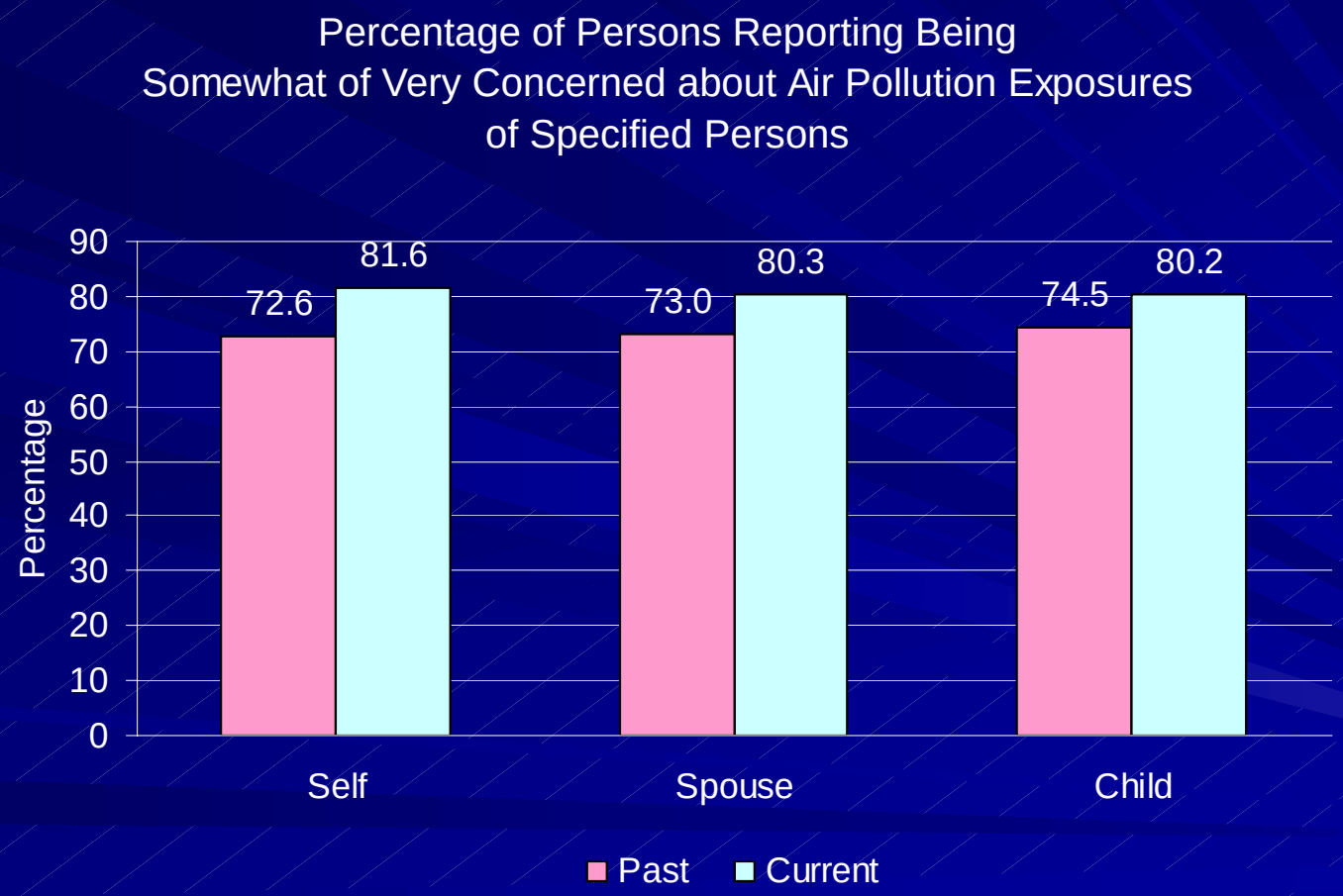


Length of Residence in Hardy County

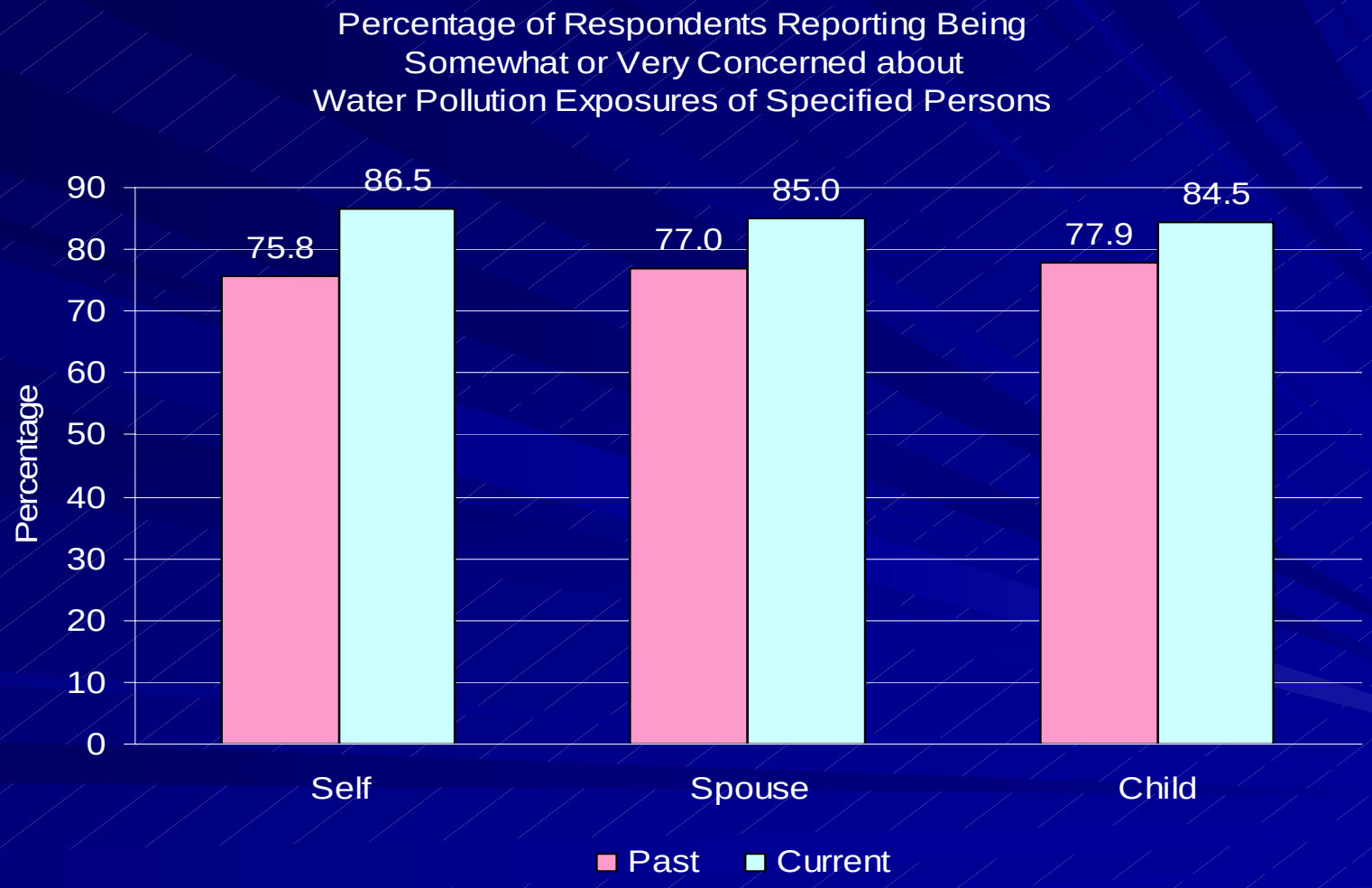
Percentage Very Concerned about Air Exposures as a Function of Length of Residence in Hardy County
(Only current Hardy County residents included.)



Concern about Air Pollution



Concern about Water Pollution



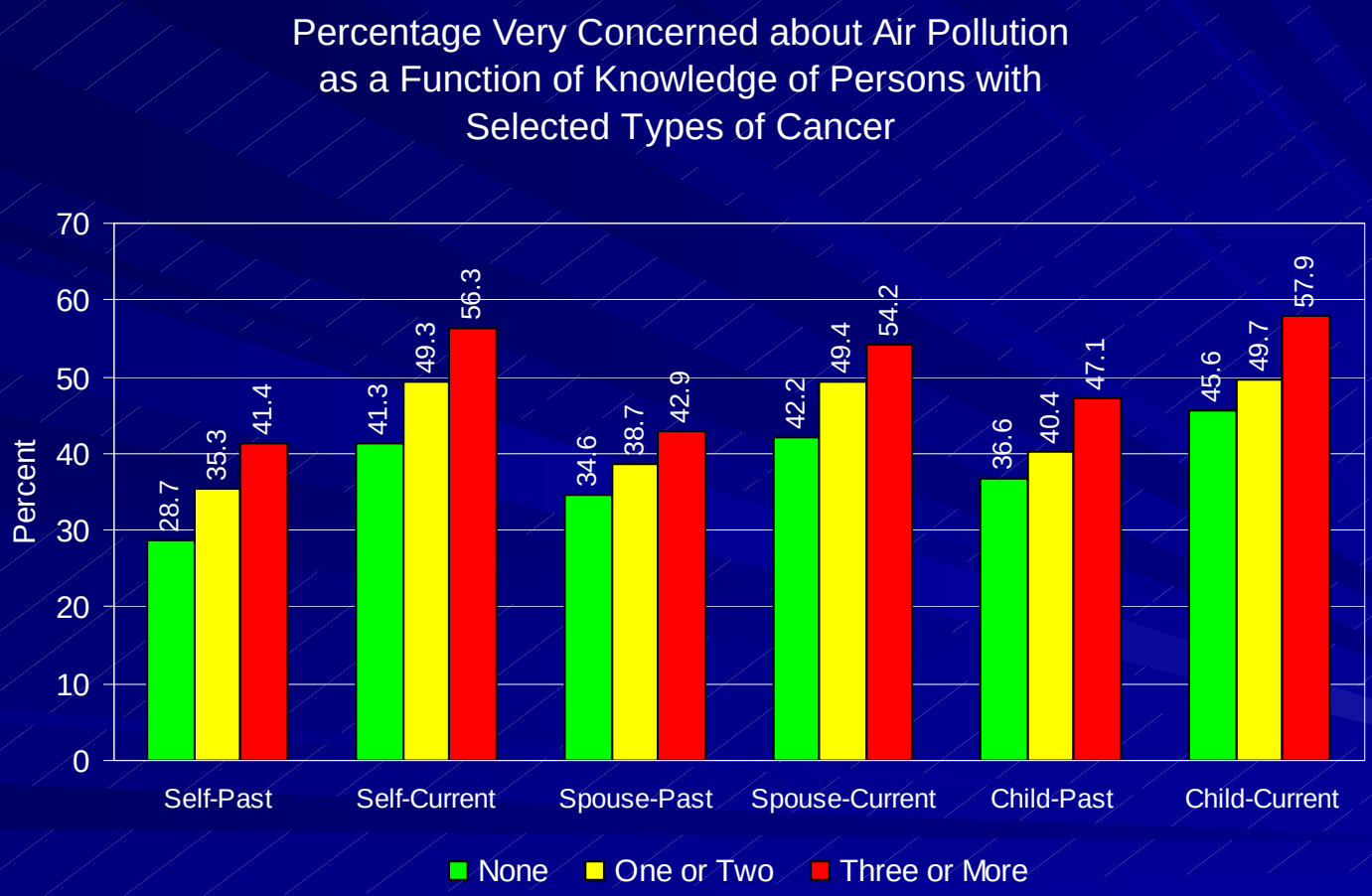
Percentage of Respondents Reporting Knowing Persons with Specific Cancers

	Self	Spouse	Children	Parents	Siblings	Other
Skin	5.4	2.8	0.8	8.1	3.4	0.7
Colon	1.8	1.2	0.2	5.8	2.8	0.8
Lung	0.6	1.3	0.1	6.2	3.2	0.9
Breast	0.2	0.2	0.0	5.2	4.5	1.5
Ovary	1.6	0.2	0.5	3.3	2.1	0.6
Prostate	0.8	1.0	0.1	4.4	1.4	0.5
Liver	0.3	0.6	0.1	2.8	1.2	0.3
Bone	0.2	0.2	0.0	2.1	1.4	0.4

Percentage of Respondents Reporting Knowing Persons with Specific Cancers

	Self	Spouse	Children	Parents	Siblings	Other
Brain	0.2	0.4	0.2	1.8	1.2	0.3
Bladder	0.5	0.6	0.1	1.5	0.6	0.3
Kidney	0.7	0.4	0.1	1.4	0.8	0.1
Leukemia	0.7	0.4	0.1	1.4	0.8	0.1
Non-Hodgkin	0.5	0.2	0.1	1.2	0.6	0.1
Multiple Myeloma	0.4	0.5	0.0	1.0	0.3	0.2
Testis	0.1	0.3	0.1	0.3	0.3	0.2
Hodgkin Lymphoma	0.0	0.1	0.0	0.7	0.1	0.1

Concern about Air Pollution



Cancer Data Review

Responding to Clusters

Clinical Analysis

- Case verification:
  - Primary (not summary) material
  - Pathologic confirmation preferred
  - Most apparent clusters do not progress beyond this point

Cancer Case Ascertainment: The Issue

- West Virginia healthcare facilities and providers report cancer data directly to the West Virginia Cancer Registry (WVCR)
- Facilities and providers from other states report to their state registry, which provides data to WVCR under data sharing agreements
  - There are sometimes questions about timeliness, quality and completeness of such data

Cancer Case Ascertainment: The Issue

- Residents of West Virginia's border counties are particularly likely to seek services out of state
  - Thus, border counties may be particularly impacted by the concerns about timeliness, quality and completeness of shared data

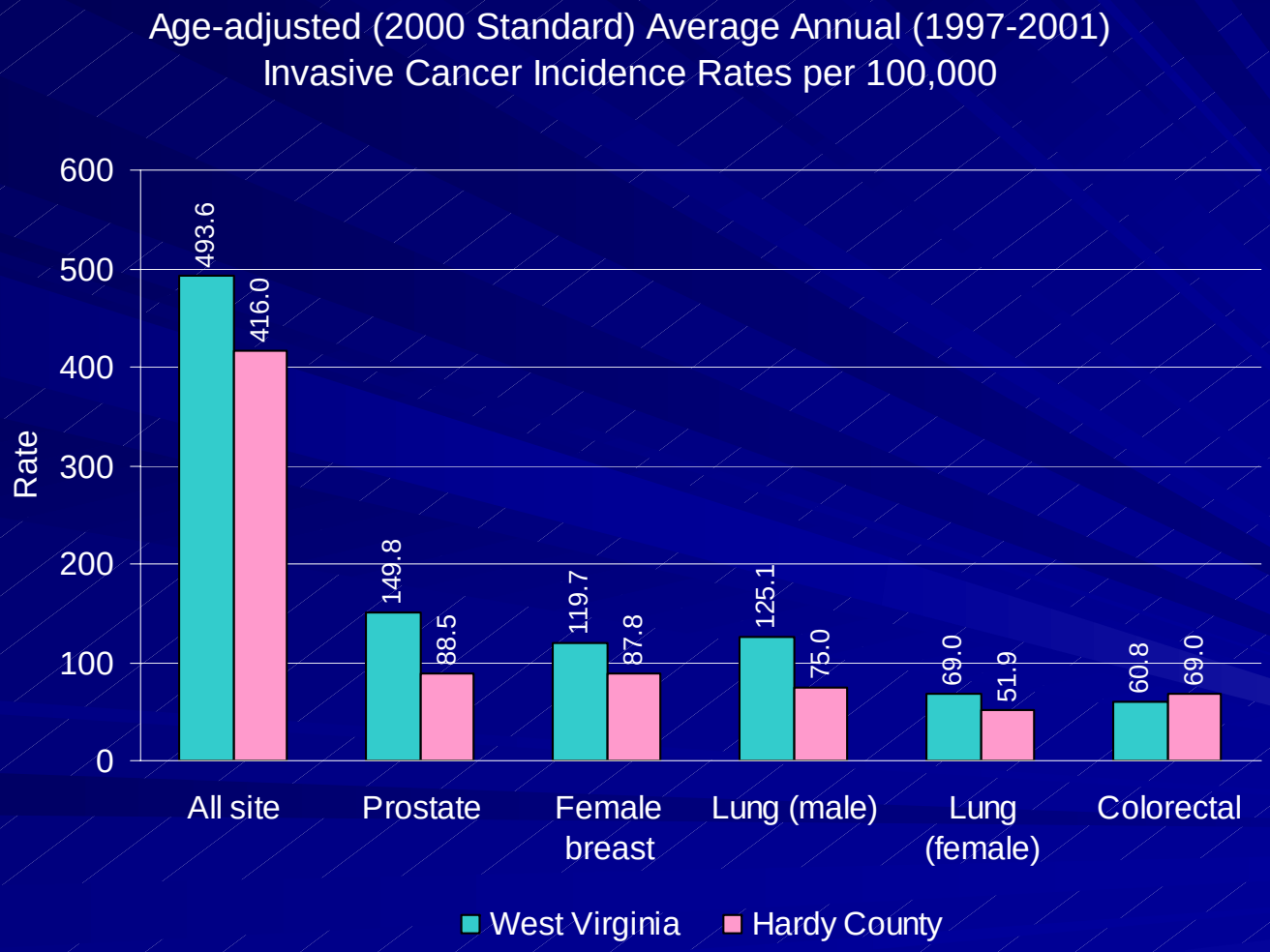
Cancer Case Ascertainment: The Solution

- WVCR initially worked directly with the state registries in border states to speed data sharing
  - **Although data were shared more rapidly, concerns about quality and completeness remained**
- With the help of community members, healthcare providers, and other state registries, WVCR identified key out-of-state facilities and worked directly with those facilities to get data
  - **This resulted in the ascertainment of 37 new cases, 17 of which should already have been shared with WVCR by other state registries**

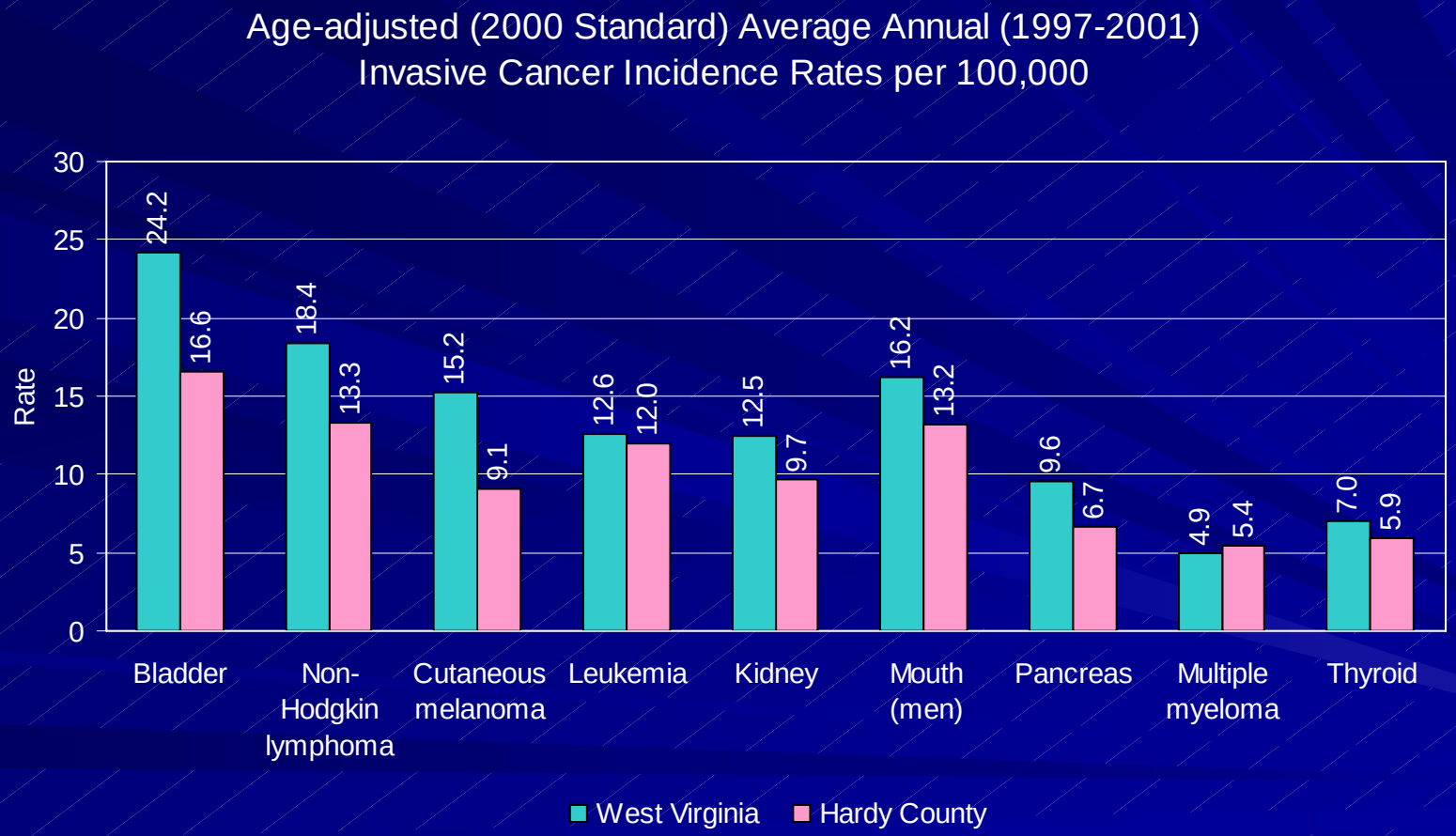
Invasive Cancer Incidence Rates

- Age-adjusted average annual invasive cancer incidence rates in Hardy County are typically similar to or even slightly lower than those of West Virginia as a whole, as well as those of counties matched on
  - **Behavioral risk factors such as tobacco use, obesity, and lack of exercise**
  - **Agricultural chemical use**
  - **Population size and rate of change**

Cancer Incidence

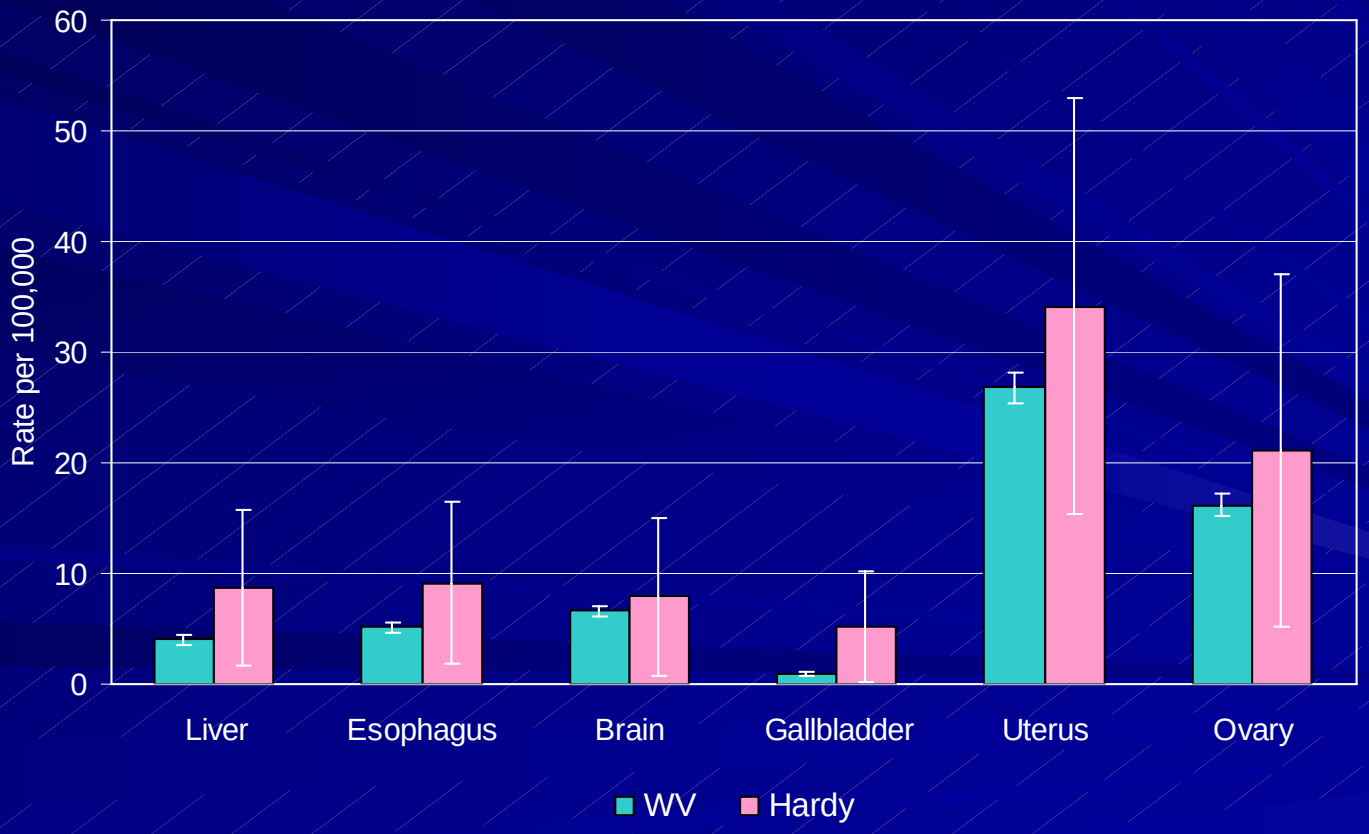


Cancer Incidence



Cancer Incidence

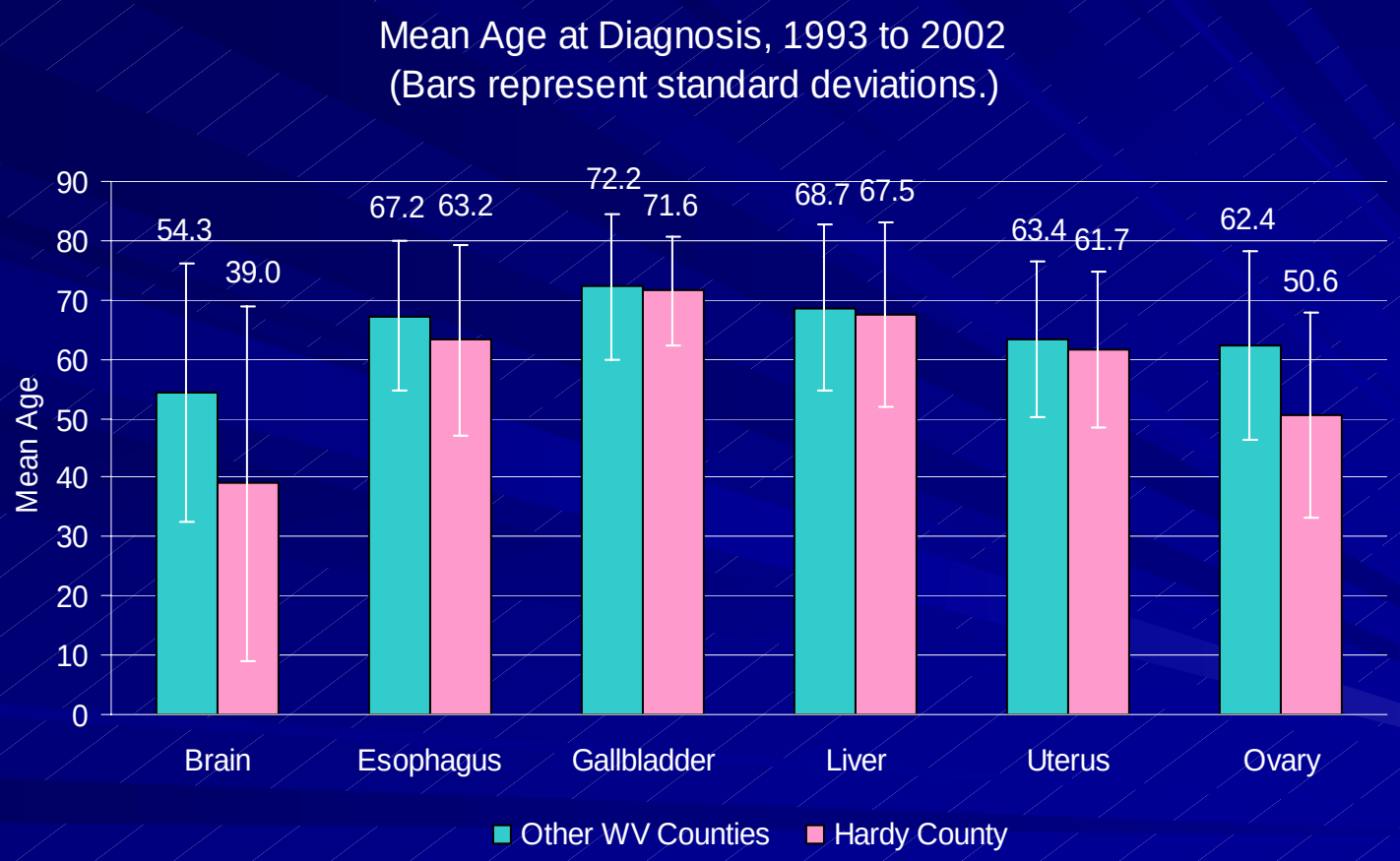
Age-adjusted (2000 Standard) Average Annual (1997-2001)
Incidence Rates per 100,000
(Bars represent 95% confidence intervals.)



Invasive Cancer Incidence Rates

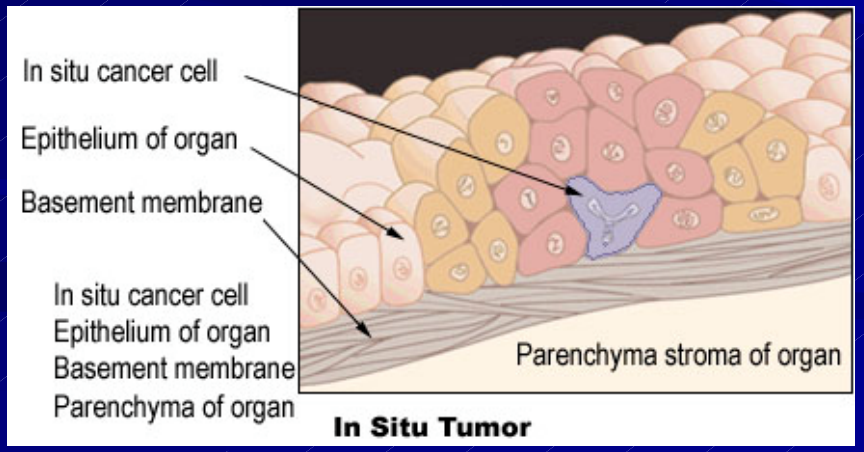
- Certain cancers tend to have both higher rates and be diagnosed at an earlier age in Hardy County, including cancer of the
  - **Brain**
  - **Esophagus**
  - **Gallbladder**
  - **Liver**
  - **Uterus**
  - **Ovary**
- Cancers of the esophagus, gallbladder, liver, uterus and ovary may be estrogen sensitive
  - **Studies by the US Geological Survey suggest the presence of endocrine disrupters in the South Branch of the Potomac, which supplies water to Moorefield**

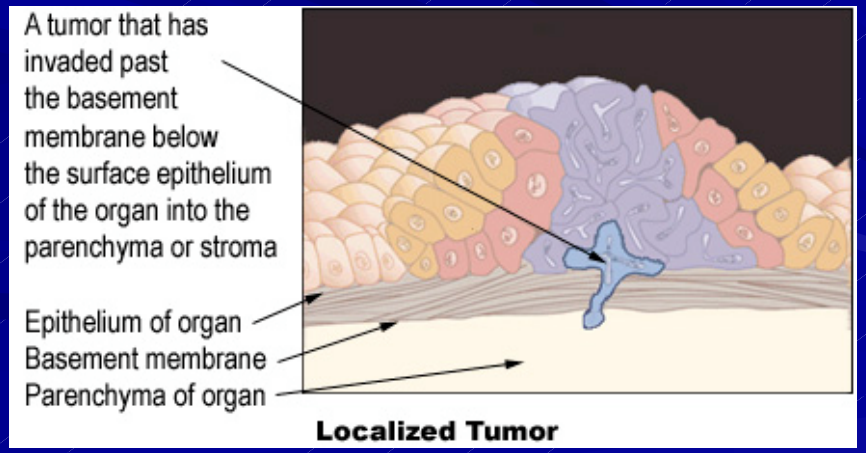
Mean Age at Diagnosis



Cancers Identified in Community Survey as Being of Concern

- Female breast cancer:
  - **The incidence rate of invasive breast cancer is lower in Hardy County than in West Virginia as a whole**
  - **However, the percentage of Hardy County breast cancer cases diagnosed at the in situ stage, and thus excluded from analysis of invasive cancer, is nearly twice that of West Virginia as a whole**





Cancers Identified in Community Survey as Being of Concern

- Brain:
  - Hardy County rates have varied greatly from year to year, and remain slightly higher than those for West Virginia as a whole
  - No cases in children or adolescents have been reported for diagnosis years after 1999, although adult cases have been reported
- Non-Hodgkin lymphoma:
  - Hardy County rates are consistent with those of West Virginia and of matched counties

Responding to Clusters

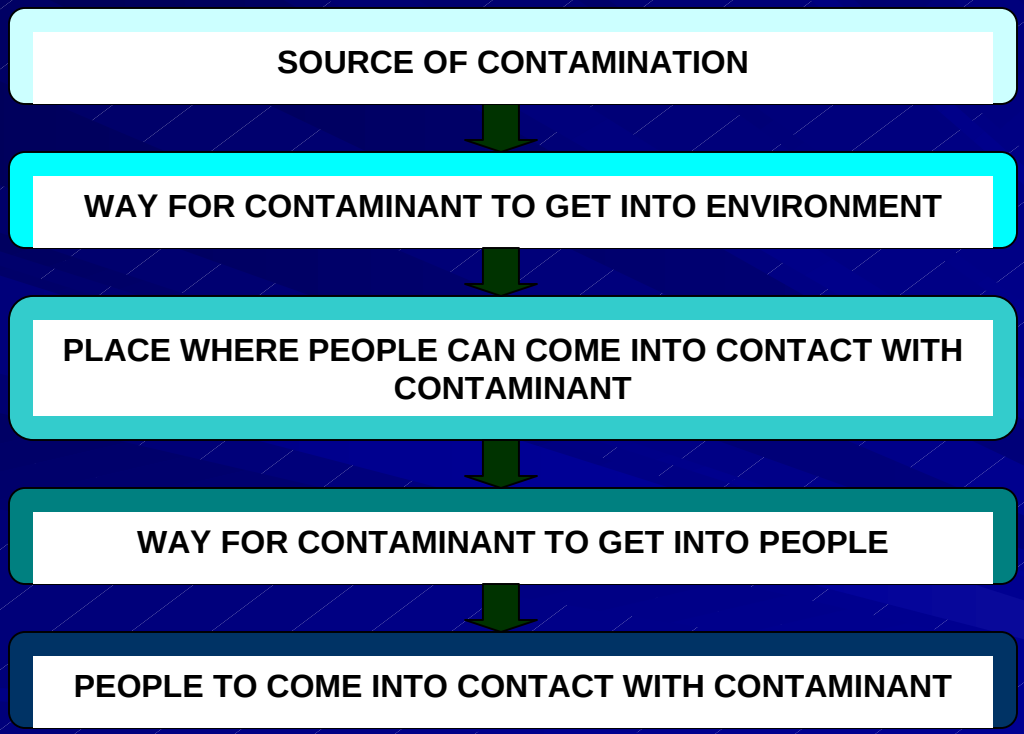
Clinical Analysis

- Knowledge base:
  - Literature search
  - Are likely etiologies known?
- Patient characteristics:
  - Pertinent possible etiologies in index cases
  - Inherent risk factors for index cases
  - “Nested case control”

Statistical Significance

- Presence does not prove biological importance.
- Absence cannot rule out causation, but it does decrease interest.

Exposure Pathway



Clusters in Context

- Example 1:
  - Three of 25 people living on my block have peripheral neuropathy.
- Example 2:
  - Three of 100 people living in my neighborhood have developed peripheral neuropathy since the batteries were dumped.

Other “Issues”

- Involvement of powerful people
  - Politicians
  - Business owners
- Lawsuits and the threat of lawsuits
- Media coverage
- “Turf conflicts”
- Resources

What Caused My Child's Cancer?

N = 500

Environmental Exposures	303
Family History	270
World Dissonance	24
Cancer Cluster	23
Stress	22

Ruccione, 1990

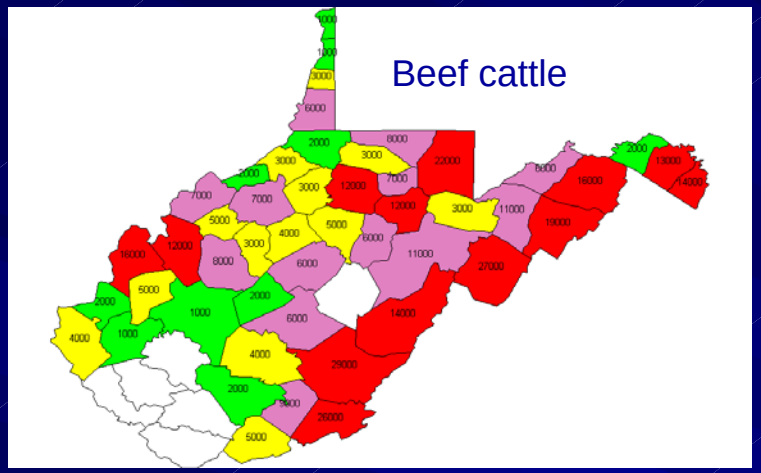
Making Causal Attributions: An Oft-Repeated Observation

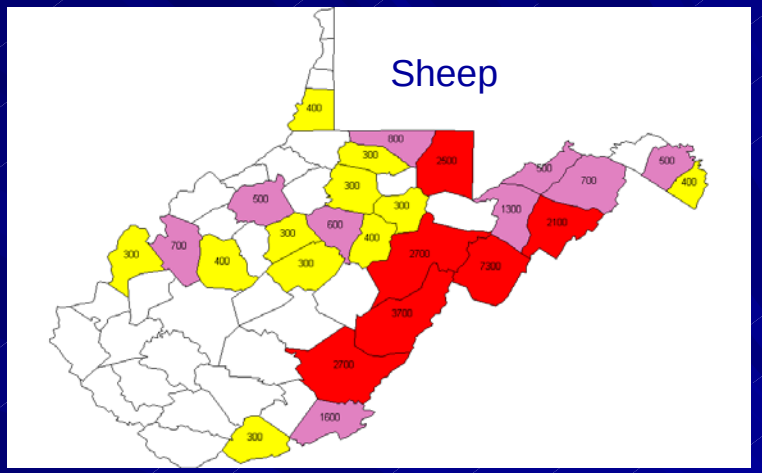
- If it's good, we caused it ourselves
  - I'm healthy because I work hard at doing what's right for my body, mind, and spirit.
- If it's not good, someone else caused it
  - I have health problems because:
    - I inherited bad genes
    - Someone polluted my neighborhood

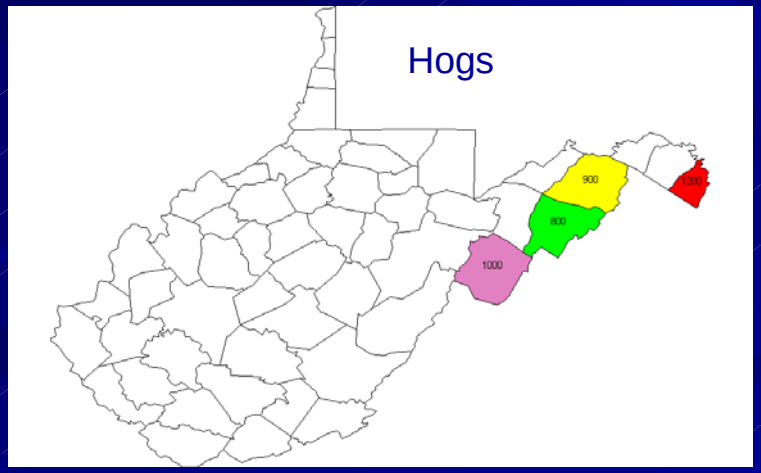
Other Health Issues

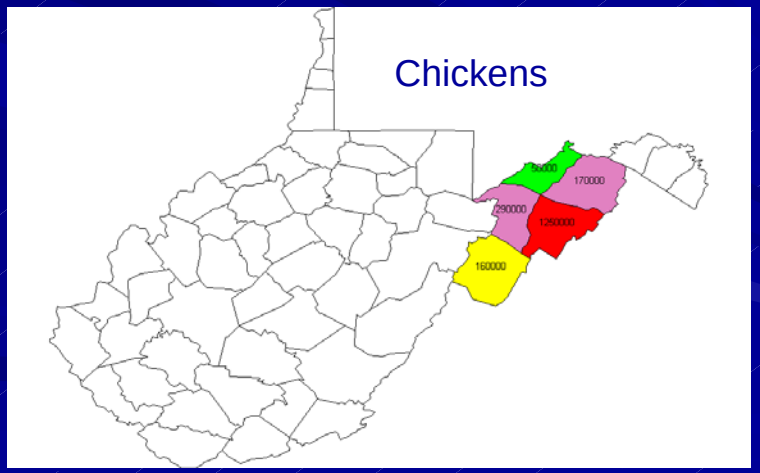
- In meetings with community members, health concerns other than cancer were also expressed
  - **WVCR reviewed a wide range of demographic, health data and environmental data to assist the community in identifying priorities**
- Issues identified include:
  - **Rapid population growth, including a rapidly growing elderly population**
  - **Chronic disease, including diabetes and heart disease**
  - **Motor vehicle accidents**
  - **Crime**
  - **Healthcare access**
  - **Pollution**

Livestock (USDA Ag Census)









Lowest quartile

2nd quartile

3rd quartile

Highest quartile

Agricultural Chemical Use Rates per 10,000 Acres (USDA Census)

	WV Median	Hardy County
Insecticide use rate	6.7	101.4
Nemicide use rate	0.0	20.5
Herbicide use rate	24.4	144.2
Defoliant use rate	0.0	3.0

Hardy County Toxics Release Inventory Reports, 1988-2001

	Total (lbs)	Average Annual (lbs)
1,2,4-Trimethylbenzene	105,343	26,335.80
Acetone	51,868	12,967.00
Ammonia	158,939	13,244.90
Certain Glycol Ethers	209,734	34,955.70
Chlorine	7,536	1,884.00
Ethylbenzene	440,084	48,898.20
Lead Compounds	1,725	1,725.00
Methanol	2,637,365	188,383.20
Methyl Ethyl Ketone	2,602,340	185,881.40
Methyl Isobutyl Ketone	285,196	23,766.30
N-Butyl Alcohol	847,653	60,546.60
Nitrate Compounds	1,559,106	311,821.20
Phosphoric Acid	11,170	11,170.00
Styrene	85,271	6,090.80
Toluene	4,141,170	295,797.90
Xylene (Mixed Isomers)	3,531,083	252,220.20

Hypothesis 1

- Sediment and/or water fractionations will alter estrogen-regulated processes and gene expression in medaka fish.
- Advantages
  - easy to control
  - short generation time
  - mixture/fraction capability
  - well-understood biology
- Problems Addressed
  - dose/mixture, i.e., running start on detailed study based on active fractions
- Worry – will it work?

Hypothesis 2

- Geographic information systems can identify water system-based changes in disease
- Advantages
  - retrospective, yet data exist
  - inexpensive
- Problems
  - bias
  - sample size
  - variability in individual water use patterns over time

Hypothesis 3

- Breast cancer estrogen receptors will differ in human exposure and control groups
- Advantages
  - tissue exists and can be evaluated for expression in a deidentified fashion
- Problems
  - a long shot
  - ecologic
  - obtaining tissue, especially from out-of-state hospitals, may be challenging

Hypothesis 4

- A. Hardy County water supplies and sediment extracts will upregulate estrogen-sensitive processes in human cells.
- B. Hardy County water supplies and sediment extracts will alter immune responses such as cytokine production of human cell lines.
- Advantages:
  - Flexible and precise
- Problems Addressed:
  - Dose/mixture, i.e., running start on detailed study based on active fractions

Endocrine Disruptors in Humans

- Examples: plasticizers such as bisphenol A and phthalates (saran wrap), certain pesticides (vinclozolinin in grapes), and possibly PFOA (teflon precursor).
- Issues: low-dose exposures altering fetal development, adult carcinogenesis, hormone-mediated immune response, or reproduction. Easily seen in reptiles, fish, minks.
- Reason: probably the “shape” of the chemical triggers endocrine response.

Example of Endocrine Disruptor Hypothesis at Work

- Auto workers exposed to machine oils in late adolescence and early adulthood have an increased risk of prostate cancer. The risk is less clear if machine oil exposure across the lifespan is evaluated.
- Cancer hypotheses that support the inference (if true)
  - Hormonal, endocrine disruptor
  - Long latency

Agalliu I, et al. *Cancer Causes Control 2005;* 16: 323-31.

Examples of Endocrine Disruptor Topics

- Environmental chemicals and reproduction
  - Neuroendocrine function
- Developmental abnormalities
  - DES
  - Hypospadius?
- Orotoxicity
- Dietary phytoestrogens

Examples of Endocrine Disruptor Topics

- Estrogens, xenoestrogens, androgens, antiestrogens, antiandrogens (notably (TCDD), and neoplasms
- Molecular mechanisms
- Male infertility and sexual dysfunction
- Prostate cancer and its treatment
- Metal ions

Example of Research Question

- Human: Is the secular rise in testicular cancer in developed countries due to endocrine disruption?
- Fish: What activates the vitellogenin-making gene in male smallmouth bass?
- Environmental Health: Are these related questions?

Best Practices: The Clinician's View

- Open communications
- Public health model
  - conservative
  - inclusive
  - appropriate expertise
    - knowledgeable leader
    - external review if advised
    - no staff vetoes
- Publishable quality and intent
- Recommendations that help the community!!

Epidemiology Supercourse

- www.pitt.edu/~super1/
  - ~ 1500 Lectures, including
    - Disease Clusters
    - Causation: Overview for Occupational and Environmental Medicine
    - Hill's Criteria: 9 rules of evidence re: causal relationship

Other Resources

- A.M. Ducatman article on disease clusters: www.atsdr.cdc.gov/HEC/CSEM/cluster/index.html
- American Journal of Epidemiology, July 1990: http://aje.oupjournals.org/content/vol132/issue1/index.shtml
- Occupational Dermatoses: www.cdc.gov/niosh/ocderm.html