

Provocative Questions RFA

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BSA Meeting
June 20, 2011

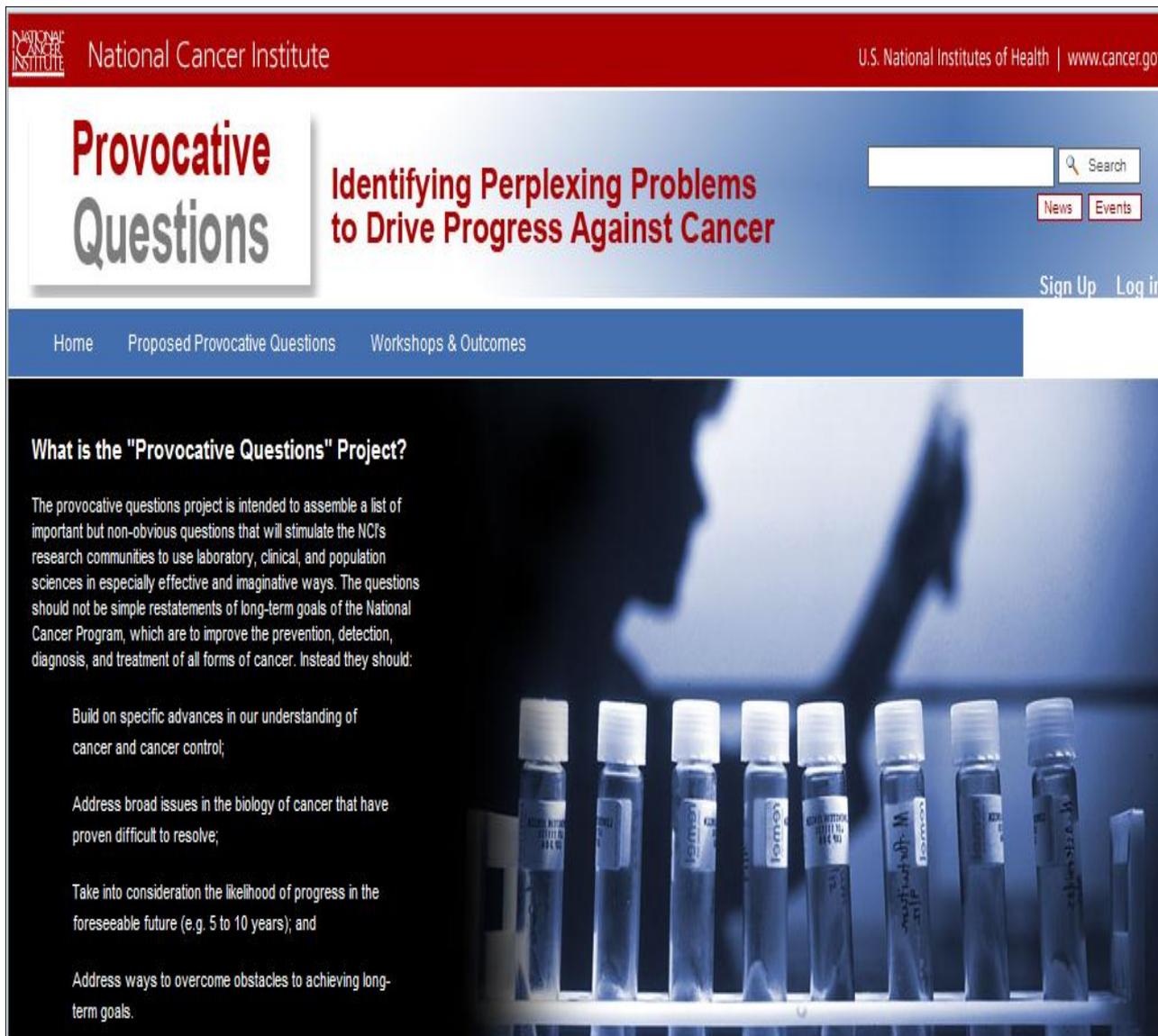
THE PROVOCATIVE QUESTIONS PROJECT

- **Challenge the scientific community to think about and answer important but non-obvious questions that will stimulate NCI's research communities to use laboratory, clinical, and population research in especially effective and imaginative ways.**
 - **The power of a good question: excite the research community**
- **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**

DEVELOPMENT OF THE PQ'S

- **An interactive, iterative process still in progress**
- **A series of small workshops + website**
- **Four workshops held thus far (Oct, Feb):**
 - **Exploratory**
 - **Clinical and translational sciences**
 - **Behavior, population, epidemiology, and prevention sciences**
 - **Basic sciences**
- **More workshops planned (July, Aug)**
 - **Seattle, San Francisco, Los Angeles, San Diego, Bethesda**

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



The image shows a screenshot of the National Cancer Institute website. At the top, there is a red header with the National Cancer Institute logo and the text "National Cancer Institute" on the left, and "U.S. National Institutes of Health | www.cancer.gov" on the right. Below the header, the main content area has a blue background. On the left, the text "Provocative Questions" is displayed in a large, bold, serif font. To its right, the subtitle "Identifying Perplexing Problems to Drive Progress Against Cancer" is written in a smaller, bold, sans-serif font. Further right, there is a search bar with a magnifying glass icon and the word "Search", and two buttons labeled "News" and "Events". At the bottom right of this section, there are links for "Sign Up" and "Log in". Below this is a navigation bar with links for "Home", "Proposed Provocative Questions", and "Workshops & Outcomes". The main content area features a large image of a person's silhouette looking at a computer screen, with a rack of test tubes in the foreground. The text "What is the 'Provocative Questions' Project?" is followed by a paragraph explaining the project's purpose. Below this, there are four bullet points describing the project's goals.

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 News Events 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.

SELECTION OF PQ'S

- **PQ's developed and selected from meetings and those submitted to website**
 - **Goal for this RFA: 15-20 PQ's**
- **Many types of PQ's: e.g., epidemiology, pathogenesis, prognosis, risk modification, prevention, diagnosis, therapeutics, and behavior**
- **Verify the PQ's are understudied: portfolio analysis by the Office of Science Policy and Analysis (OSPA)**

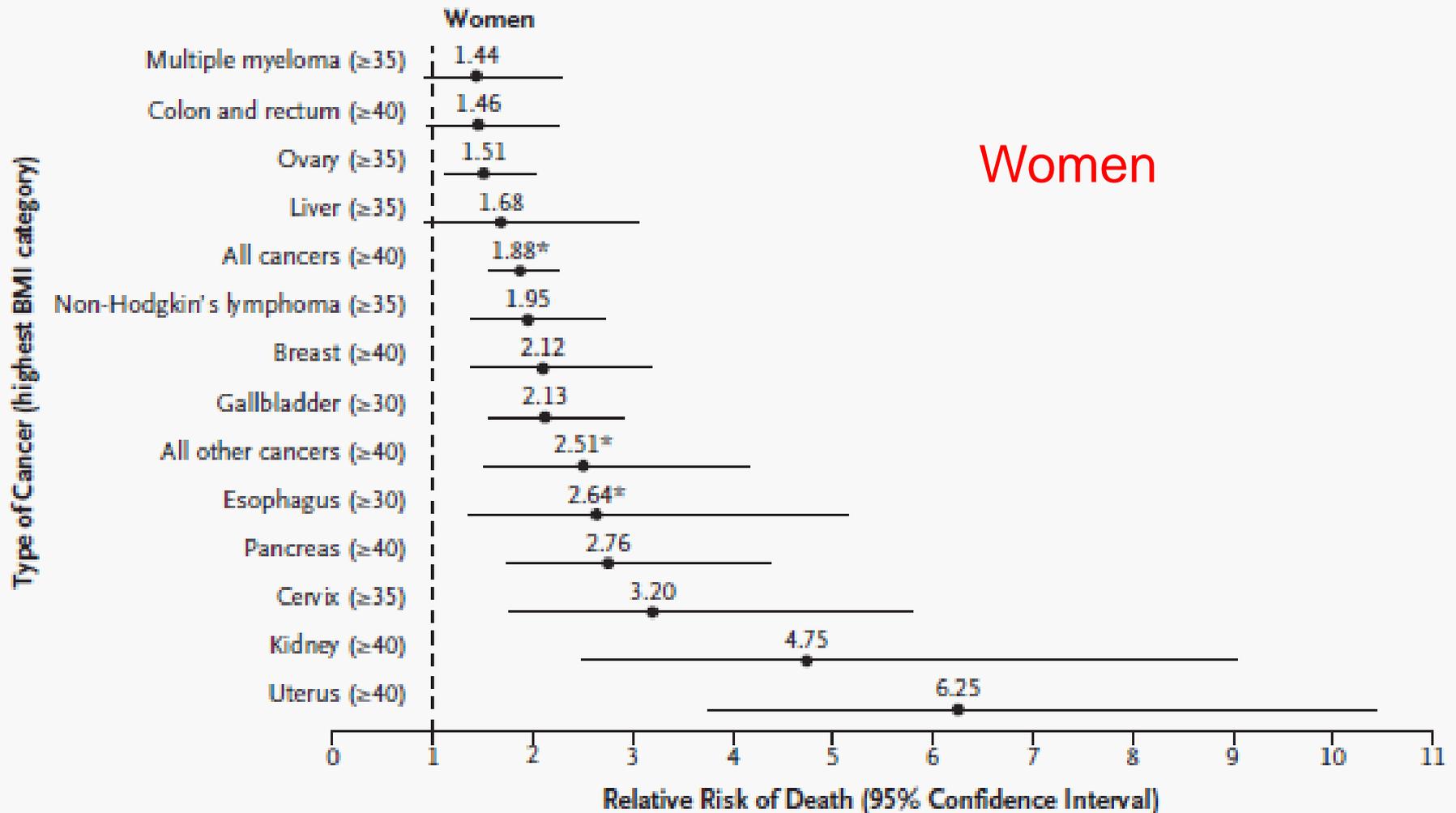
RFA, R21, R01, BUDGET

- **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

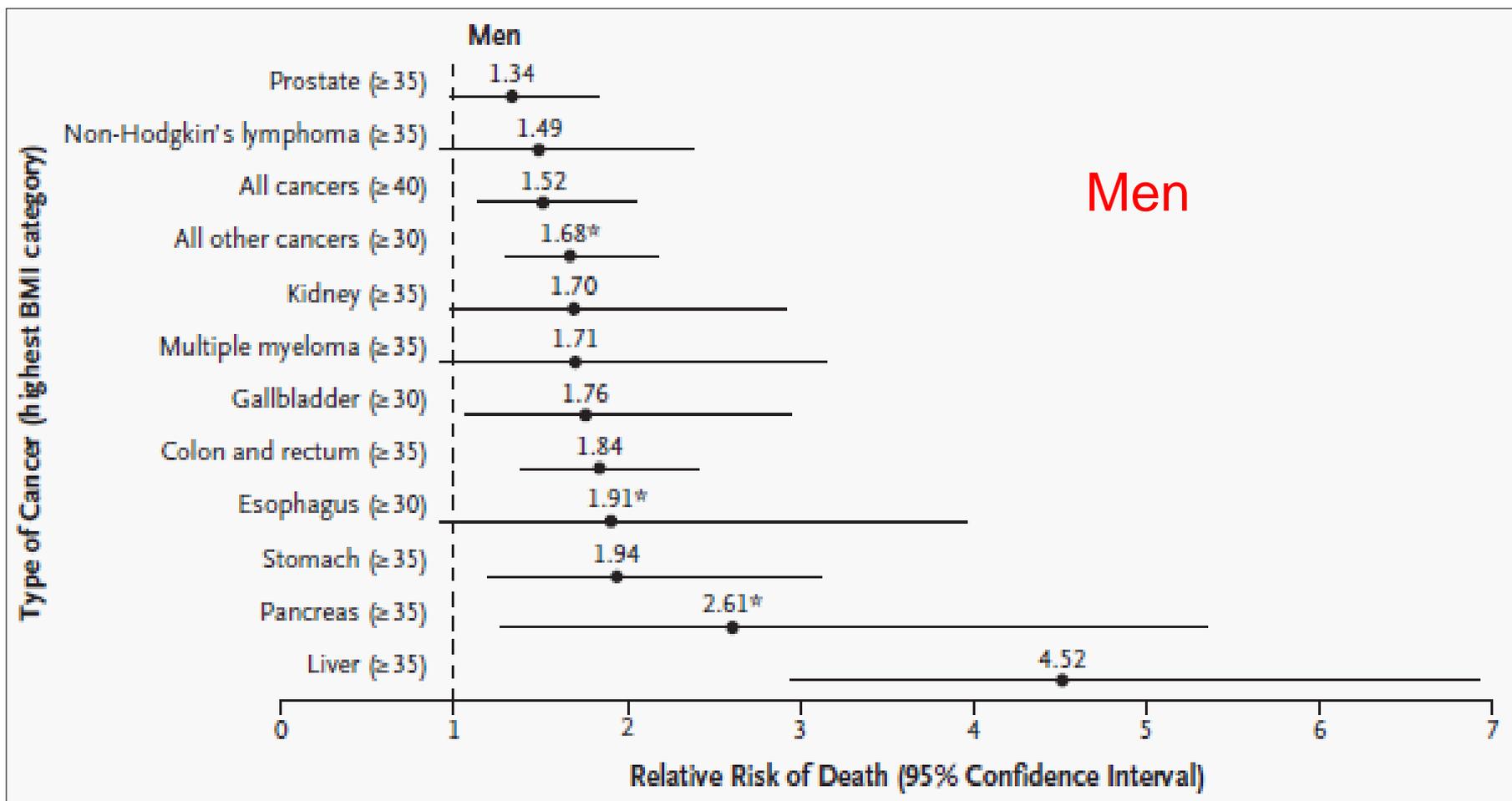
- **The 5 standard review criteria (Significance, PI, Innovation, Approach, and Environment)**
- **Applications may come from PI's new to a field**
 - **strength of the applications judged in large part on the power of the *ideas* behind the proposed research**
 - **preliminary data unnecessary**
 -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

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.

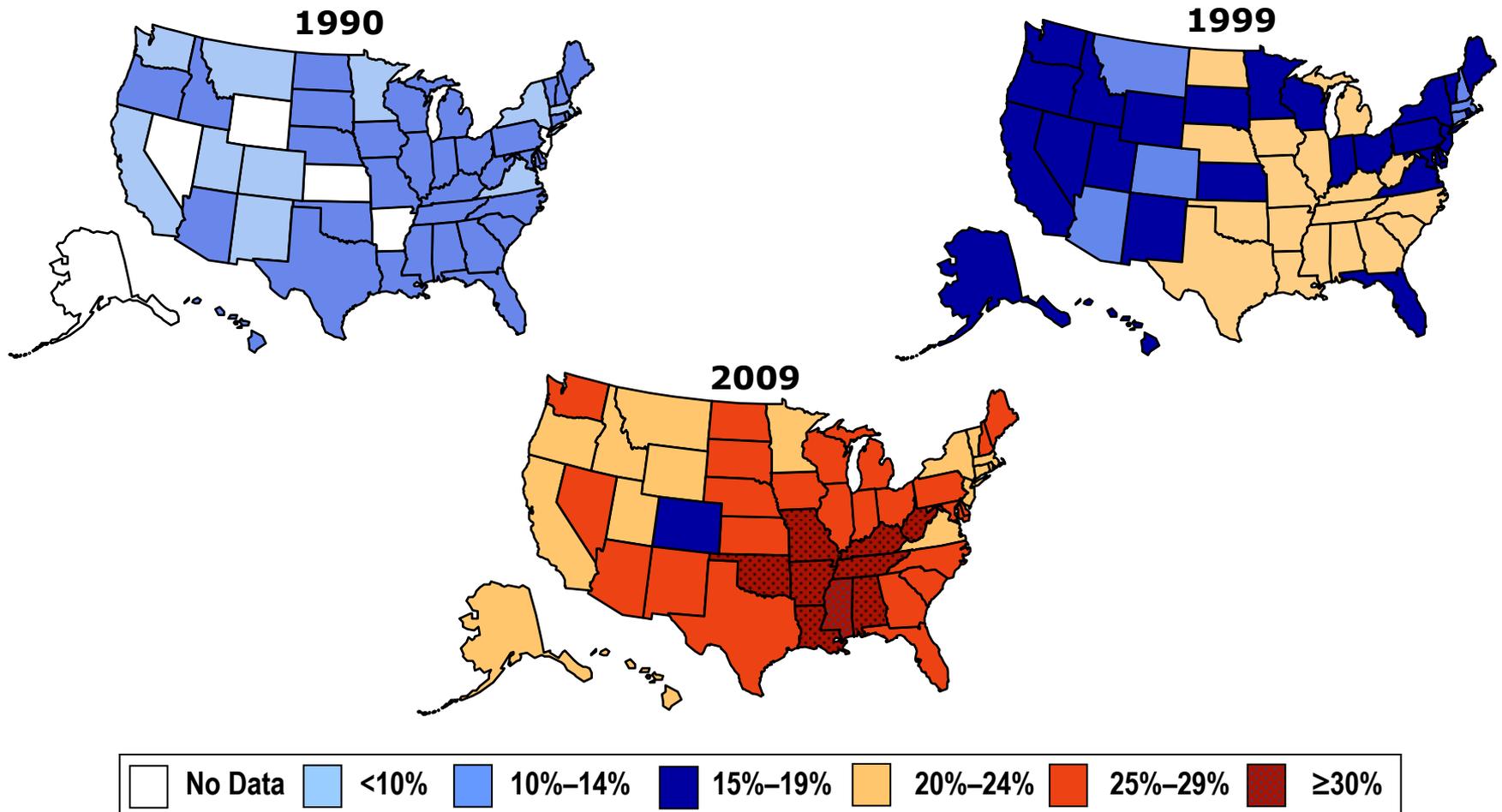
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HOW DOES OBESITY CONTRIBUTE TO CANCER RISK?

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



Source: Behavioral Risk Factor Surveillance System, CDC

LONG-TERM MORTALITY AFTER GASTRIC BYPASS SURGERY

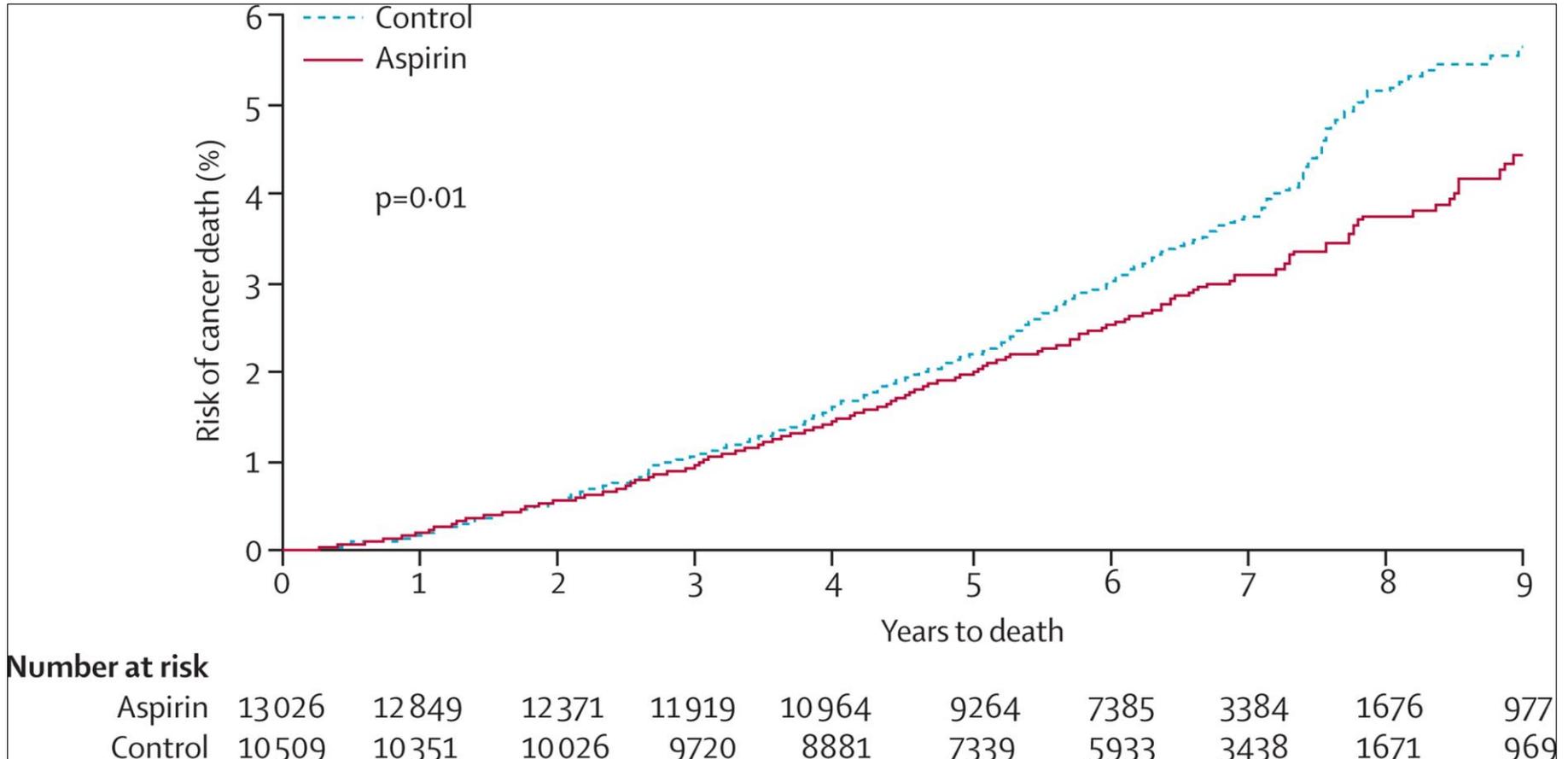
Distribution of Deaths and Death Rates per 10,000 Person-Years*

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.

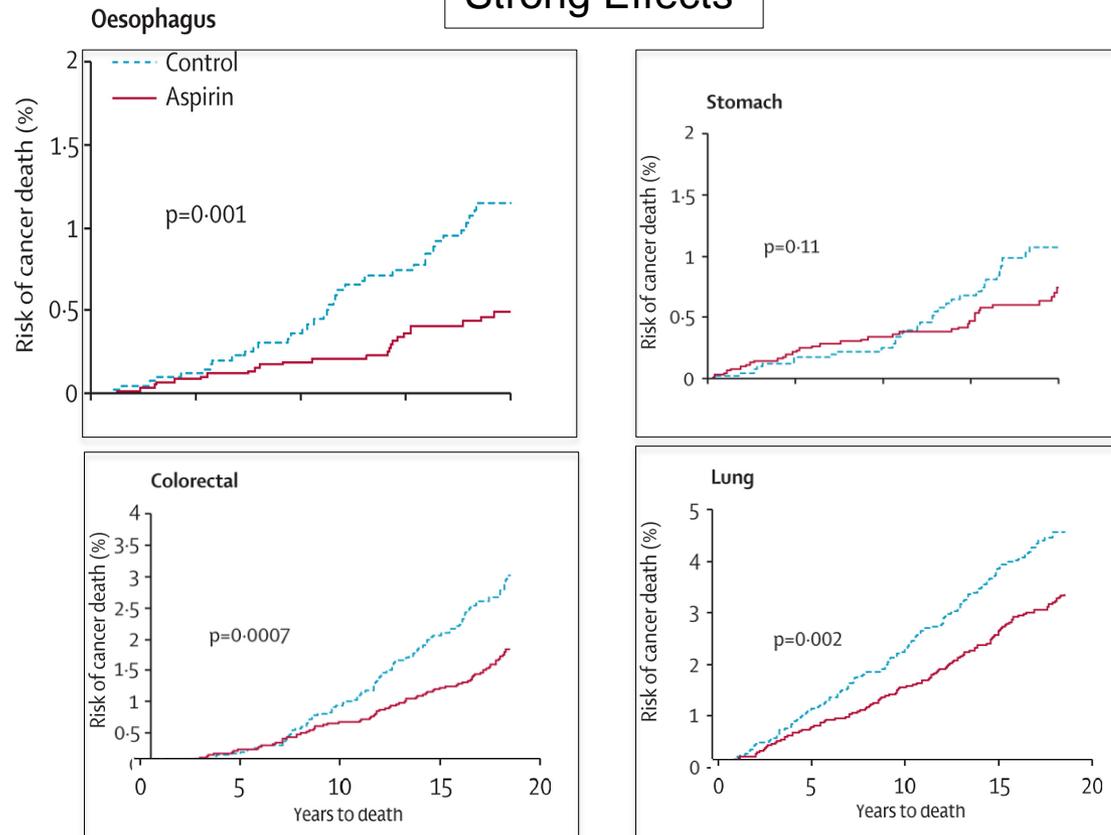
DO DRUGS THAT ARE COMMONLY AND CHRONICALLY USED FOR OTHER INDICATIONS PREVENT CANCERS AND, IF SO, HOW?



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.

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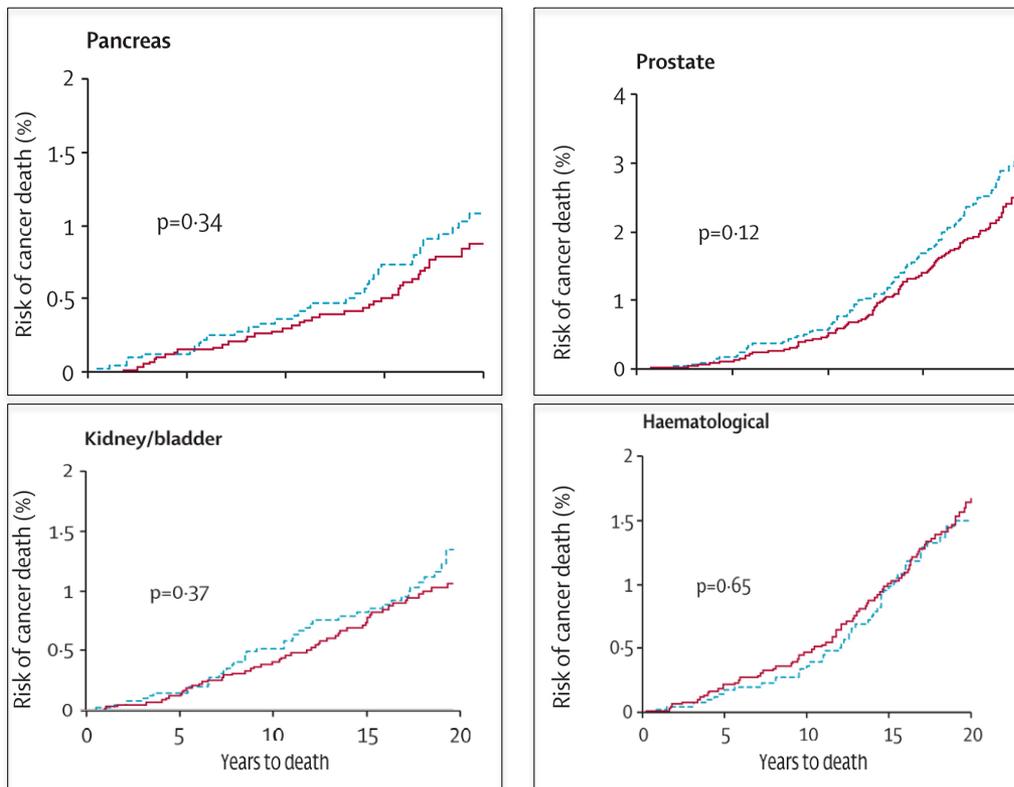
Strong Effects



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.

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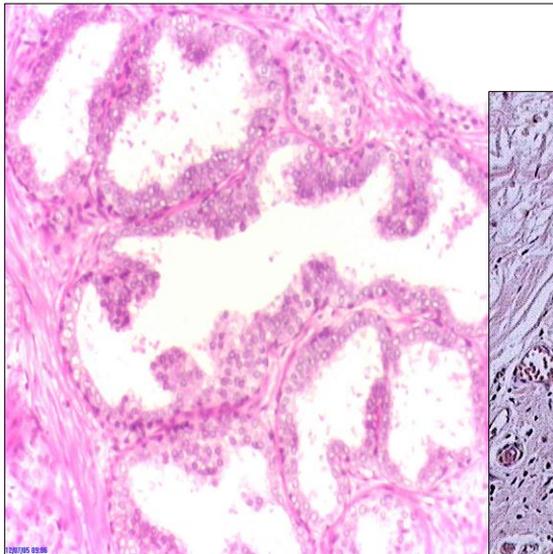
Weak or No Effect



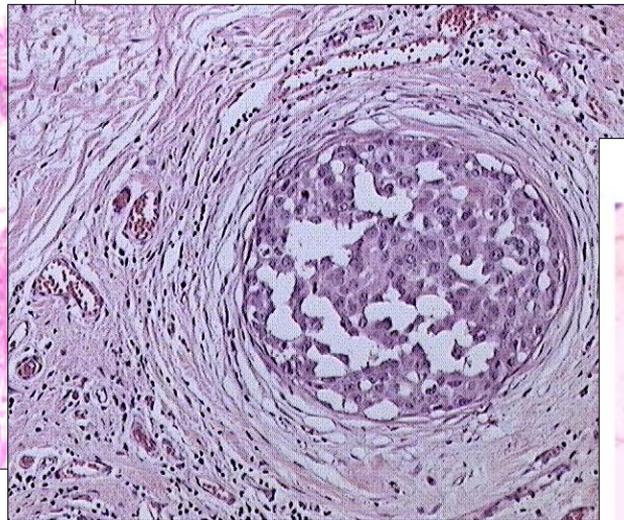
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WHAT PROPERTIES OF NON-MALIGNANT LESIONS (IN SITU CA'S) PREDICT THE LIKELIHOOD OF INVASIVE DISEASE?

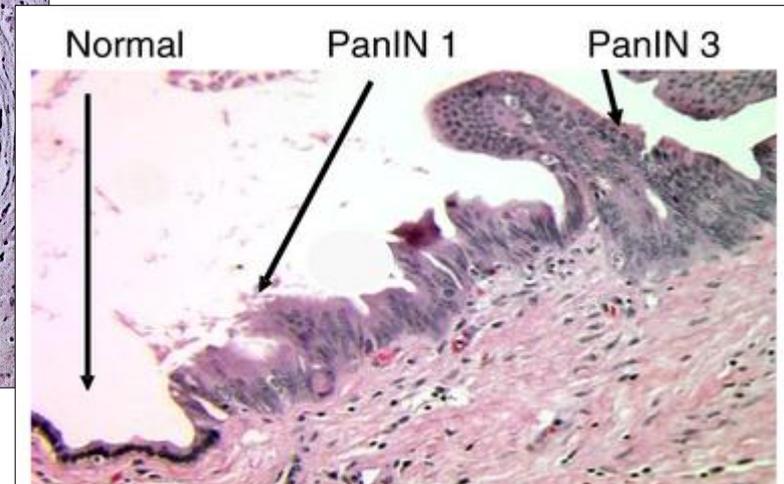
**Prostatic
Intraepithelial
Neoplasia (PIN)**



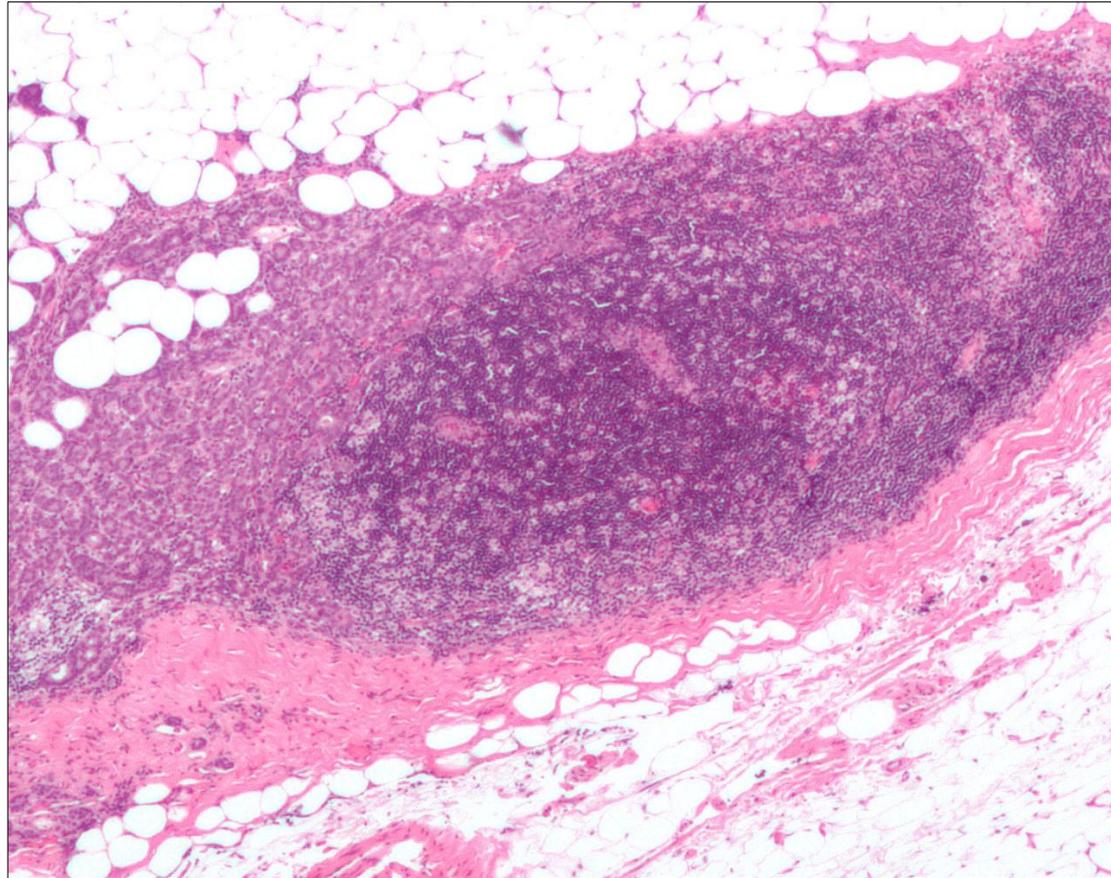
**Ductal Carcinoma
In Situ (DCIS)**



**Pancreatic Intraepithelial
Neoplasia (PanIN)**

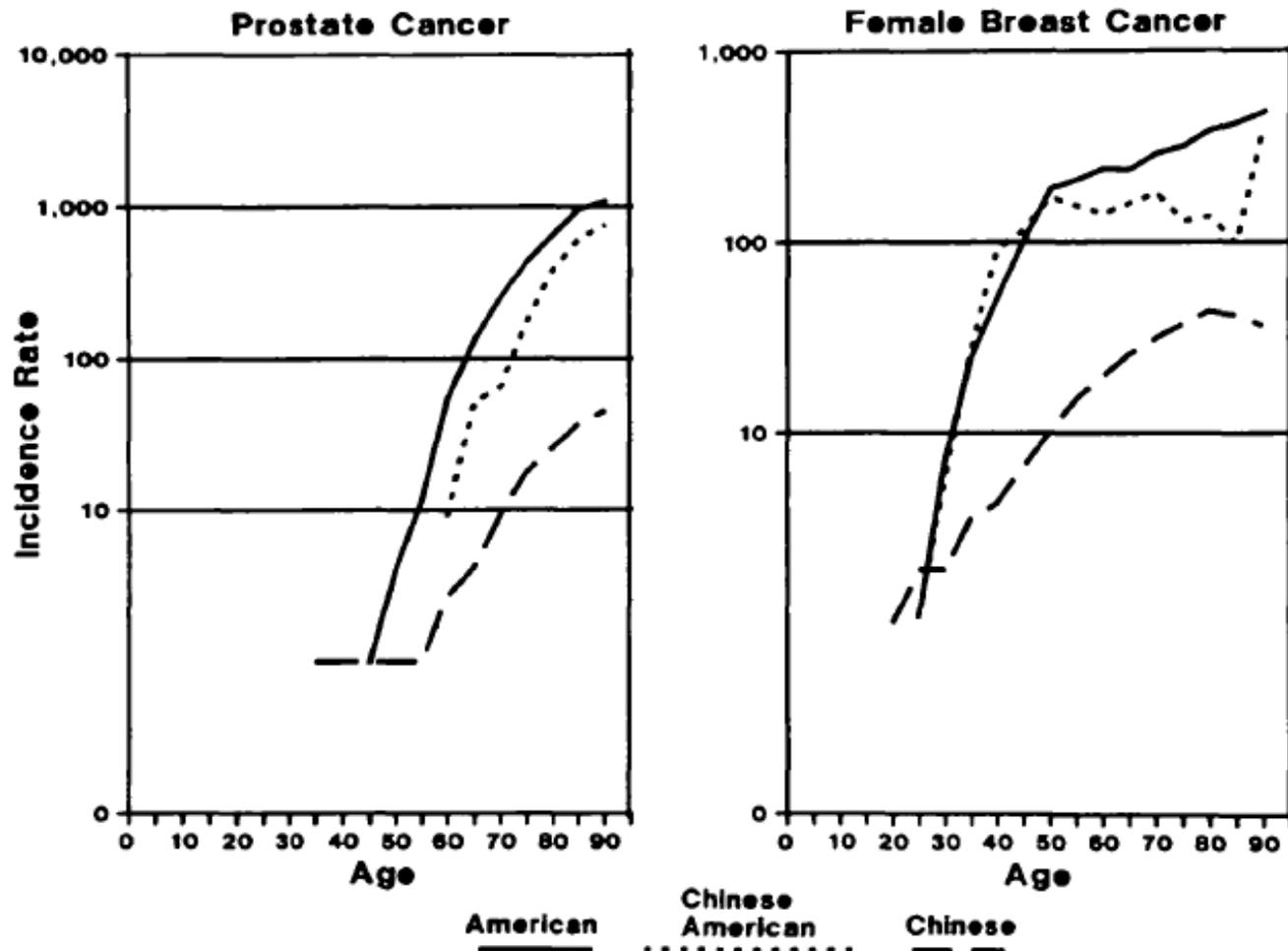


***WHAT IS THE CLINICAL SIGNIFICANCE OF FINDING
CELLS FROM A PRIMARY TUMOR AT ANOTHER SITE?***



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?

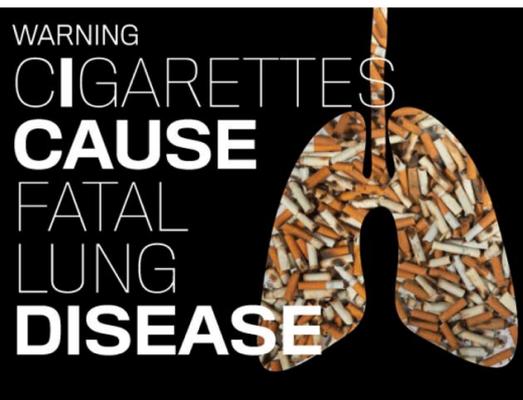


Yu H., et al. Comparative epidemiology of cancers of the colon, rectum, prostate and breast in Shanghai, China versus the United States. *International Journal of Epidemiology* 1991, 20: 76-81.



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!**

WHY ARE SOME DISSEMINATED CANCERS CURED BY CHEMOTHERAPY ALONE?



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.

THANKS

**Coordination and Portfolio Analysis: Margaret Ames,
Lisa Stevens, OSPA staff, Maureen Johnson**

Web Designers: Lisa Cole, Clint Malone

**RFA Concept: Dinah Singer, Barbara Spalholz, Judy
Mietz, Anne Lubenow, Jerry Lee**

BSA SUBCOMMITTEE QUESTIONS

“The PQ RFA is an excellent idea but....”

- **Analogous NCI/NIH programs?**
- **Complexity and challenge of the review process**
 - **Getting enough competent reviewers for the two-tiered process?**
 - **“Non-responsive” to RFA: stringent or permissive?**
 - **“Enforcing” the importance of ideas vs. preliminary data?**
 - **Proscribe preliminary data?**
 - **Automatic submission of triaged applications to a regular CSR study section?**