

Provocative Questions RFA

Ed Harlow

NCAB Meeting
September 13, 2011

Honoring the Question

If you don't ask, you don't get.

[Mahatma Gandhi](#)

A prudent question is one-half of wisdom.

[Francis Bacon](#)

If you do not know how to ask the right question, you discover nothing.

[W. Edwards Deming](#)

Honoring the Scientific Question

Examples of its use:

- Organize our daily work in lab, clinic, community
- Basis of scientific rigor
- Set scientific direction

Honoring the Scientific Question

Examples of its use:

- Organize our daily work in lab, clinic, community
- Basis of scientific rigor
- **Set scientific direction**

PROVOCATIVE QUESTIONS

- Challenge NCI's scientific community to ask and frame important but non-obvious questions
- Stimulate NCI's research communities to use laboratory, clinical, and population research in especially effective and imaginative ways.
- The proposals should:
 - Build on specific advances in our understanding of cancer and cancer control
 - Address broad issues in the biology of cancer that have proven difficult to resolve
 - Take into consideration the likelihood of progress in the foreseeable future (e.g., 5 to 10 years)
 - Address ways to overcome obstacles to answering the question

THE PROVOCATIVE QUESTIONS RFA

An experiment... **Develop good questions?**

- Oct '10 Workshop asks whether useful questions can be identified (and was the process fun)?

THE PROVOCATIVE QUESTIONS RFA

An experiment... **Develop good questions?**

An experiment... **Questions reach top level?**

- Feb '11 Workshops build collection of high quality questions in population, clinical, and basic science
- July and Aug '11 West Coast workshops determine how rich is the question building exercise
- Aug '11 Trainees' workshop extends experience net
- Throughout, community adds and comments on questions through the web

THE PROVOCATIVE QUESTIONS RFA

An experiment... Ask good questions?

An experiment... Questions reach top level?

An experiment... Expand research portfolio?

- RFA based on 24 Provocative Questions
- Broad spectrum of questions
- Portfolio review to determine current work in area
- Closes Nov 14, 2011
- Careful review process focused on best ideas

THE PROVOCATIVE QUESTIONS RFA

An experiment... Ask good questions?

An experiment... Questions reach top level?

An experiment... Expand research portfolio?

An experiment... Repeat?

- How creative and powerful is the response?

<http://provocativequestions.nci.nih.gov/>

NATIONAL CANCER INSTITUTE National Cancer Institute U.S. National Institutes of Health | www.cancer.gov

Provocative Questions

Identifying Perplexing Problems to Drive Progress Against Cancer

Search

[Sign Up](#) [Log in](#)

[Home](#) [Proposed Provocative Questions](#) [Workshops & Outcomes](#)

What is the "Provocative Questions" Project?

The provocative questions project is intended to assemble a list of important but non-obvious questions that will stimulate the NCI's research communities to use laboratory, clinical, and population sciences in especially effective and imaginative ways. The questions should not be simple restatements of long-term goals of the National Cancer Program, which are to improve the prevention, detection, diagnosis, and treatment of all forms of cancer. Instead they should:

- Build on specific advances in our understanding of cancer and cancer control;
- Address broad issues in the biology of cancer that have proven difficult to resolve;
- Take into consideration the likelihood of progress in the foreseeable future (e.g. 5 to 10 years); and
- Address ways to overcome obstacles to achieving long-term goals.

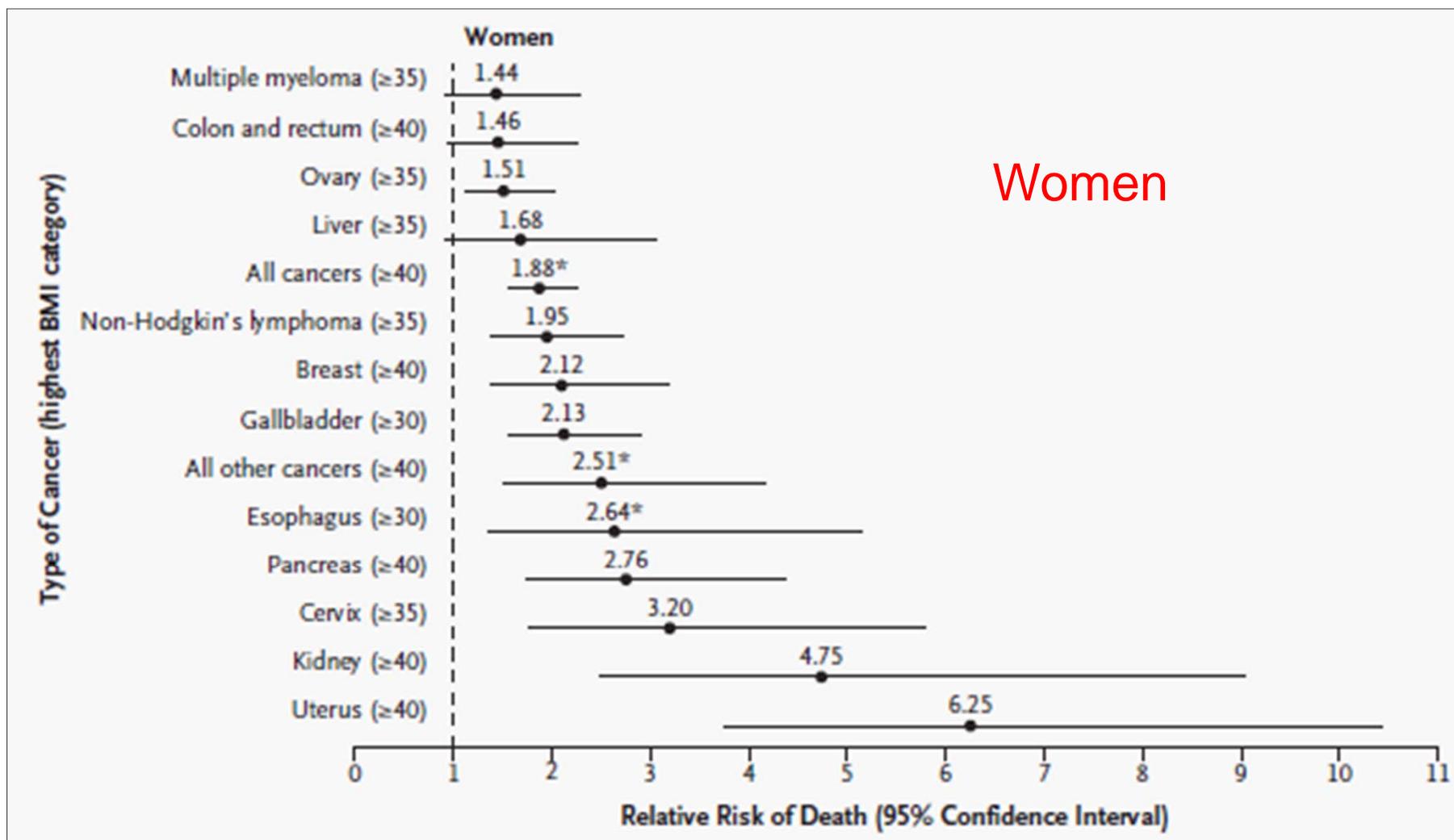
RFA, R21, R01, BUDGET

- RFA: To highlight research issues that are not well studied
 - To move research into these areas quickly and effectively
- R21 and R01: Well understood formats
 - R21: 2 years funding; R01: 4 years funding
- Budget: up to \$15 million
 - Sufficient to generate community interest and make multiple awards
 - Total amount awarded will depend on the number of highly meritorious applications

REVIEW CRITERIA

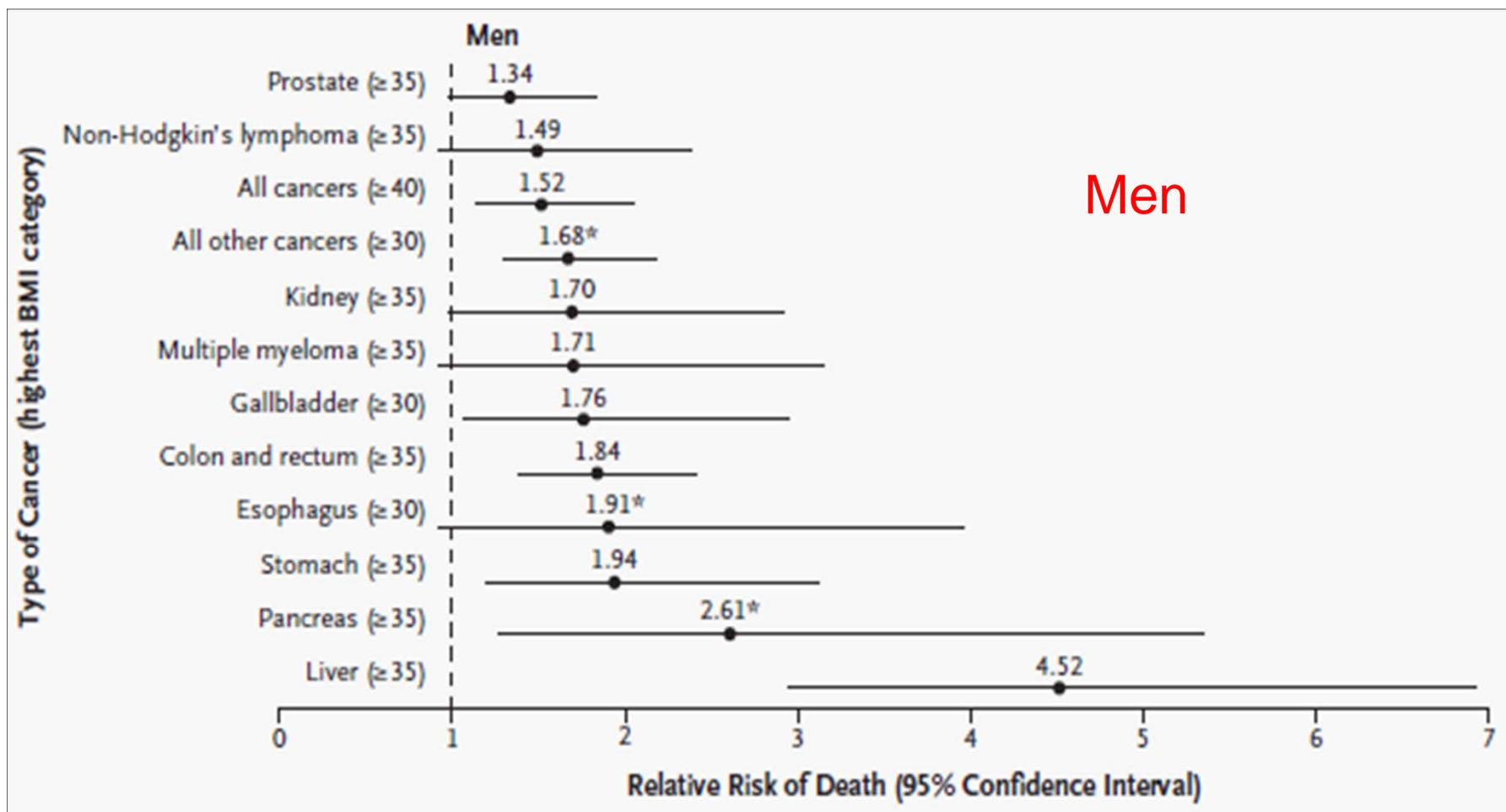
- The 5 standard review criteria (Significance, PI, Innovation, Approach, and Environment)
- Applications may come from PI's new to a field
 - strength of the applications judged in large part on the power of the *ideas* behind the proposed research
 - preliminary data unnecessary
 - track record in the field should not be weighed as heavily as in other reviews

PQ1. How does obesity contribute to cancer risk?



Calle, EE et al., Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. N Engl J Med 2003;348:1625-38.

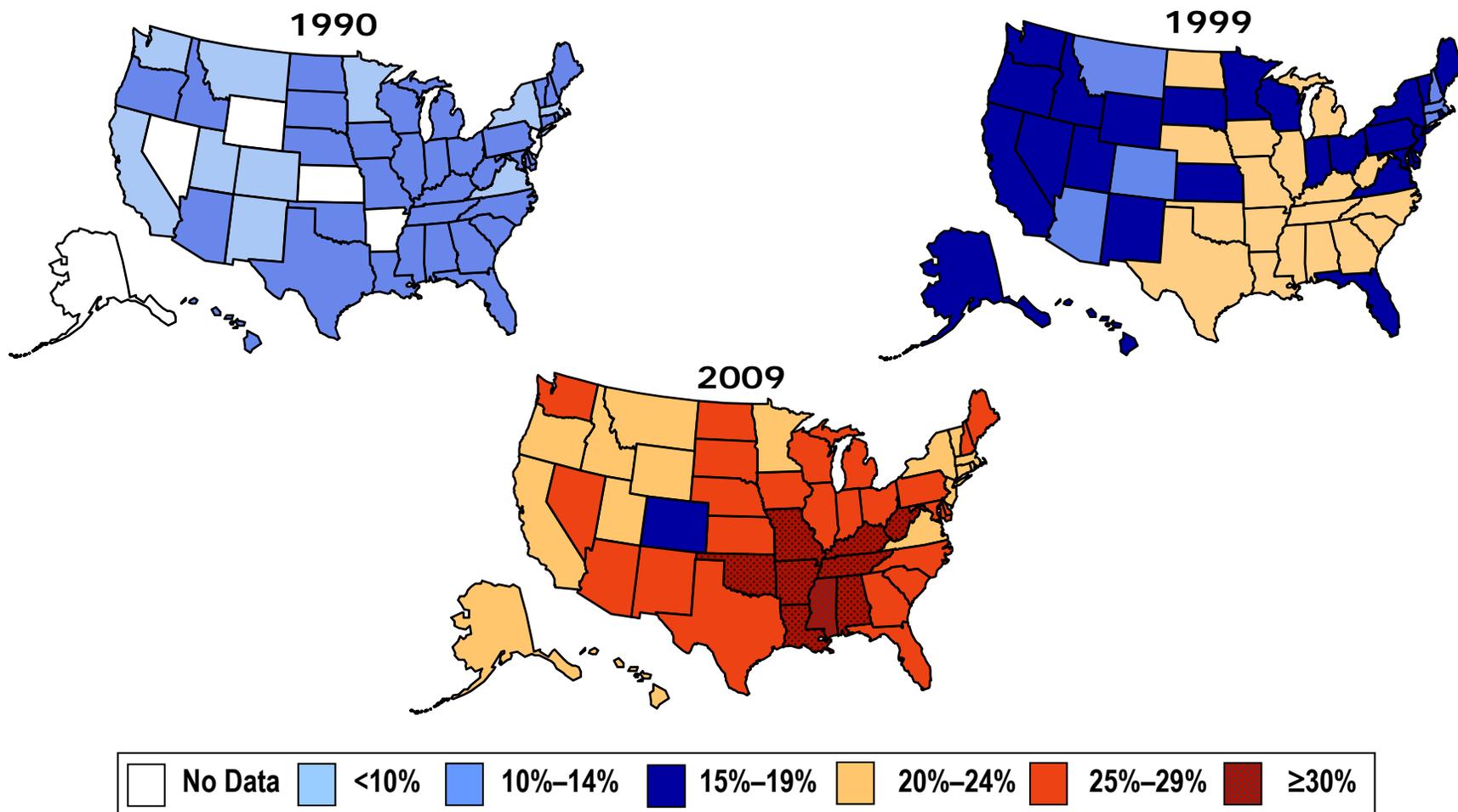
PQ1. How does obesity contribute to cancer risk?



Calle, EE et al., Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. N Engl J Med 2003;348:1625-38.

PQ1. How does obesity contribute to cancer risk?

Obesity Trends (BMI ≥ 30) Among U.S. Adults



Source: Behavioral Risk Factor Surveillance System, CDC

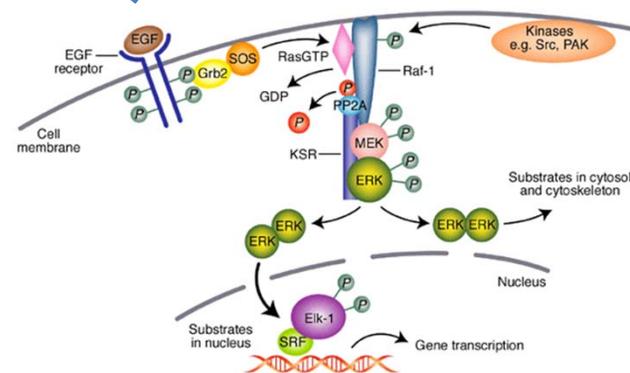
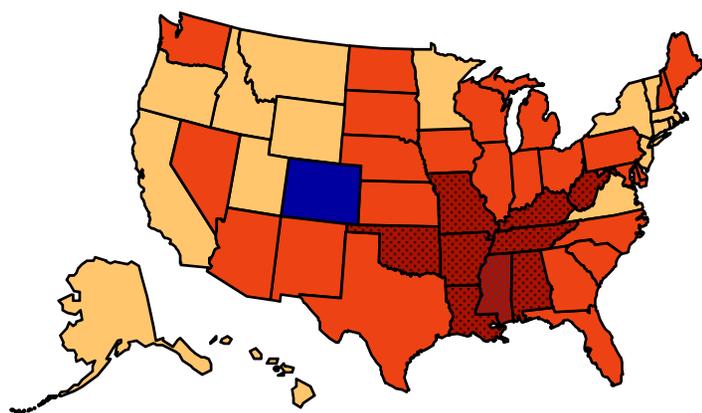
PQ1. How does obesity contribute to cancer risk?

Distribution of Deaths and Death Rates per 10,000 Person-Years*				
End Point	Matched Subjects			
	Surgery Group (N=7925)		Control Group (N=7925)	
	no.	no./10,000 person-yr	no.	no./10,000 person-yr
All causes of death	213	37.6	321	57.1
Cardiovascular disease	55	9.7	104	18.5
Diabetes	2	0.4	19	3.4
 Cancer	31	5.5	73	13.3
Other diseases	62	11.0	89	15.5
All non-disease causes	63	11.1	36	6.4

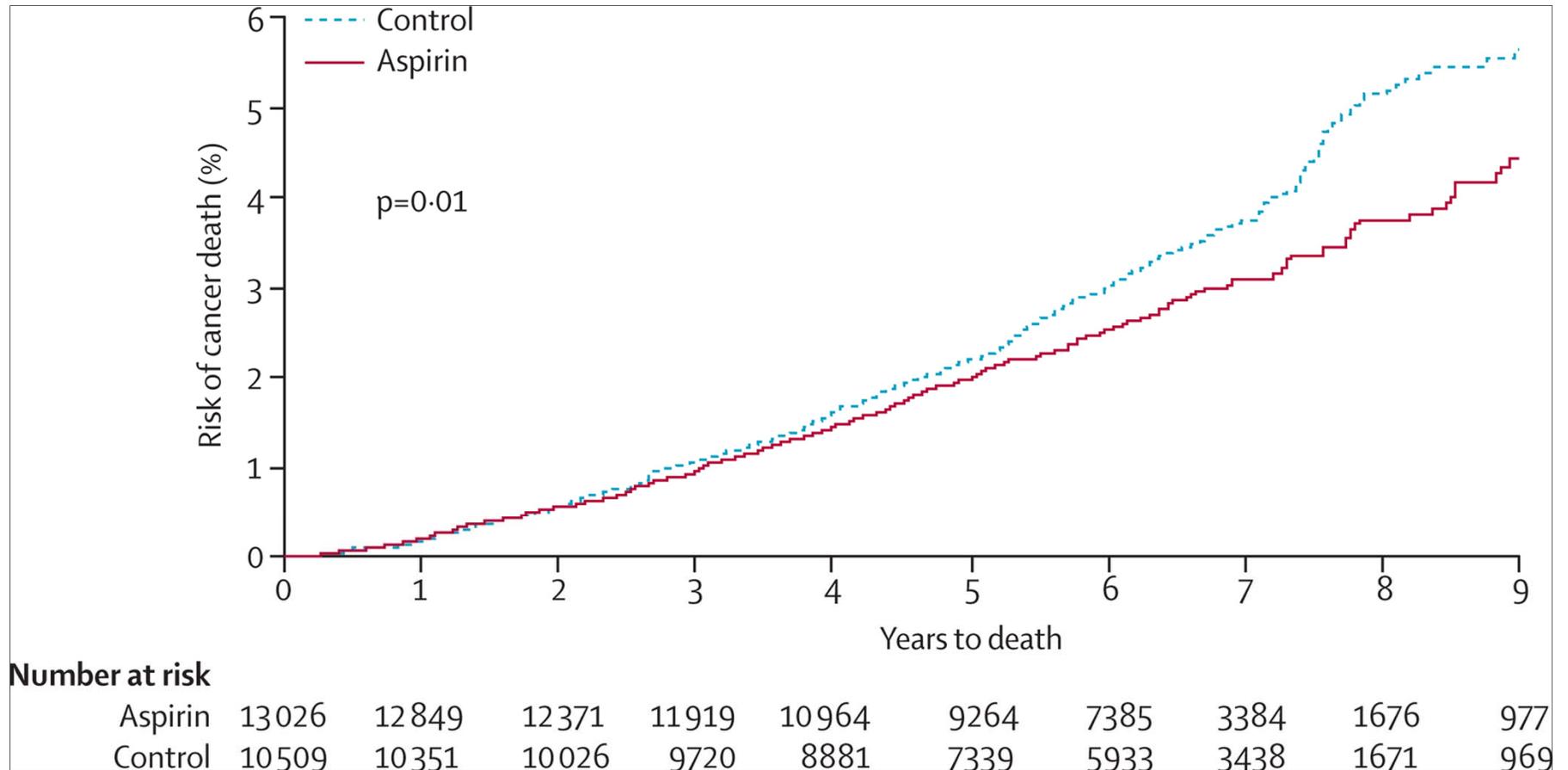
*Deaths that were caused by disease include all deaths minus those caused by accidents unrelated to drugs, poisonings of undetermined intent, suicides, and other non-disease deaths.

Adams, TD et al., Long-term mortality after gastric bypass surgery. N Engl J Med 2007; 357:753-61.

PQ1. How does obesity contribute to cancer risk?



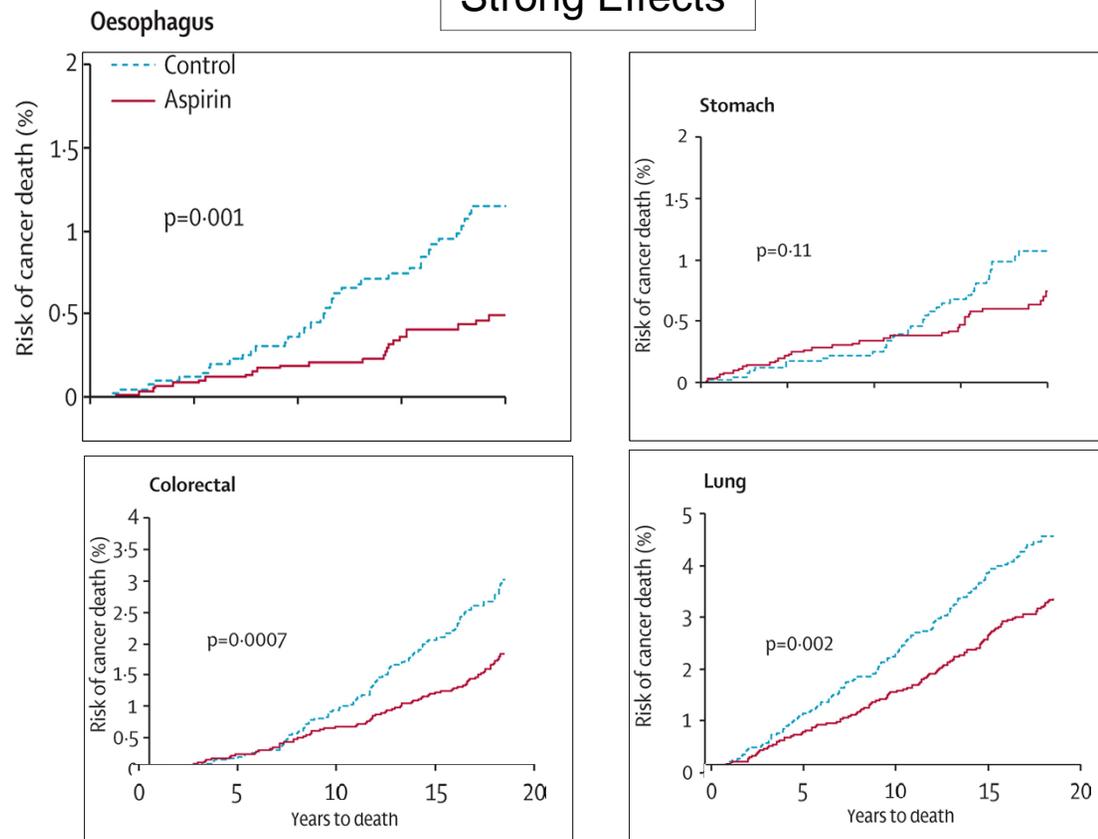
PQ5. Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?



Rothwell et al., Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41. Epub 2010 Dec 6.

PQ5. Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?

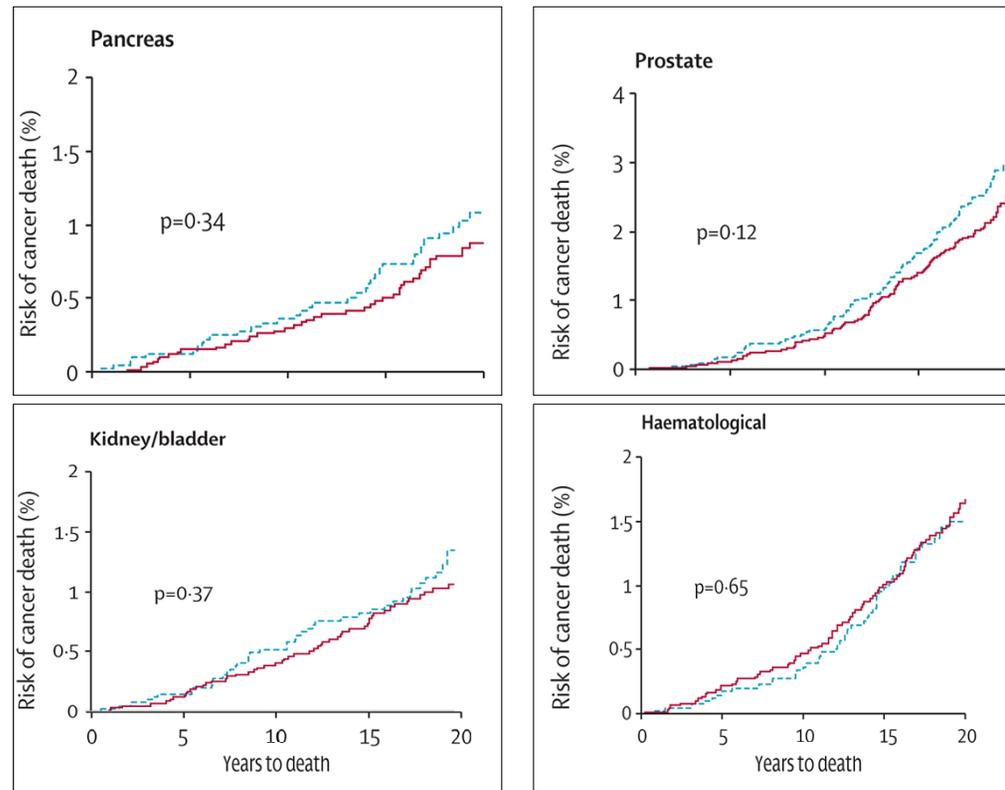
Strong Effects



Rothwell et al., Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41. Epub 2010 Dec 6.

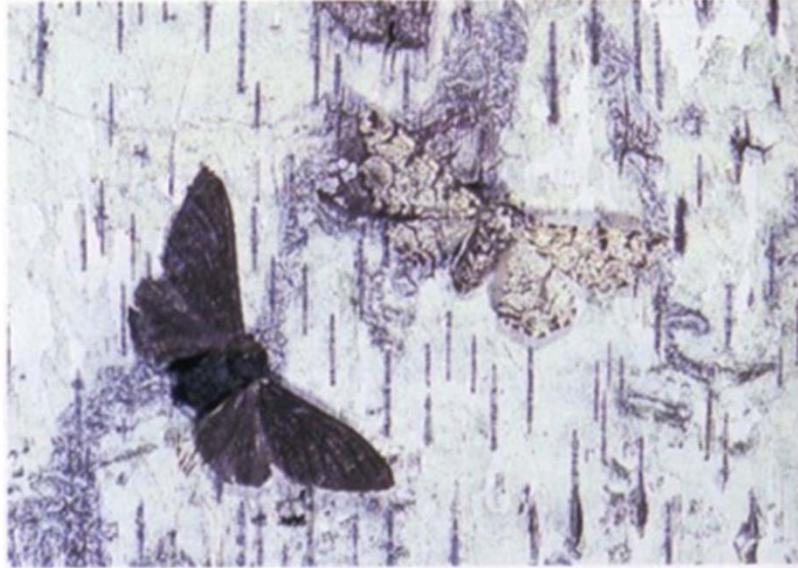
PQ5. Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?

Weak or No Effect



Rothwell et al., Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41. Epub 2010 Dec 6.

PQ21. Given the appearance of resistance in response to cell killing therapies, can we extend survival by using approaches that keep tumors static?



PQ19. Why are some disseminated cancers cured by chemotherapy alone?



VALUE OF PROVOCATIVE QUESTIONS PROJECT

- **Highlights new research questions**
- **Engages the community in setting agenda**
- **Pushes research to new areas**

Particularly important in tight budgetary times

- Rebalances portfolio
- Fights against conservative choices for
both applicants and reviewers

SUMMARY

- **Stimulate research in compelling, understudied areas**
- **Evaluation of success**
 - **Shorter term:**
 - A plethora of exciting applications—reissuance
 - **Intermediate term:**
 - PI's continue their studies through traditional grant mechanisms
 - **Longer term**
 - Answers to the questions
 - Better understanding of neoplasms
 - Improved risk assessment, prevention, treatment, etc.

Heartfelt THANKS

Coordination: Maureen Johnson, Lisa Stevens

Portfolio Analysis: Samantha Finstad, Elizabeth Hsu, Margaret Ames and OSPA staff

Web Designers: Lisa Cole, Clint Malone

**RFA Concept: Chris Seiman, Jan Woynarowski,
Jerry Lee**

I wish I had an answer to that
because I'm tired of answering
that question.

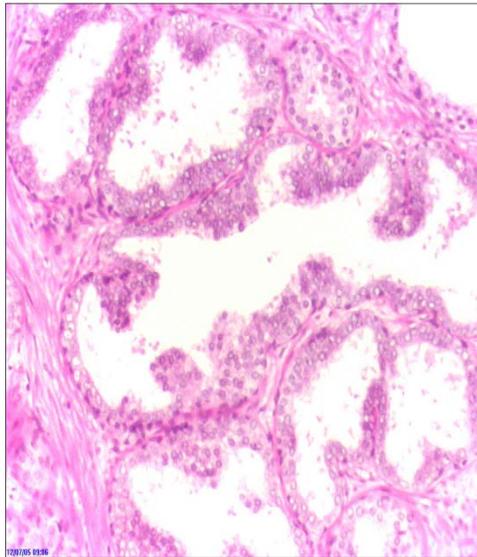
Yogi Berra

We are all agreed that your theory is crazy. The question which divides us is whether it is crazy enough to have a chance of being correct. My own feeling is that it is not crazy enough.

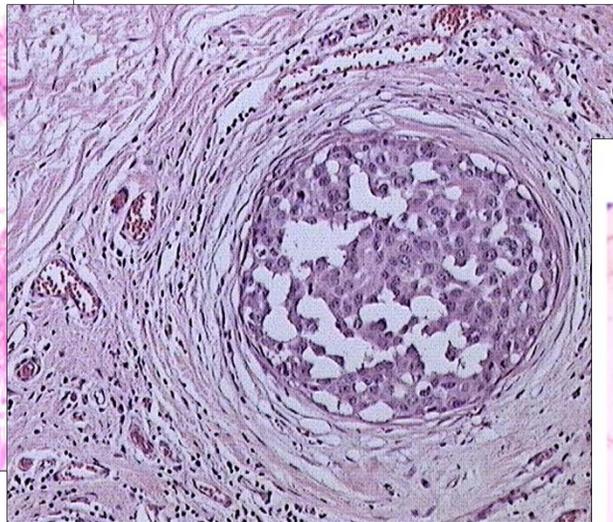
Niels Bohr

WHAT PROPERTIES OF NON-MALIGNANT LESIONS (IN SITU CA'S) PREDICT THE LIKELIHOOD OF INVASIVE DISEASE?

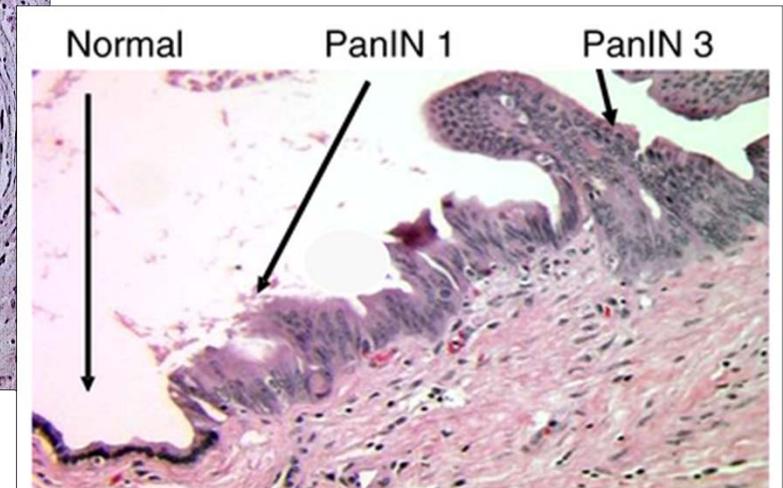
**Prostatic
Intraepithelial
Neoplasia (PIN)**



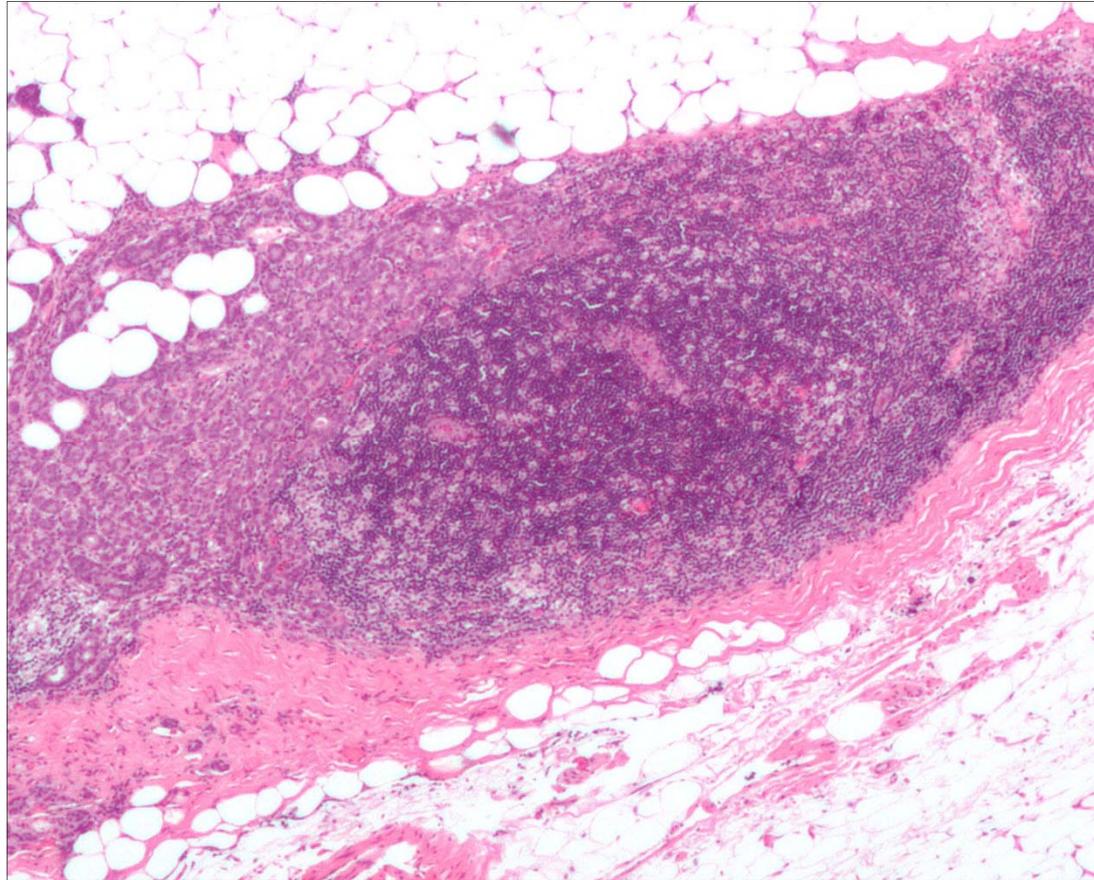
**Ductal Carcinoma
In Situ (DCIS)**



**Pancreatic Intraepithelial
Neoplasia (PanIN)**

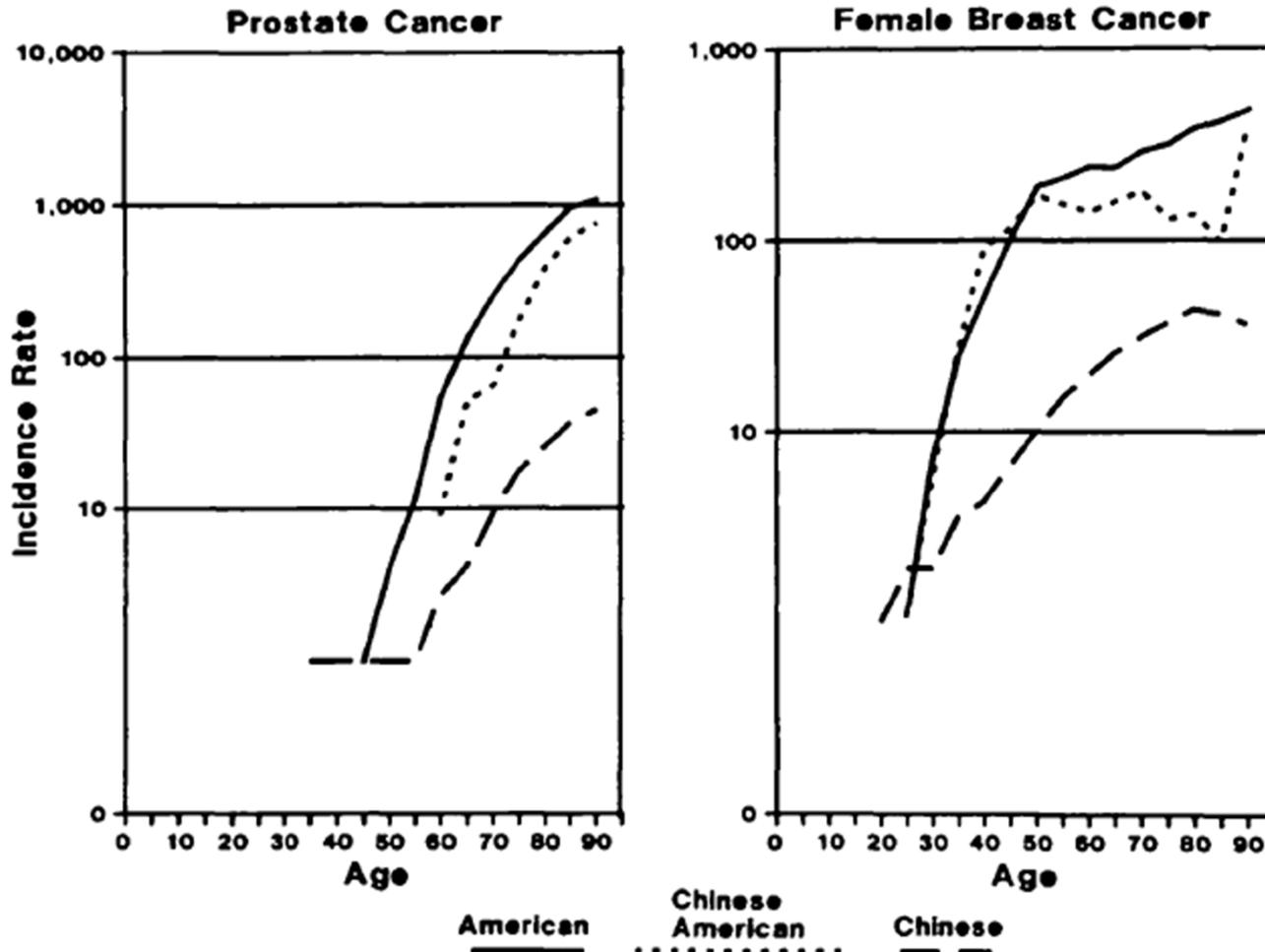


***WHAT IS THE CLINICAL SIGNIFICANCE OF FINDING
CELLS FROM A PRIMARY TUMOR AT ANOTHER SITE?***



Lymph node invaded by ductal breast carcinoma

WHAT ENVIRONMENTAL FACTORS CHANGE THE RISKS OF VARIOUS CANCERS WHEN PEOPLE MOVE FROM ONE GEOGRAPHIC REGION TO ANOTHER?



Yu H., et al. Comparative epidemiology of cancers of the colon, rectum, prostate and breast in Shanghai, China versus the United States. *International Journal of Epidemiology* 1991, 20: 76-81.



***WHY DON'T MORE PEOPLE ALTER BEHAVIORS
KNOWN TO INCREASE THE RISK OF CANCERS?***

- The message itself is not designed optimally for impact
- The message is not effectively delivered
- The interventions to facilitate behavior change are not optimal



Why are different animals with different sizes and different life spans so different with respect to cancer incidence?

Turtles



Mice



Sharks



**Whales....except
belugas from the SLE!**