

# Diagnosing Cancer Causality: problems with IARC and Bradford Hill

Raymond Richard Neutra

# Medical Diagnosis as Metaphor for “diagnosing” cancer causality

- Is this patient’s chest pain due to MI, pulmonary embolism, pleurisy, esophageal spasm etc is a question similar to:
- Is this epidemiological association due purely to causal factors, to bias, to confounding or some mixture of bias and confounding?

# In Medical Diagnosis and in Causal Assessment we use Tests

- The anatomy of a test:
  - Test question: “What blood enzyme level?”
  - Test question: “What is the RR?”
  - Result metric: “ X enzyme units”
  - Result metric: “  $RR = X$ ”
  - Zones of interpretation: “Upper and lower 95<sup>th</sup> percentile are ‘abnormal’”
  - Zones of interpretation: “RR of 15 with narrow Confidence intervals are usually causal”

# The Anatomy of a Diagnostic Argument

- Every argument involves :
  - some factual “grounds”. In medical diagnosis these involve the prior odds of the possible causes of the patients syndrome and the test results.
  - The claim of some post testing odds of the possible causes of this syndrome
  - A general inferential rule that “warrants” the claim after seeing the test results and the prior
  - Backing for that inferential rule

# Backing

Studies show that certain blood enzymes are more elevated in patients with myocardial infarction than in those with other causes of chest pain

# Warrant

If a patient has elevations in certain blood enzymes and has chest pain one is warranted in increasing one's certainty the he has myocardial infarction (MI)

# Grounds

On the basis of age and weight alone one suspects MI  
*a priori.*

The patient's blood enzymes are elevated.

There is chest pain

# Claim

One should increase one's degree of certainty that the chest pain is caused by MI as opposed to other causes.

# Rebuttal

All other evidentiary tests being equal



# Bayes Theorem the Universal Warrant

- All probabilistic inference involves considering the pre test probability of the hypotheses ( e.g. diseases) and the likelihood of the pattern of evidence under hypothesis (disease) “a” RELATIVE to the likelihood of the pattern of evidence under alternative hypotheses (all the other diseases)

# BAYES THEOREM THE UNIVERSAL WARRANT

Prior Odds \* Relative Likelihood of Evidence =  
Posterior Odds

# Bad Test Habits

- Phrasing test questions dichotomously
- Assuming that the force of positive and negative tests are always symmetrical (vs “rule in” and “rule out” tests)
- Assuming test results can be free of the context of the underlying causal model
- Converting test results to “1” and “0” and adding up the “1s”.
- Stating the prior plausibility after seeing the test results



# ASSYMETRY OF RL CONVEYED BY + OR-

- Most of Hill's and Koch's criteria are specific but not sensitive
- Hence the likelihood ratio conveyed by a “yes” is farther from 1.0 than that conveyed by a “no”
- Sensitivity = 10%, Unspecificity = 1%
- LR conveyed by “yes” =  $10/1 = 10$
- LR conveyed by “no” =  $90/99 = 0.91$

# Wages of these Sins

- Falsely extreme degrees of certainty
- Stating “yes” “no” instead of degrees of certainty, thereby disempowering those who might act in a precautionary manner with modest degrees of certainty

# IARC test Questions and Misleading Resulting Labels

- Is the animal toxicological body of evidence clearly incriminating? Yes or No?
- Is the body of epidemiological evidence clearly incriminating? Yes or No?
- The result is really a “Type of Evidence” classification, but IARC uses context free “probability of causality” labels:
  - Carcinogen, probable carcinogen, possible carcinogen, inadequate evidence (= no evidence or confusing evidence)

# Venues where Bradford Hill “Tests” are Used

- In discussion sections of individual epidemiological studies to assess results
- In evaluating bodies of epidemiological evidence for risk assessment purposes
- In grant proposals justifying new studies.
- In tort law suits

# Perils of Dichotomous Thinking

- If the answer to each criterion or postulate is yes=1 and no = 0 then what is the LR conveyed by each?
- Independent LRs should multiply or their logs should add. 1 and 0 are implausible log LRs
- Do I need to get “yes” on each criterion?

# Incomplete Warrants

- Criterion, “If OR is “strong” I am warranted to believe in causality” is incomplete.
- What am I warranted to believe if OR is moderate or very near 1.0?
- What is the backing for these warrants?

# A COMPLETE WARRANT FOR “STRENGTH”

- Test: What odds ratio is conveyed by the evidence for this hypothesis?
- If far larger than known effects of confounders and bias, I am warranted to increase belief a lot
- If OR is about the size of confounders and bias, am warranted to maintain prior belief
- If close to 1.00, am warranted to decrease belief
- Backing: Size of bias/conf. in previous studies

# COHERENCE

- Poorly defined in Hill and Susser
- I view it as confirmation of deductions from the examined hypothesis as seen in data within the study or in other relevant data, existing at the time of the evaluation.
- Coherence types of results are symmetrical in that either confirmatory or un-confirmatory results can convey likelihood ratios far from 1.0



# Parting Advice

- Don't promise to be 100% sure of causality.
- The result of your evaluation is a transparent reasoned willingness to certify causality. You can be: virtually certain that you can certify causality, strongly believe you can certify, be prone to certify etc.
- This willingness should be influenced by your pre “test” willingness to certify( from “plausibility”) and the likelihood ratios conveyed by all the test results.