

# Epidemiology

# **Epidemiology**

**Translational Research in Clinical Oncology**

**October 19, 2020**

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# A Population Perspective

## A Population Perspective on Cancer

- ***What is epidemiology?***
- *What has epidemiology accomplished?*
- *What can go wrong?*
- *What can go really wrong?*
- *What next?*

# What is epidemiology?

## A Population Perspective on Cancer

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# Cigarettes and culture

80 years ago cigarettes were an accepted part of the culture.....  
Trusted figures of doctors were used to address health fears



According to a recent **MORE DOCTORS SMOKE CAMELS** nationwide survey: **THAN ANY OTHER CIGARETTE!**

...The doctor on duty, the one who is always on hand, and always on the job for you, is the one who is always on the job for you...

...These results, which prove that the doctor on duty, the one who is always on hand, and always on the job for you, is the one who is always on the job for you...

**CAMELS** *Cooler*  *Tobacco*

...The doctor on duty, the one who is always on hand, and always on the job for you, is the one who is always on the job for you...



**20,679<sup>®</sup> Physicians** say "**LUCKIES** are *less irritating*"

**"It's toasted"**

Your Throat Protection against irritation against cough

# Decades of change

It takes decades to change the perception of the publics and physicians



# Epidemiology

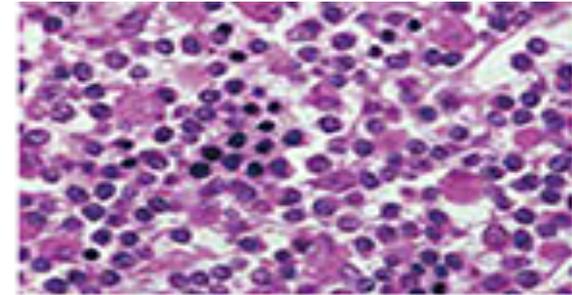
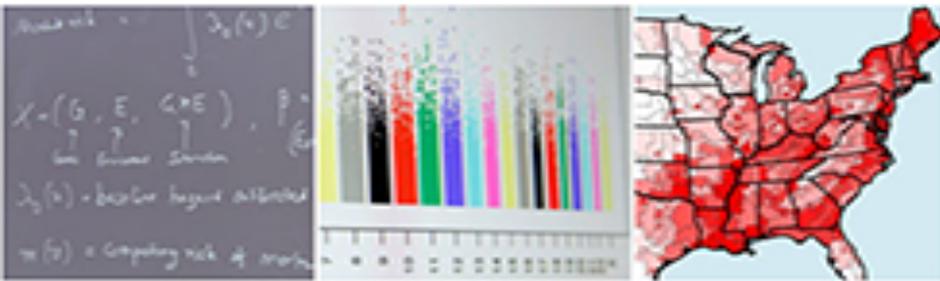
**Epidemiology** is concerned with human **populations**  
= *epi* (upon) + *demos* (the people) + *logia* (talk about)



**OBSERVATIONAL** science (like astronomy, evolutionary biology)

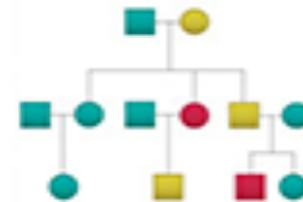
- Contrast with *experimental*
- Investigator does NOT get to pick who is exposed or unexposed
- Free-living people make choices about participating...introduces **BIAS**

# DCEG

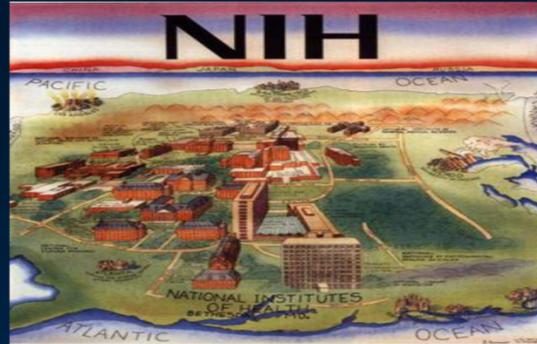


## NCI's Division of Cancer Epidemiology and Genetics

### Occupation and Environmental Epidemiology Branch



# NIH epidemiology



↓  
National Cancer Institute

→ We are **INTRAMURAL**  
~ 85% \$\$ are extramural

↓  
Division of Cancer Epidemiology and Genetics

↓  
**Genetic Epidemiology Branch**

→ Cancer **ETIOLOGY**

→ Other Branches focus on  
Nutrition, Hormones, Infection,  
Occupation, Statistics, Radiation

# DCEG

NIH



NCI



DCEG

**NIH** NATIONAL CANCER INSTITUTE  
Division of Cancer Epidemiology & Genetics

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Discovering the causes of cancer and the means of prevention

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### Confluence Project Now Accepting Information from Interested Studies

The Confluence Project will develop a large research resource to uncover breast cancer genetics through genome-wide association studies.

- Learn more about the Confluence Project
- Complete the inventory for interested studies

Postmenopausal Bleeding and Endometrial Cancer | Confluence Project Launches | Novel Susceptibility Loci for Ewing Sarcoma

### Fellowships

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Learn about our training programs

### Scientific Position Openings

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@NCIEpTraining #

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### Research News and Highlights

- Low-dose Radiation Exposure Linked to Leukemia in Retrospective Study
- Coffee Consumption and Mortality Risk
- Scientific Highlights - March - June 2018

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### People in the News

- AuthorArranger Tool Helps Quickly Format Manuscript Title Pages
- Douglas Lowy and John Schiller Appointed DCEG Adjunct Investigators
- Margaret Tucker Retires from DCEG

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# Collaborations

## Collaborations around the world



# Major public health advances

## Major public health advances

### **Regulatory changes**

- Drinking water
- Gasoline (less benzene)
- Workplace safety (diesel)
- Safer farming

### **Clinical practice**

- Cancer susceptibility syndromes
- Second cancers among cancer survivors

### **Preventive interventions**

- Safer CT scans
- Risk-reducing surgeries for individuals at high-risk
- Benefits of healthy weight and physical activity
- Efficacy of human papillomavirus vaccine for cervical cancer
- Eliminating indoor pollution

# Cancer risk

## Cancer risk assessment tools

### Breast Cancer Risk Assessment Tool

An interactive tool to help estimate a woman's risk of developing breast cancer



### Melanoma Risk Assessment Tool

An interactive tool to help estimate a person's risk of developing invasive melanoma



### Colorectal Cancer Risk Assessment Tool

An interactive tool to help estimate a person's risk of developing colorectal cancer



# Observational vs. Experimental

## Observational vs. Experimental

Epidemiologists are ethically prohibited from doing experiments on people

So, we observe large populations and see how their outcomes relate to what people do (i.e., smoke, drink, eat, etc.)

*This weakness of the 'observational' argument were exploited by tobacco companies to deny evidence linking cigarettes and cancer.....*

# Goals

## *Goals of epidemiology*

1. Identify the **causes** of cancer
2. Quantify **risks**/identify risk groups
3. **Public health** and health services
4. Identify syndromes, trends, epidemics
5. Understand **mechanisms**
6. Prevention

# Hierarchy of studies

## Hierarchy of studies

	<b>COSTS</b>	<b>(\$)</b>
Anecdotes from individual subjects and 'astute clinicians'	NONE	
↓		
Small unrepresentative samples	LOW	$10^{2-3}$
↓		
Cross-sectional studies (prevalence)	LOW	$10^{3-5}$
↓		
Case control studies	MODERATE	$10^{4-7}$
↓		
Cohort studies	HIGH	$10^{6-7}$
↓		
Randomized clinical trials (RCT)	HIGHEST	$10^{7-9}$

# *Epidemiologists worry about **bias***

Bias= systematic deviation from truth

Epidemiologists fret about **PARTICIPATION RATES**  
**if too low.....**

study subjects not REPRESENTATIVE  
of the target populations  
results not be GENERALIZABLE  
to the general population

**Selection Bias** = subjects in the study are 'selected' and therefore nonrepresentative

# Controls for epidemiologists

<sup>6</sup>*Epidemiologists worry about **controls***

## **Population controls**

Expensive

Most representative (selection bias still possible)

Calculate ABSOLUTE risks (contrast with RELATIVE risks)

Increasingly difficult- RDD problematic!

Defined in time and space

Inclusion and exclusion criteria

High response rate!

## **'Convenience' controls are the least desirable**

Biased by differences in:

Age, risk factors, ethnicity, education,  
participation rate, access to care, SES....

# Epidemiologist as **consultant**

Questions the consulting epidemiologist will ask:

Your study design is...?

Your controls came from....?

Did you collect key covariate data?

Did you consider bias, confounding?

What was the original hypothesis? (data dredging)

Have you done power calculations?

How did you validate your marker?

Epidemiologist is helpful when a question involves the **population** (as opposed to an individual, organ, cell, etc.)

# Participation rate. Can you explain

## Pilot studies: participation rate

**30%**

- Phone Survey

**49%**

- Invitation letter
- Follow-up by phone
- In hospital
- Advertisements
- Cash award
- Physicians' letter
- Home/hospital

**73%**

- **New interviewers**
- Physicians' call
- **Gas coupon**
- TV ads
- New invitation letter
- Mayor's letter
- Toll-free phone line

**Total number of subjects in pilot investigations:  
156 Cases - 212 Controls**

- Clinical data: 99%
- Questionnaires: 87%
- Biospecimens: 97%



# Most common question

The **most common question** epidemiologists get!

Can you explain why.....

My grandmother smoked all her life.  
her exercise was the TV remote,  
she never used a seat belt,  
she ate bacon and donuts for breakfast...  
she drank shots on her 90<sup>th</sup> birthday  
  
she outlived all her doctors.....

*The race is not to the swift or the battle to the strong,  
nor does food come to the wise or wealth to the brilliant or favor to the learned;  
but time and chance happen to them all. (Ecclesiastes)*

**Probabilistic - Deterministic**

# Consultant

## *Epidemiologist as consultant*

**Questions the consulting epidemiologist will ask:**

- 1. Your study design is...?**
- 2. Your controls came from....?**
- 3. Did you collect key covariate data?**
- 4. Did you consider bias, confounding?**
- 5. What was the original hypothesis? (data dredging)**
- 6. Have you done power calculations?**
- 7. How did you validate your (bio)marker?**

**Epidemiology is relevant when a question involves a **population** (as opposed to an individual, organ, cell, etc.)**

# Epidemiologists worry about

*Epidemiologists worry about ....*

***correlation vs. causation***

***After eliminating obvious statistical  
and non-statistical flaws,  
How to epidemiologists infer  
causality?***

*How do you prove a cause?*

(TODAY)

- 1. Mendelian Randomization*
- 2. Molecular Epidemiology*
- 3. Mediation analysis*

# Population Perspective

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# Causation

**Causation** (population perspective)

*How do you prove a cause?*

(population PERSPECTIVE)

1. *It should confer **high risk***
2. *It should be consistent*
3. *Dose response*
4. *Cause occurs first (temporal) !*
5. *Biology makes sense (mechanism)*

Hill AB. The environment and disease: association or causation  
Proc Royal Soc Med 1965; 58, 295-300.

# Overall risk

*Which of the following is more convincing?*

Lung cancer is associated with cigarette smoking  
OR=20

Colon cancer is associated with Red Meat consumption  
OR=1.2

Considerations that call into question **low risks**:

- 1- risk is NOT clinically significant (absolute risk small)
- 2- residual confounding from smoking (other shared risks)
- 3- meat eaters have unhealthy features: drink more, exercise less, sedentary, poor, less educated etc.
- 4- diet associations: sugar, processed fats, 'french fries', etc.

# Meat consumption

5 systematic reviews and editorial in *Annals of Internal Medicine* (Oct 2019)

“little evidence for adverse cancer or cardiovascular outcomes....”

## Annals of Internal Medicine

### Meat Consumption and Health: Food for Thought

For some time, medical and science organizations have been leading the drum that red and processed meat are bad for you. For almost as long, they have lamented that their efforts to inform the public have not convinced enough people to change their consumption. This matters, because, as stated in the *Thought for the Day*:

The fact of our dual responsibilities is plagued by observational studies that have concluded the opposite analyses, accompanied by likely erroneous conclusions (1). Many studies selectively report results, and many lack an a priori hypothesis. Many use notoriously unreliable self-reports of food consumption while failing to collect or appropriately control for data on numerous potential confounders.

Let's start with the evidence for the health-related needs to change our diets. There is continuing evidence that the consumption of meat, and what kind of meat, leads to poor health outcomes, such as cancer and cardiovascular disease. Although many studies report health risks (2), many more men examining the same data sets as those reporting a significant risk (2) do not. Some reviews of the literature conclude that processed meat is carcinogenic, and red meats are “probably carcinogenic” (3). Other reviews conclude that evidence supporting the association between red meat consumption and colon cancer and cardiovascular disease is weak (3).

Four meta-analyses join the evidence base this month, and because they reanalyze all the evidence that came before, they cannot be accused of cherry-picking. The first was a meta-analysis of cohort studies that focused on how dietary patterns, including differing amounts of red or processed meat, affected all-cause mortality, cardiovascular outcomes, and cancer incidence and mortality (4). More than 120 studies included 10 million participants were analyzed. The overall conclusions were that dietary patterns, including differences in meat consumption, were weak to only small differences in risk outcomes in more living people.

The new study was a meta-analysis that looked in specifically an cohort studies examining how red meat, red and processed meat, and/or processed meat consumption and mortality (5). It included 110 studies with more than 5 million participants, and it, too, found that the “possible impact of red and/or processed meat on mortality was weak to only small differences in risk outcomes in more living people. The third study was a meta-analysis of cohort studies that looked specifically at meat consumption and cardiovascular outcomes, including mortality and morbidity (6). More than 120 studies included 10 million participants were analyzed. The overall conclusions were that dietary patterns, including differences in meat consumption, were weak to only small differences in risk outcomes in more living people.

Of course, and over again, they stressed that even if the results were statistically significant, their certainty was low and the absolute differences seen were small and potentially confounded.

Higher quality interventions studies would be better. They also cited in a fourth analysis in this issue (3), researchers assessed numerous observational trials that compared diets with differing amounts of red meat consumption for at least 5 months. They found 12 eligible studies, but one of them—the Women's Health Initiative—was so large (almost 49,000 women) that it dominated the analysis. We can wish for more studies, and we could hope that they had more homogeneous outcomes and better ability to assigned diets, but the overall conclusions from what they had were that “red meat may have little or no effect on cardiovascular morbidity and mortality and on cancer mortality and incidence.”

When this was offered with little or very low certainty. Despite this lack of credible evidence, the case has long been made for reducing meat consumption to reduce risk for cardiovascular disease and various cancers. Indeed, reduction of meat intake is generally endorsed in dietary guidelines.

A WHO article this month is a new guideline, however, based on these reviews (7). It was voted on by 55 members, including 2 community members, from 7 countries and had strict criteria concerning conflicts of interest. The overall recommendations, contrary to almost all others that exist (4, 5, 11, 12), suggested that adults continue to eat their current levels of red and processed meat, unless they feel inclined to change their behaviors.

This is sure to be controversial, but it is based on the most comprehensive review of the evidence to date. Because that review is inclusive, those who seek to dispute it will be hard pressed to find scientific evidence with which to build an argument.

The final article on this topic (13) reports on 4 systematic reviews on “meat consumption” as it relates to all-cause mortality and cardiovascular morbidity and mortality, and red and processed meat consumption, and that will impress to change their consumption habits on the basis of health concerns (13). Reasons for eating meat include enjoyment, a satisfying meal essential to a healthy diet, considering meat to be part of one's culture, and uncertainty about preparing adequate and tasty meals that did not include meat. None of these are really a surprise, nor is the fact that participants more frequently responded to these concerns than to concerns about weight

to argue that this is a disconnected set of beliefs. Research suggests that presenting an individual with information that opposes their beliefs could result in them holding on more tightly to those beliefs (14). Some of this is due to the Dunning-Kruger effect, which describes the inverse relationship between actual and perceived knowledge about a topic. The less people know, the more they actually think they know (15). Although some of this effect relates to a lack of knowledge and thus a lack of context to evaluate one's own beliefs in understanding, a third class is in their eagerness to fight their own beliefs, and their views may vary little to do with intelligence (16).

But in this case, it's not even clear that those who believe what they hear about meat are wrong. We have reported that men eat with awareness about the dangers of red meat. It would be hard to find someone who doesn't “know” that experts think we should all eat less. Continuing to insist that fat, salt, sugar, and more likely studies involving potential small relative risks, is not changing anyone's mind.

Moreover, I may be the last person producing observational research in this area. These meta-analyses include millions of participants. Further research involving much smaller cohorts has limited value. High-quality randomized controlled trials are outcomes, but only if they're designed to tell us things we don't already know.

It's also probably time for a major overhaul of the methods for summarizing nutritional data in ways that might get through to target populations and change health outcomes. One finding from the studies reviewed by Wall and colleagues (13) that may hold promise is that there are many reasons other than health to reduce meat consumption. Ethical concerns about animal welfare may be important, as can concerns about the effects of meat consumption on the environment. Both of these issues might be more likely to target people, and they have the added benefit of empirical evidence behind them. And if they result in reducing meat consumption, and even if there is small health benefit as a side effect, it's worth a try.

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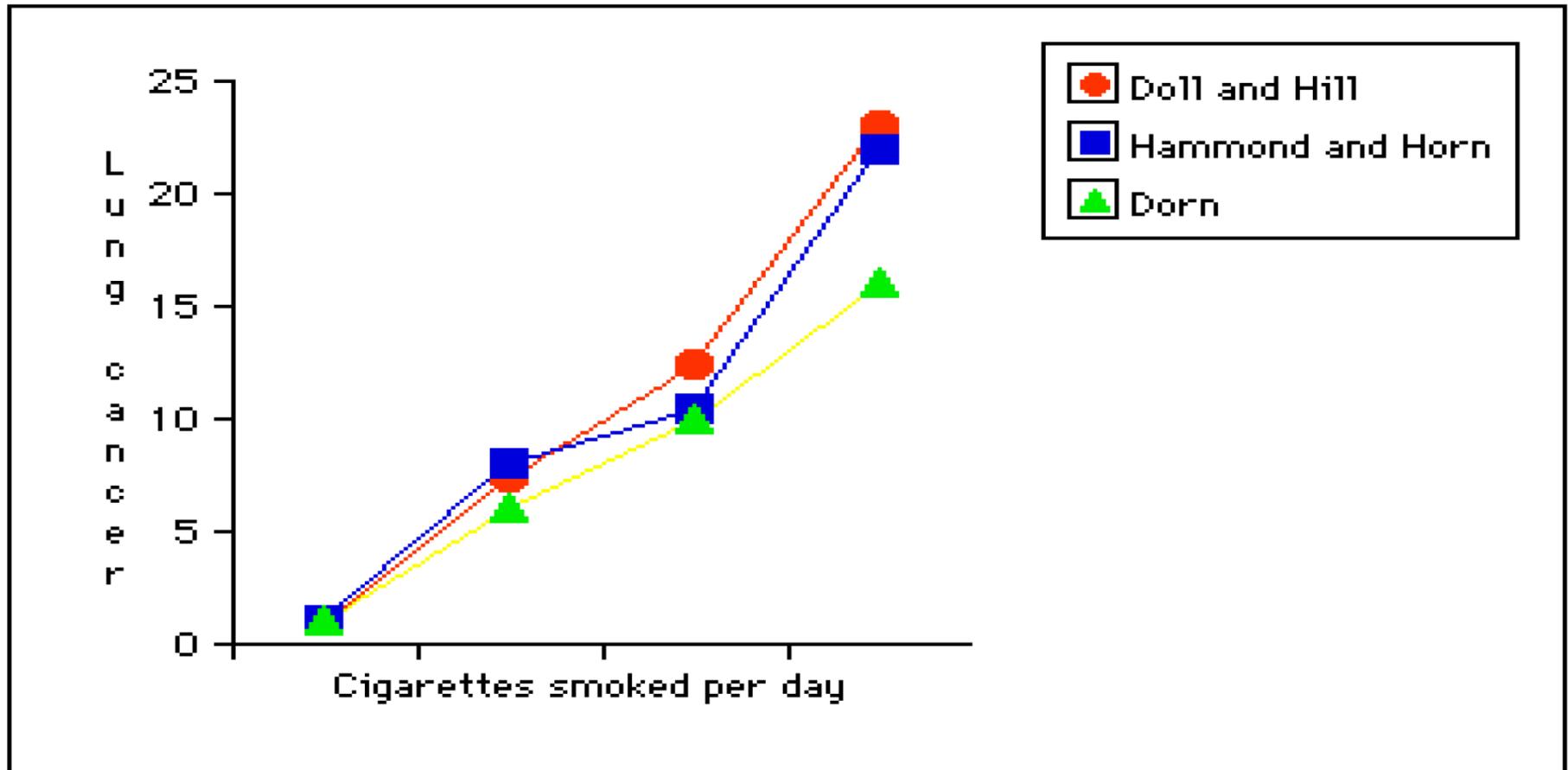
Disclosure: Dr. Carroll has written a book on nutrition and disease (*The Blue Zones Diet*), but she has no financial relationships. Author has named how have declared no conflicts of interest. Disclosure: Dr. Carroll has no financial or non-financial relationships with any of the companies mentioned in this article.

Conflict of interest statement: The authors declare no conflict of interest.  
Ann Intern Med. doi:10.1001/ajtm.2019.1200

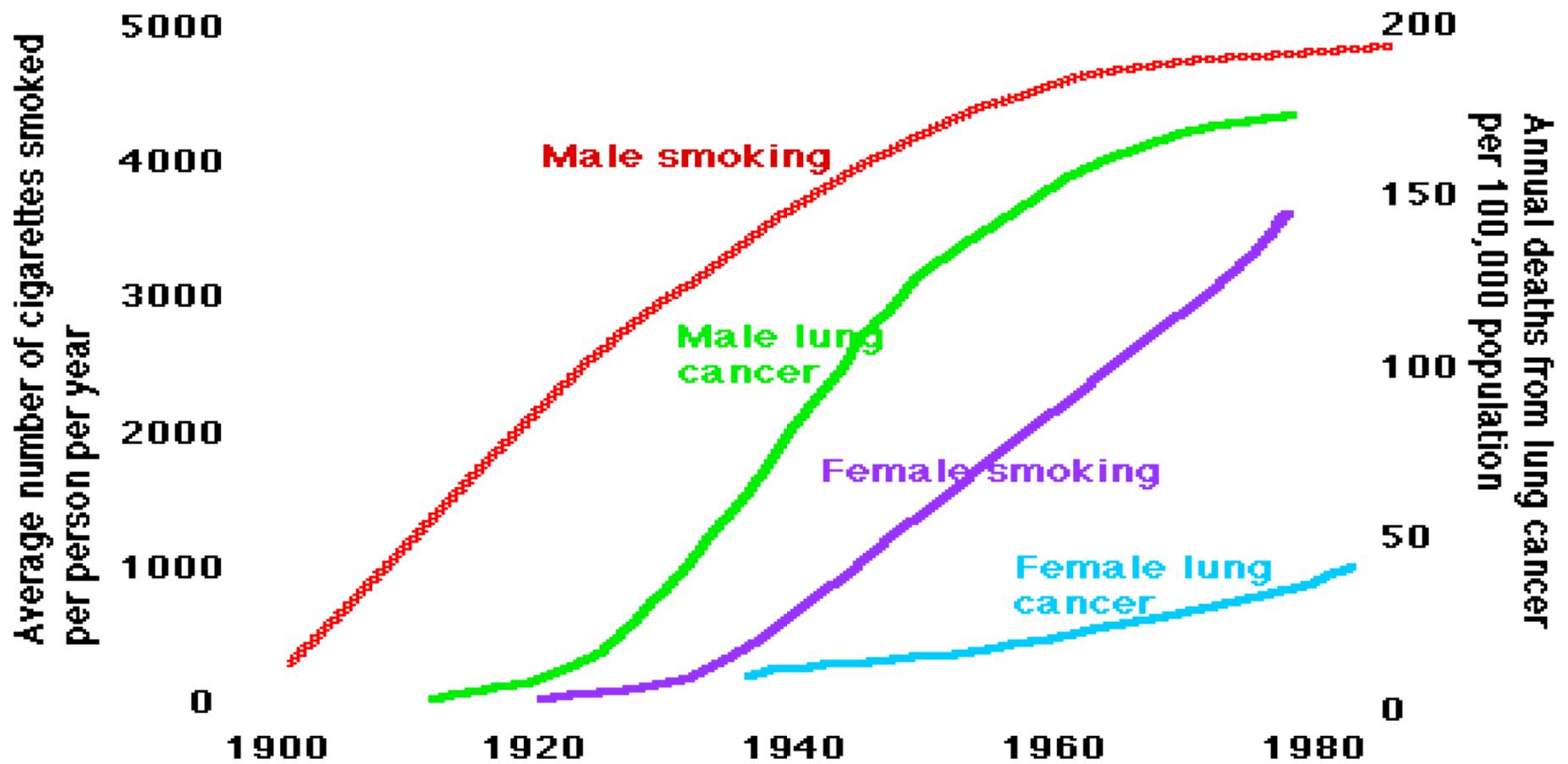
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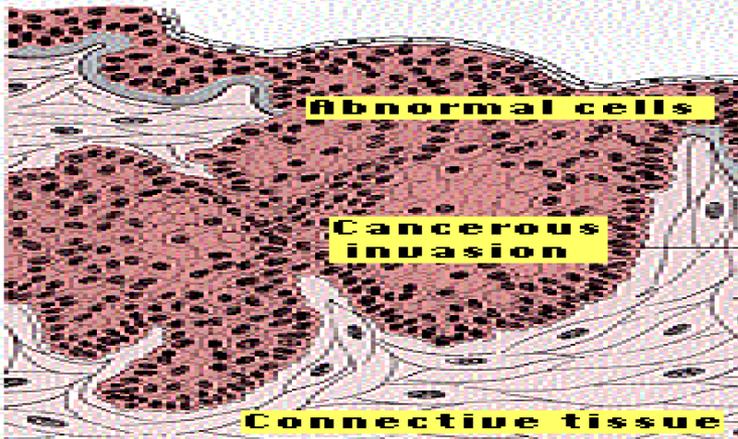
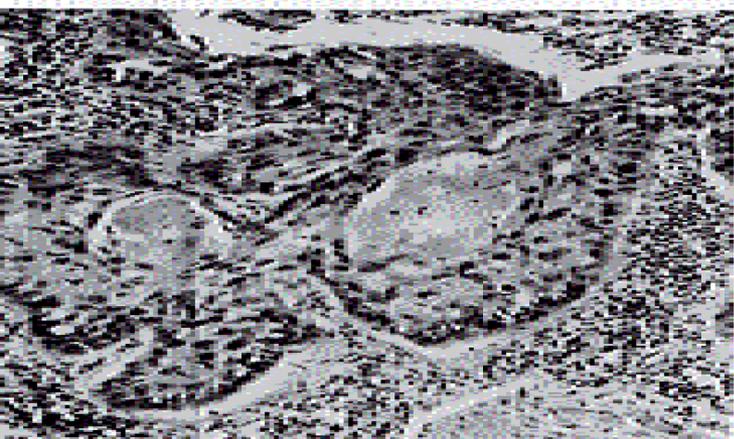
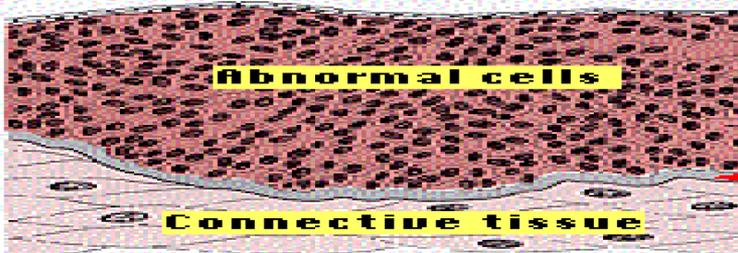
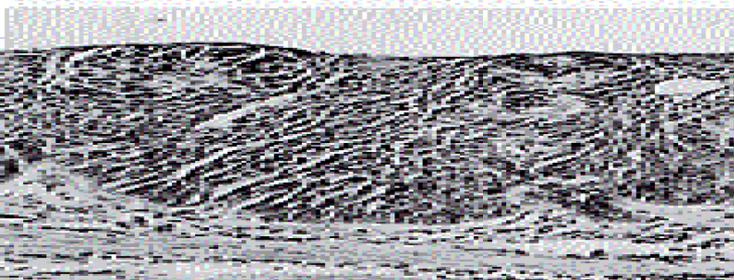
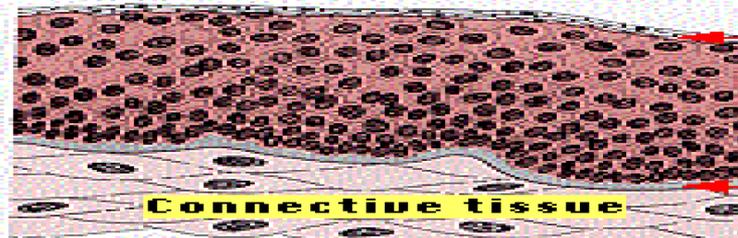
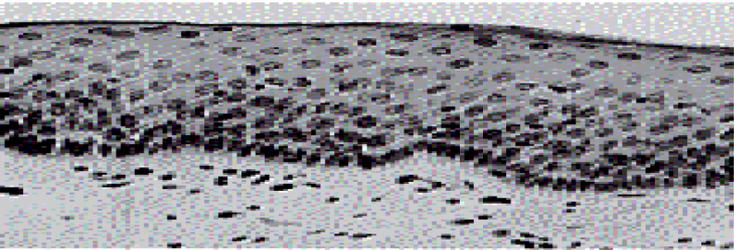
# Lung Cancer and smoking



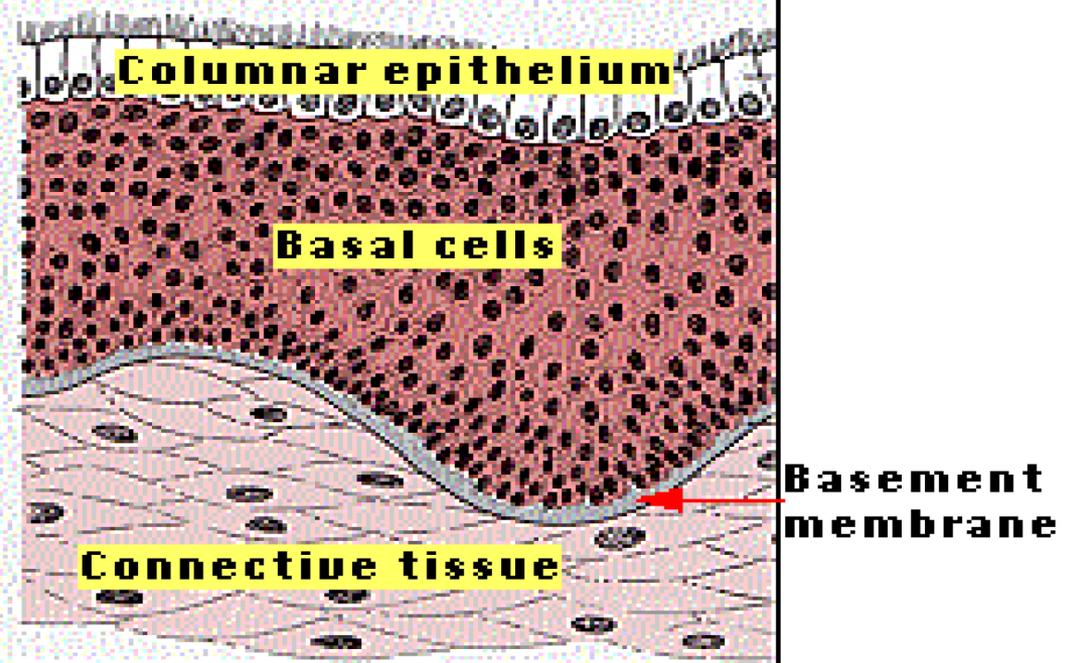
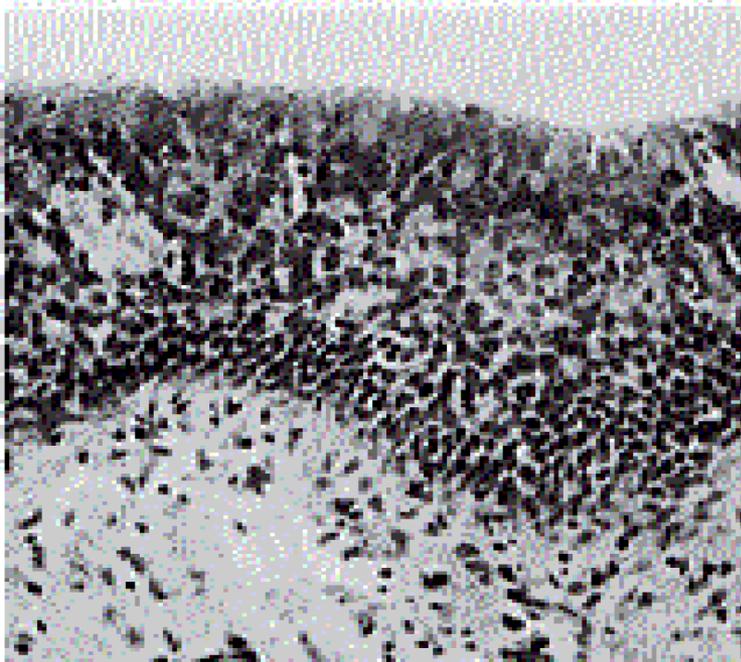
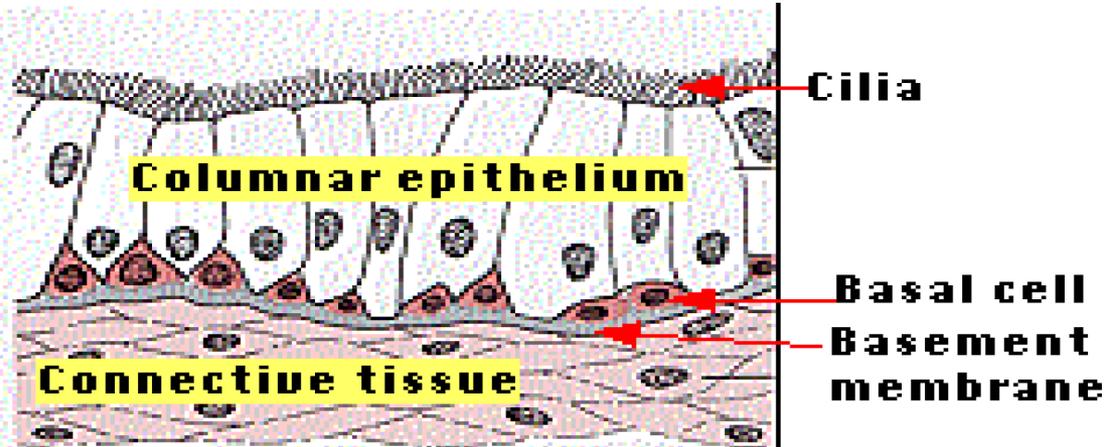
# Lung cancer



# Lung cancer

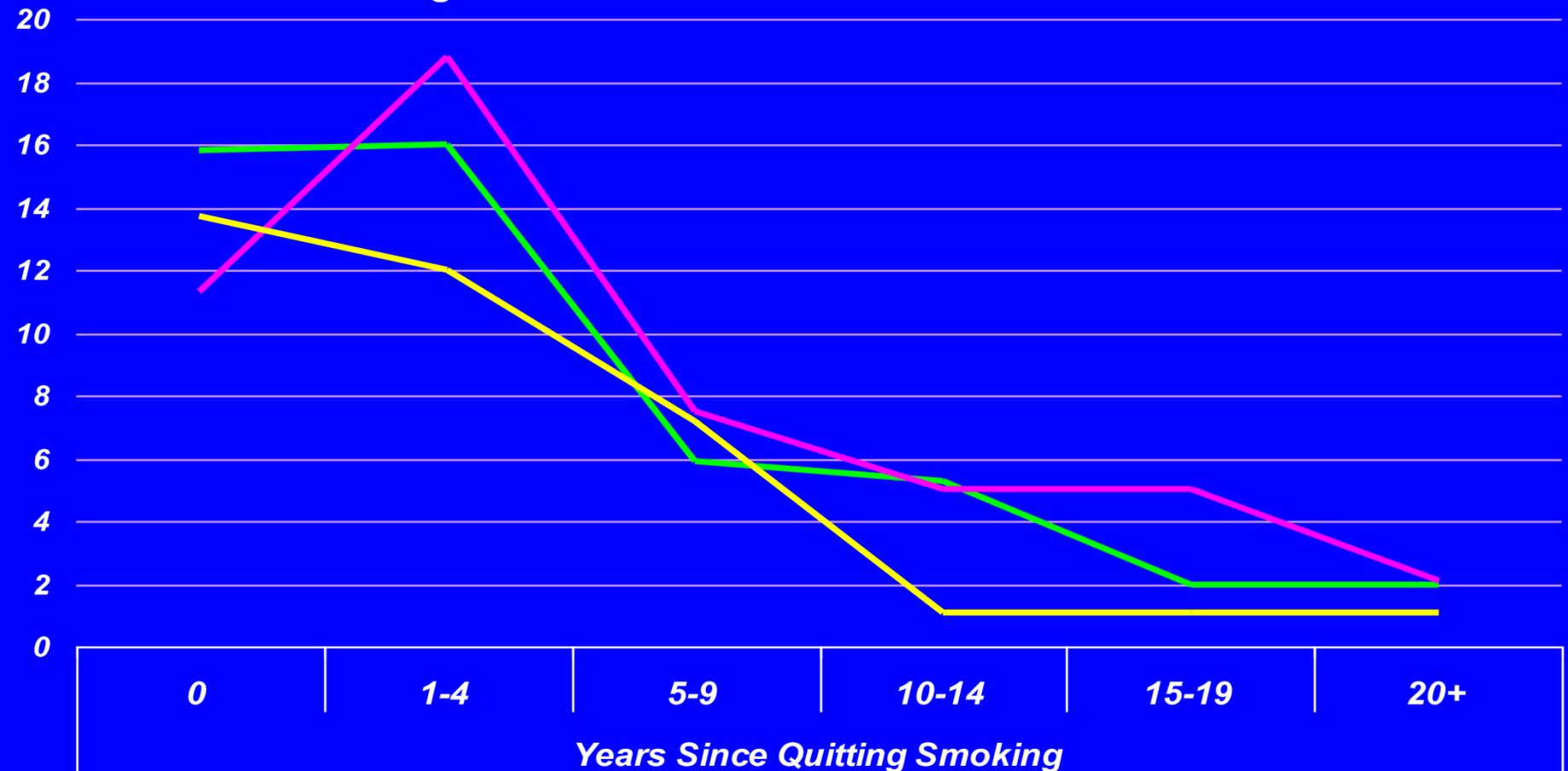


# Lung cancer



# Lung cancer risks

Relative Risks of Lung Cancer According to Years Since Quitting Smoking among Males in Three Cohort Studies of Smokers



# Population perspective

## A Population Perspective on Cancer

- *What is epidemiology?*
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# Accomplishments

*Accomplishments (highly selected!)*

*Identification of the general and specific **causes** of cancer*

*Advocates of **public health**/ prevention*

***Tobacco** as causal factor for lung cancer*

*Role of **secondary tobacco smoke***

***Molecular Epidemiology***

Cancer Epidemiology and Prevention. Third Edition:  
Edited by David Schottenfeld and Joseph F.  
Fraumeni, Jr. 

ISBN-13: 978-0-29-514963-6, Oxford University Press, New York/New York (Telephone:  
800-845-9314, FAX: 919-677-1380, E-mail: customers.us@oup.com), 2006, 1382 pp.,  
\$220.00 Hardcover

# Crisis communications over the decades

- Silicone breast implants
- Chernobyl accident
- Oral cancer and mouthwash (alcohol)
- Abortion and breast cancer
- Cell phones and brain tumors
- Fukushima disaster
- Role of HPV in cancer and public health
- COVID-19

# Population perspective

## A Population Perspective on Cancer

- *What is epidemiology?*
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- *What are some classic controversies?*
- *What can go wrong?*
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# Classic controversies

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# Genes or environment

Is the fundamental  
cause of cancer

**genes** or the **environment**?

# Environment

## Most Cancer is due to the Environment

Dramatic differences in cancer rates by geography and over time are only compatible with extrinsic environmental causes

Established by a vast body of descriptive, ecological, and analytical epidemiology

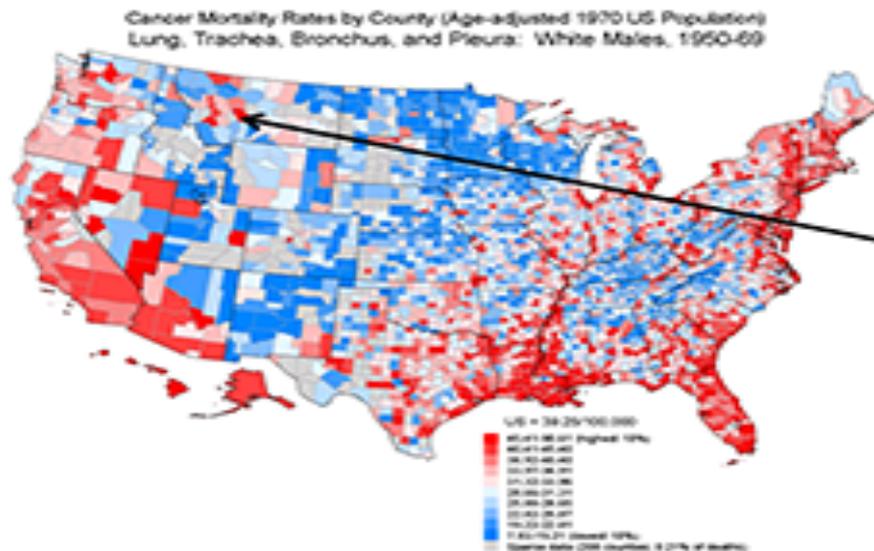
# Cancer rates

## International Variation in Cancer Rates

<i>Type of cancer</i>	<i>H/L</i>	<i>highest</i>	<i>lowest</i>
Melanoma	155	Australia	Japan
Nasopharynx	100	Hong Kong	UK
Prostate	70	US (Blacks)	China
Liver	50	China	Canada
Cervix	28	Brazil	Israel
Stomach	22	Japan	Kuwait
Lung	19	US (Blacks)	India
Colon	19	US (Whites)	India
Bladder	16	Switzerland	India
Pancreas	11	US (Blacks)	India
Ovary	8	Maori (NZ)	Kuwait
Breast	7	Hawaii	Israel
Leukemia	5	Canada	India

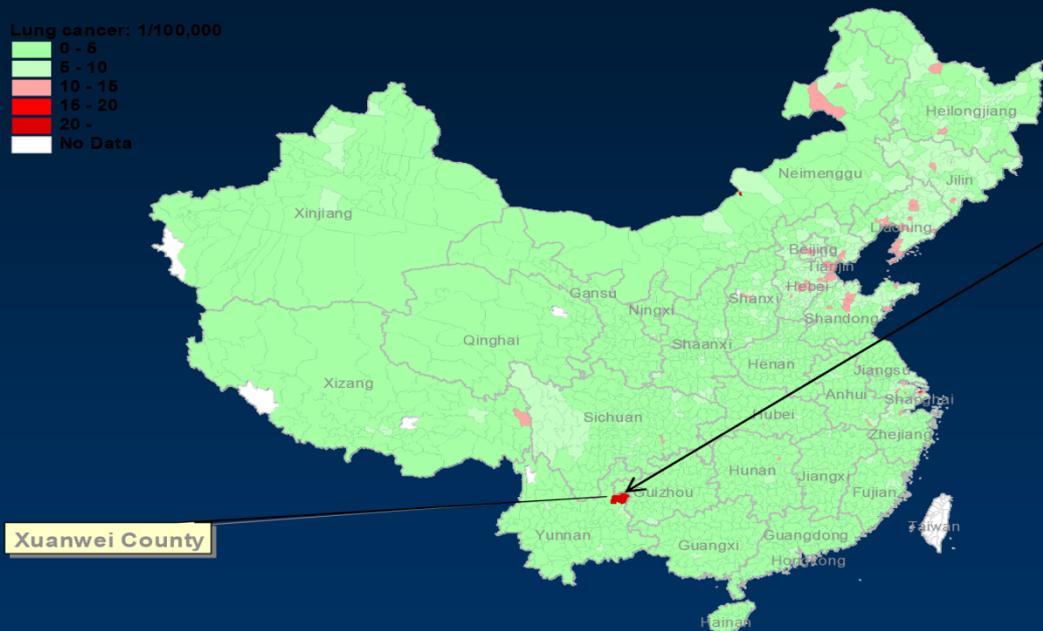
# Cancer maps and exposure

## Cancer maps implicate exposures



# Lung cancer mortality

**Lung cancer mortality rate in Xuan Wei is among the highest in China**



Why here?

**County-specific female lung cancer mortality rates  
(per 100,000, 1973-75)**

# Cancer and prevention

Causes of cancer and potential reduction in burden through prevention

<b>CAUSE</b>	<b>%Caused</b>	<b>DeathsUSA</b>	<b>%Reduction possible</b>
Smoking	33	188,744	75
Obesity	20	114,390	50
Diet	5	28,600	50
Exercise	5	28,600	85
Occupation	5	28,600	50
Viruses	5	28,600	100
Alcohol	3	17,200	50
Family Hx	5	28,600	50
UV	2	11,400	50

# Skull with cigarette



## *Skull With Cigarette*

**van Gogh**

*JAMA*, cover, 1966,  
Feb 28, 1986

# ***Tobacco and public health***

*major cause of preventable morbidity & mortality*

*1/5 US deaths (450,000 USA, 3M world/y)*

*10 million tobacco deaths/yr (2030, WHO)*

*30% of all cancer, 8 sites, all difficult to treat*

*tobacco related disease costs*

*Medicare/ Medicaid > \$10B/yr each*

*In spite of widespread knowledge of the health*

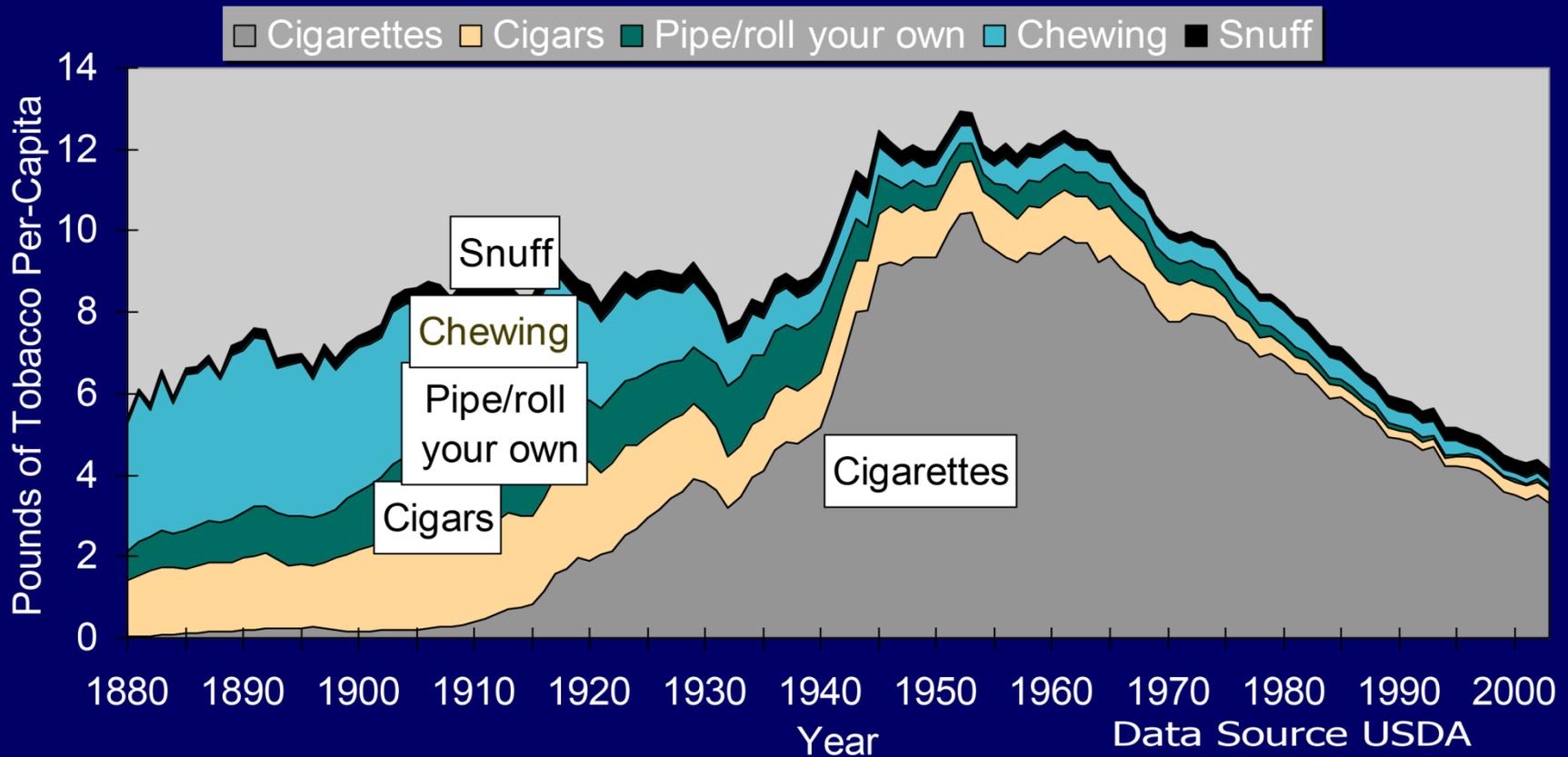
*consequences of smoking*

*- rates in US adults, 15% (2014)*

*- individual smoking cessation very difficult*

# Tobacco consumption

## Per-Capita Consumption of Different Forms of Tobacco in The U.S. 1880-2003



# **Environmental Tobacco Smoke (ETS)**

**never-smoking women spouses of smokers at higher risk**

then spouses of non-smokers (*Hirayama, Trichopoulos, 1981*)

NRC Report

Nonsmoking spouses have 30% increased risk

25% of cases in non-smokers due to smoking

~ 3000 deaths per year

ETS classified as Class A human carcinogen

Surgeon General Report (1986) and EPA Review (1992)

Metanalyses conclude that ETS (both workplace and at home)

is a significant risk factor, e.g. *Law, 1997*

***Summary:***

***Evidence implicating ETS suggests dose-response***

***extends to lowest exposures, i.e. no threshold***

# LITS

## Light and Intermittent Smoking (LITS)

- Fastest growing segment among smokers past 15 years
  - Smoke < 1-10 cig/day- don't smoke every day
- over 20% current smokers

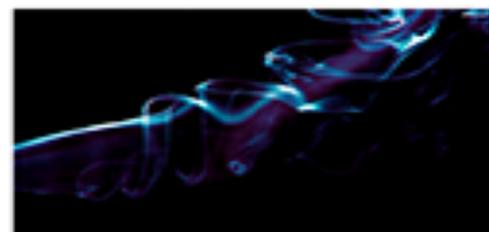
### 3 National Surveys

- National Health Interview Survey (NHIS)
- National Survey Drug Use & Health (NSDUH)
- National Health & Nutrition Exam Survey (NHANES)

### Proportion of LITS highest in:

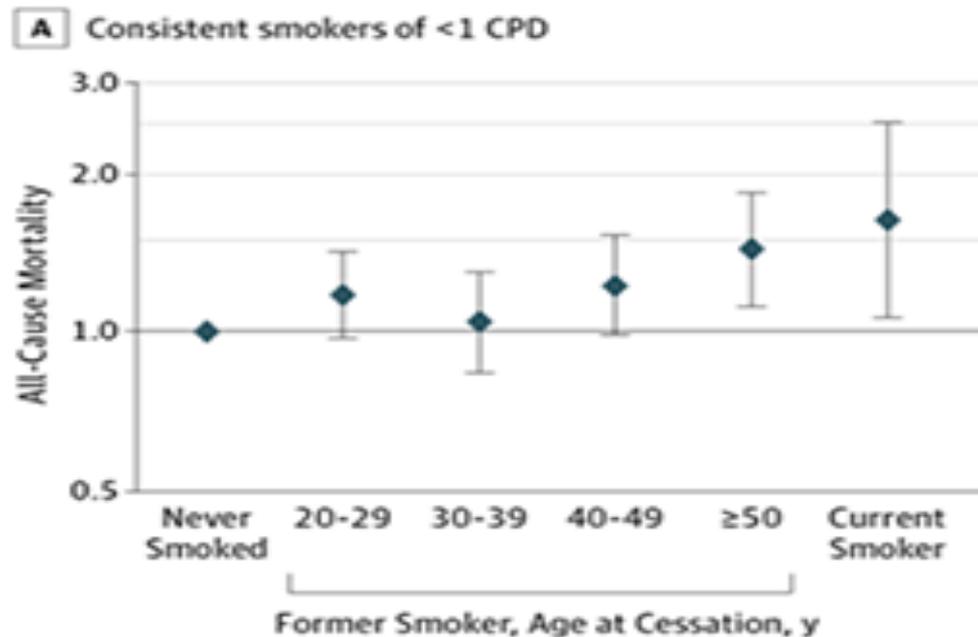
African Americans, Hispanics  
Higher education  
Young smokers  
Started smoking later

**Less dependent smokers**



# Smoking increases mortality

Smoking....even a little bit....increases mortality substantially



# ***What are alcohol-associated cancers?***

**Oral**

**Pharynx**

**Esophagus**

**Larynx**

**Liver**

# Coffee drinking

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Association of Coffee Drinking with Total and Cause-Specific Mortality

Neal D. Freedman, Ph.D., Yikyung Park, Sc.D., Christian C. Abnet, Ph.D.,  
Albert R. Hollenbeck, Ph.D., and Rashmi Sinha, Ph.D.

### ABSTRACT

#### BACKGROUND

Coffee is one of the most widely consumed beverages, but the association between coffee consumption and the risk of death remains unclear.

#### METHODS

We examined the association of coffee drinking with subsequent total and cause-specific mortality among 229,119 men and 173,141 women in the National Institutes of Health–AARP Diet and Health Study who were 50 to 71 years of age at baseline. Participants with cancer, heart disease, and stroke were excluded. Coffee consumption was assessed once at baseline.



From the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD (N.D.F., Y.P., C.C.A., R.S.); and AARP, Washington, DC (A.R.H.). Address reprint requests to Dr. Freedman at the Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, 6120 Executive Blvd., EPS/320, MSC 7232, Rockville, MD 20852, or at [freedmanne@mail.nih.gov](mailto:freedmanne@mail.nih.gov).

# ***Ionizing Radiation***

**Leukemia (AML, but not CLL\*)**

**Breast**

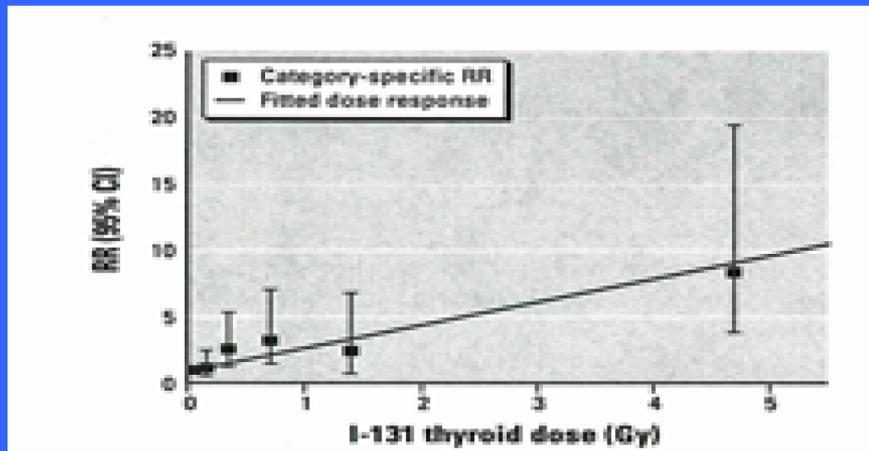
**Lung**

**Thyroid**

**Head and neck cancer**

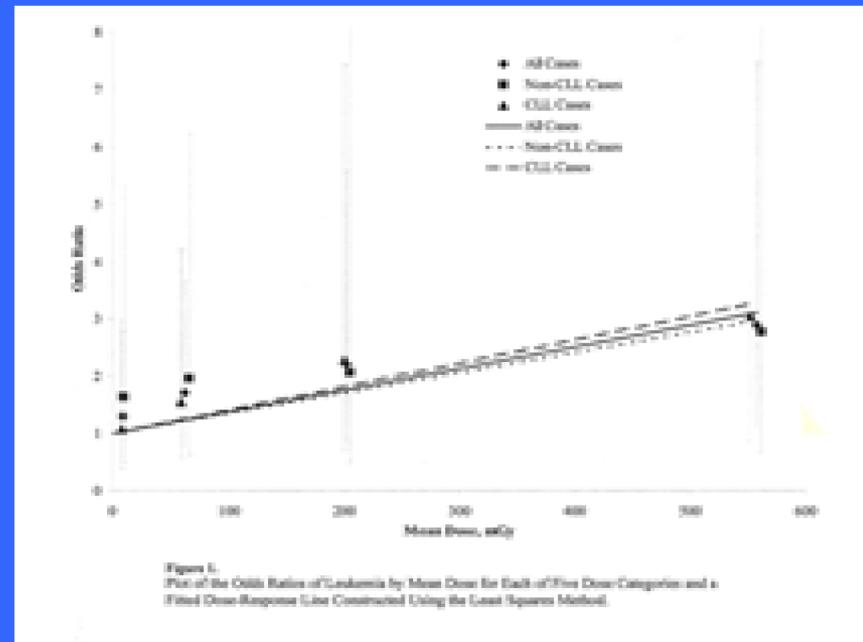
# Cancer risk

## Cancer Risks Following Chernobyl Accident



- I-131 dose-response for thyroid cancer significantly elevated ( $ERR=2.2/Gy$ ) in residents  $<18$  yrs
- Elevated risks persisted for 2 decades; no decrease to date

Brenner...Hatch...Lubin...Bouville...Ron.  
*Environ Health Perspect* 2011



Dose-response similar for chronic lymphocytic leukemia (CLL) ( $ERR=4.1/Gy$ ) and for non-CLL leukemia ( $ERR=2.7/Gy$ ) in clean-up workers

Romanenko...Hatch...Bouville...Ron et al.  
*Radiat Res* 2008

# Ionizing Radiation and Cancer

Type of XRT Implicated	Study	Cancer
A-Bomb Gastric, Thy	Japan	Breast, Leuk,
A-Bomb	Marshall Island	Thyroid
Medical	Breast/Mastitis	Breast
Medical	Hemangioma	Breast, Thyroid
Medical	Hodgkin's	Breast, lung,
Thyroid		
Medical	TB-Flouroscopy	Breast
Radionuclides (Th-232)	Thorotrast	Leukemia, Liver
Radionuclides	Spondylitis	Bones (Ra-224)
Occupation	Radium Dial painters	Bone
Occupation	Rad Technicians	Leukemia
Occupation	Chernobyl Cleanup	?
Environmental	Indoor radon	Lung

# Skin cancer

## *Non-ionizing Radiation (UV/sun)*

- 1 Basal cell
- 2 Squamous cell
- 3 Melanoma

*Tanning beds !*



# Skin damage

© 1981

A close-up photograph of a woman's face, split vertically down the middle by a dashed line. The left side of her face is smooth and youthful, while the right side is wrinkled and shows signs of aging. She is wearing sunglasses on her head. In the background, a beach scene is visible with people in the distance.

**THE SUN YOU GET TODAY  
MAY NOT LOOK SO BEAUTIFUL  
TOMORROW.**

# Infections and Cancer

## Infections and Cancer

Human papillomavirus	Cervical cancer Vulvar/vaginal cancer Anal cancer Penile cancer Oropharyngeal cancer
Hepatitis B & C virus	Hepatocellular Non-Hodgkin's lymphoma
<i>Helicobacter pylori</i>	Gastric cancer
Liver flukes	Cholangiocarcinoma

# Newer infections

## Newer infectious hypotheses

### **VIRUS**

HCV

EBV

KSHV (HHV8)

HPV-16, -18, -33, -39

Polyomavirus

HIV

### **Human Cancer (hypothesized)**

hepatocellular cancer

NHL

NPC

Hodgkin's lymphoma

leiomyosarcoma

Kaposi's sarcoma

Vulvo-vaginal cancer

Anal cancer

Penile cancer

Oropharyngeal cancer

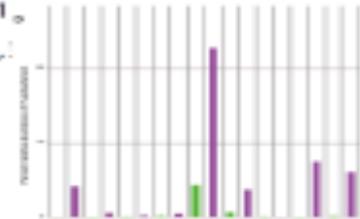
Merkel cell virus/ **CLL?**

NHL

# Fusobacterium and colorectal carcinoma

## Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma

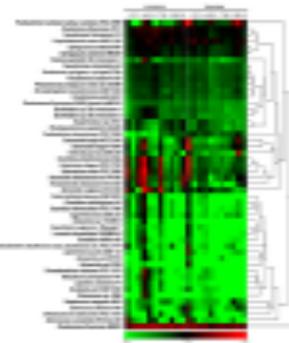
Aleksandar D. Kostic,<sup>1,2</sup> Dirk Gevers,<sup>1</sup> Chandra Sekhar Pedamallu,<sup>1,3</sup> Monia Michaud,<sup>4</sup> Fujiko Duke,<sup>1,3</sup> Ashlee M. Earl,<sup>1</sup> Akinyemi I. Ojesina,<sup>1,3</sup> Joonil Jung,<sup>1</sup> Adam J. Bass,<sup>1,5</sup> Josep Tabernero,<sup>5</sup> José Baselga,<sup>5</sup> Chen Liu,<sup>6</sup> Ramesh A. Shivdasani,<sup>3</sup> Shuji Ogino,<sup>2,7</sup> Bruce W. Birren,<sup>1</sup> Curtis Huttenhower,<sup>1,8</sup> Wendy S. Garrett,<sup>1,3,4</sup> and Matthew Meyerson<sup>1,2,3,9</sup>



## *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma

Mauro Castellarin,<sup>1,2,6</sup> René L. Warren,<sup>1,6</sup> J. Douglas Freeman,<sup>1</sup> Lisa Dreolini,<sup>1</sup> Martin Krzywinski,<sup>1</sup> Jaclyn Strauss,<sup>3</sup> Rebecca Barnes,<sup>4</sup> Peter Watson,<sup>4</sup> Emma Allen-Vercoe,<sup>3</sup> Richard A. Moore,<sup>1,5</sup> and Robert A. Holt<sup>1,2,7</sup>

<sup>1</sup>BC Cancer Agency, Michael Smith Genome Sciences Centre, Vancouver, British Columbia V5Z 1L3, Canada; <sup>2</sup>Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, British Columbia V5A 1S6, Canada; <sup>3</sup>University of Guelph, Guelph, Ontario N1G 2W1, Canada; <sup>4</sup>BC Cancer Agency, Deefey Research Centre, Victoria, British Columbia V8R 6V5, Canada; <sup>5</sup>Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia V5A 1S6, Canada



# Oropharynx cancers

## Pre-diagnostic HPV16 Antibodies Strongly Associated with Oropharynx Cancers - Nested Case-Control Study Within EPIC Cohort

HPV type and antibody	Cases N=135 N (%)	Controls N=1599 N (%)		OR (95%CI)
		Specific	Strong	
HPV16 E6	47 (34.8%)	9 (0.6%)	274 (110 to 681)	
HPV16 E7	27 (20.0%)	178 (11.3%)	2.4 (1.5 to 3.9)	
HPV16 E1	22 (16.3%)	63 (3.9%)	5.7 (3.2 to 10)	
HPV16 E2	33 (24.4%)	72 (4.5%)	9.5 (5.7 to 16)	
HPV16 L1	56 (41.5%)	329 (20.6%)	3.1 (2.1 to 4.5)	

# Occupational exposures

## OCCUPATIONAL EXPOSURES -- HUMAN CARCINOGENS

### EXPOSURE

4-Aminobiphenyl

Arsenic

Asbestos

Benzene

Benzidine

beta-Naphthylamine

Coal tars and pitches

Mineral oils

Mustard gas

Radon

Soot, tars, and oils (polycyclic hydrocarbons)

Vinyl chloride

Wood dusts (furniture)

### SITE OF CANCER

Bladder

Lung, skin

Lung, pleura,  
peritoneum

Leukemia

Bladder

Bladder

Lung, skin

Skin

Pharynx, lung

Lung

Lung, skin

Liver

Nasal sinuses

# Diesel exhaust

## Diesel Exhaust in Miners Study (OEEB, BB, NIOSH)

- Significant exposure-response based on quantitative historical exposure data, adjusting for smoking and other confounders (Silverman et al, JNCI, 2012)
- Played an influential role in IARC's reclassification of diesel exhaust as a Group 1 carcinogen



# Environment and cancer

- Contribution of **environment** to cancer
  - Universally estimated to be substantial **however**
  - **limited understanding** of extrinsic environmental risks for many cancers: prostate, leukemia's, brain, sarcomas, pediatric, lung in nonsmokers, etc.
  - International variation poorly understood
  - Small and emerging risks- difficult to study
  - Early life exposures- a large gap
  - Many exposures are difficult to access:
    - sleep, chronotype, activity, diet, circadian disruption, light, diverse and new pollutants, climate change, etc.

# Chronic Lymphocytic Leukemia

- Most common leukemia of Western world.
- 30% of adult leukemia in USA
- Less frequent in Asia and Latin America.
- Male to female ratio is 2:1.
- Median age at diagnosis is 65-70 years.
- **No extrinsic environmental causes known**
- Family history is the most important risk factor

# What about genes

## WHAT ABOUT GENES?

*New technologies have accelerated gene discovery but...*

- 1. Genes associated with common cancers confer minimal risk*
- 2. and explain only a modest portion of the variation*
- 3. and do not help much with risk models*
- 4. How G and E work in concert is poorly understood*
- 5. Many cancer families- genes remain obscure*

# Cancer and genetic changes

**All Cancer is due to  
the Genetic changes**

All cancer cells exhibit changes in their DNA that are passed on and maintain the 'malignant phenotype'

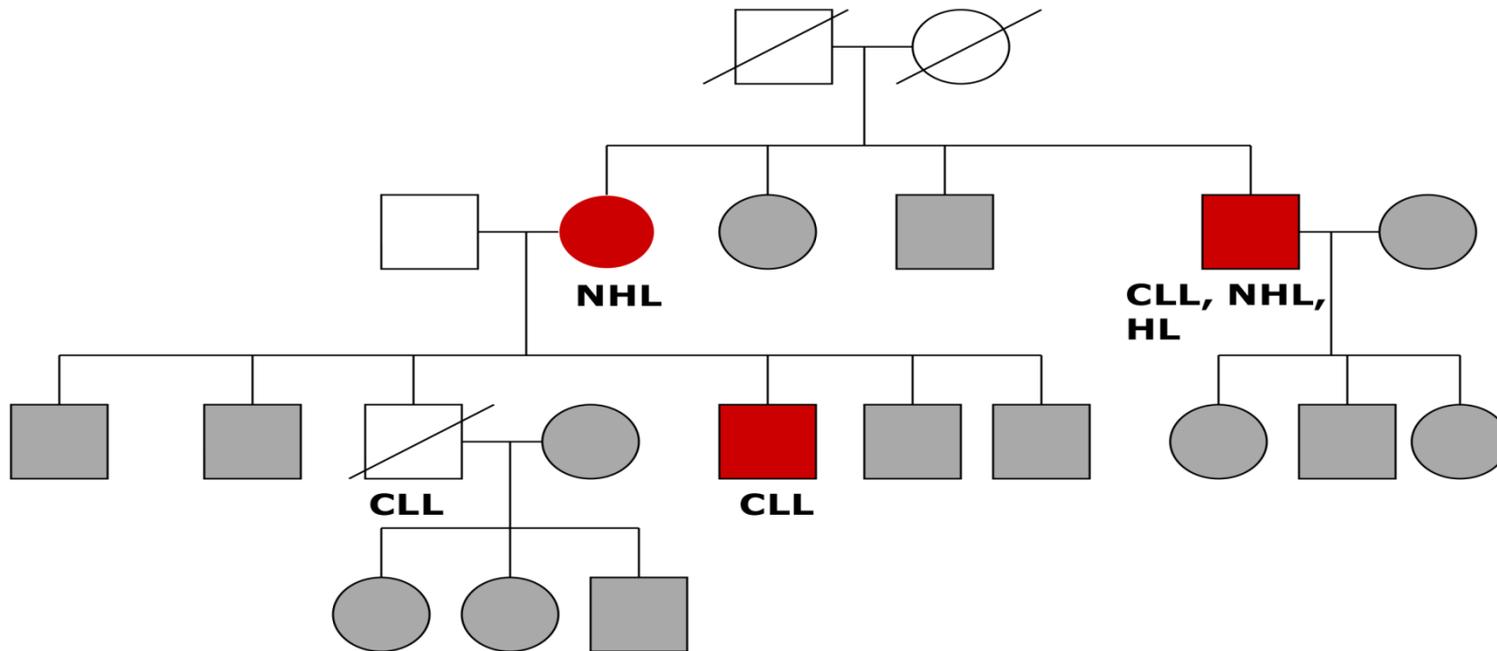
# Genetic distinctions

## Genetic distinctions

1. Germline or Somatic  
(inherited or in the tumor)
2. Family or Population  
(rare or common)
3. Candidate or Agnostic  
(candidate gene study or GWAS)

# Rare Genes

To look for **rare** genes you need families.....



High risk kindreds like this likely harbor **rare** genes that confer **high** risk- if we knew what were they would be **clinically** important....

# Cloned familial tumor

suppressor genes

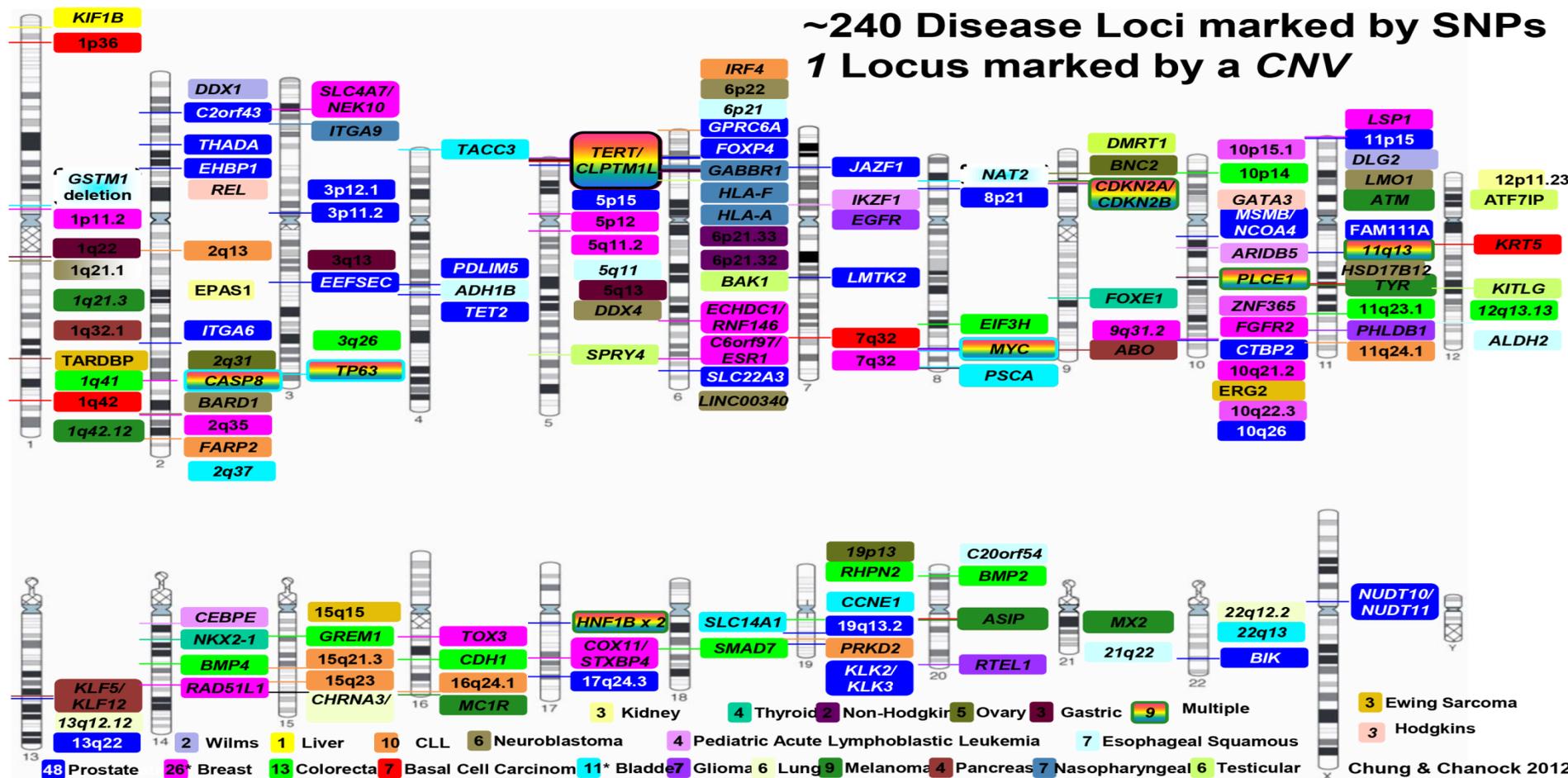
## Cloned Familial Tumor Suppressor Genes

---

Retinoblastoma	RB1	13q14	1986
Wilms' tumor	WT1	11p13	1990
Li-Fraumeni syndrome	p53	17p13	1990
Neurofibromatosis 1	NF1	17q11	1990
Neurofibromatosis 2	NF2	22q12	1993
von Hippel-Lindau	VHL	3p25	1993
Familial melanoma 1	p16	9p21	1994
Familial breast 1	BRCA1	17q21	1994
Familial breast 2	BRCA2	13q12	1995
Basal cell nevus	PTC	9q22	1996

# GWAS etiology hits

Published Cancer GWAS Etiology Hits: 8.10.12

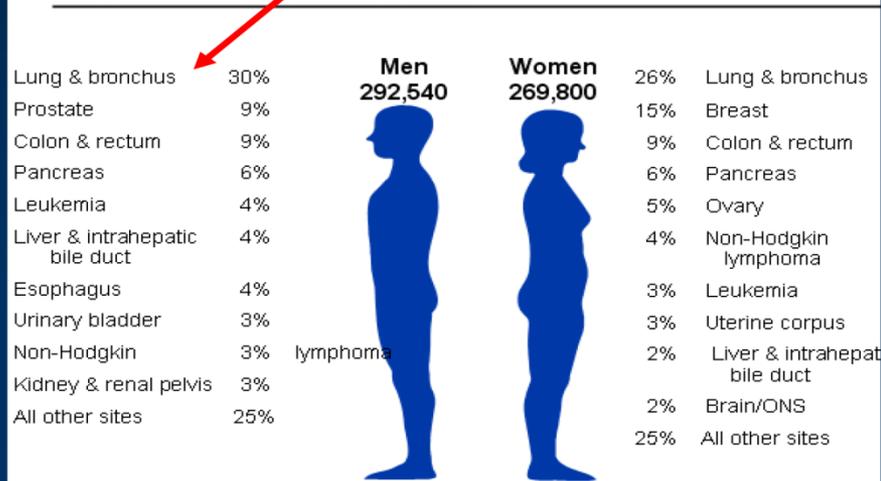


# Lung cancer challenge

## *The lung cancer challenge....*

- 1- Drives overall cancer **mortality** in the US and worldwide
- 2- **Treatment** and screening pose challenges
- 3- Lung cancer is paradigm for genetics of complex disease
- 4- Clearest example of environment and gene in cancer
- 5- The clearest example of a genetically influenced behavior associated with the leading public health problem in the world

2009 Estimated US Cancer Deaths\*



Trends in Five-year Relative Survival (%)\* Rates, US, 1975-2004

Site	1975-1977	1984-1986	1996-2004
All sites	50	54	66
Breast (female)	75	79	89
Colon	52	59	65
Leukemia	35	42	51
Lung and bronchus	13	13	16
Melanoma	82	87	92
Non-Hodgkin lymphoma	48	53	65
Ovary	37	40	46
Pancreas	3	3	5
Prostate	69	76	99
Rectum	49	57	67
Urinary bladder	74	78	81

# EAGLE

10 years ago we fielded **EAGLE**

## Environment and Genetics in Lung Cancer Etiology

- case-control study of lung cancer
- 2000 cases/2000 controls



## Innovative Areas

- 1) behavioral and smoking
- 2) biologically Intensive
- 3) integrative Epidemiology
- 4) genetics

## BMC Public Health

Study protocol  
**Environment And Genetics in Lung cancer Etiology (EAGLE) study: An integrative population-based case-control study of lung cancer**  
Maria Teresa Landi<sup>1\*</sup>, Dario Consonni<sup>2</sup>, Melissa Rotunno<sup>3</sup>, Andrea W. Bergen<sup>4</sup>, Alisa M. Cookston<sup>5</sup>, Jay H. Lubin<sup>6</sup>, Lynn Coblin<sup>7</sup>, Michael Alavanja<sup>8</sup>, Glen Morgan<sup>9</sup>, Amy F. Saibari<sup>9</sup>, Ilona Litniewska<sup>10</sup>, Fabrizio Prevedelli<sup>11</sup>, Massimo Corso<sup>12</sup>, Maurizio Bobagioni<sup>13</sup>, Barbara Marinelli<sup>14</sup>, Benedetta Alberti<sup>15</sup>, Antonio Colombi<sup>16</sup>, Margaret Tucker<sup>17</sup>, Sholom Wacholder<sup>18</sup>, Angela C. Pesatori<sup>19</sup>, Neil E. Caporaso<sup>21</sup> and Pier Alberto Bertazzi<sup>22</sup>



# Lung cancer risk

## Lung Cancer Risk and Family History

Family member	Controls	Case	OR (95% CI)*
Mother	2044 19	1817 30	2.11 (1.11-4.41)
Father	1890 108	1678 139	1.37 (1.01-1.87)
Sibling	1356 93	1152 140	1.53 (1.10-2.12)
<b>Any family member</b>	<b>1430 213</b>	<b>1142 294</b>	<b>1.57 (1.25-1.98)</b>

- Adjusted for 5 year age-interval, sex, residence (5 areas), education (5 categories), personal smoking status (packs/day, duration in years, and years since the last cigarette)  
- Data on family history available on 2116 controls and 1946 cases  
Squamous (32%), Adenocarcinoma (51%), 195 (12%), large (4.5%)

# Traditional epidemiology

## Traditional epidemiology



Exposure

Disease

Tobacco

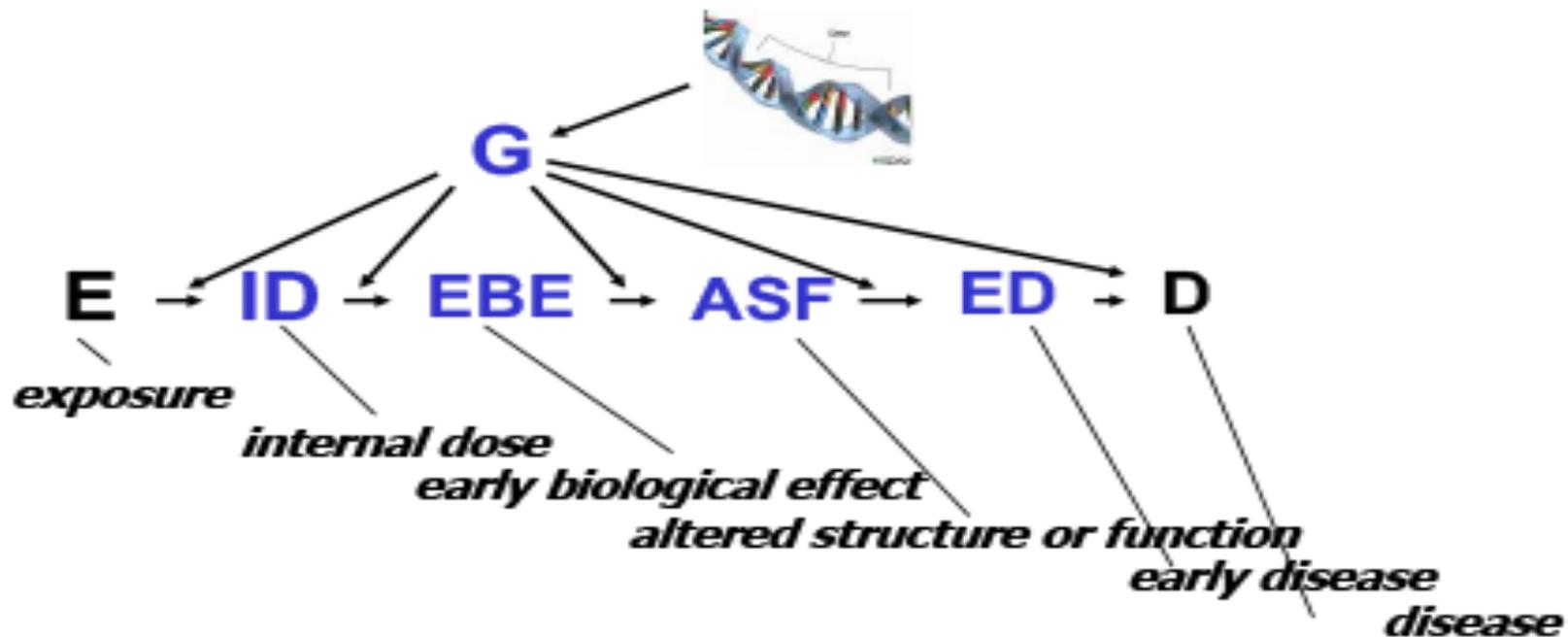


Lung Cancer



# Molecular epidemiology

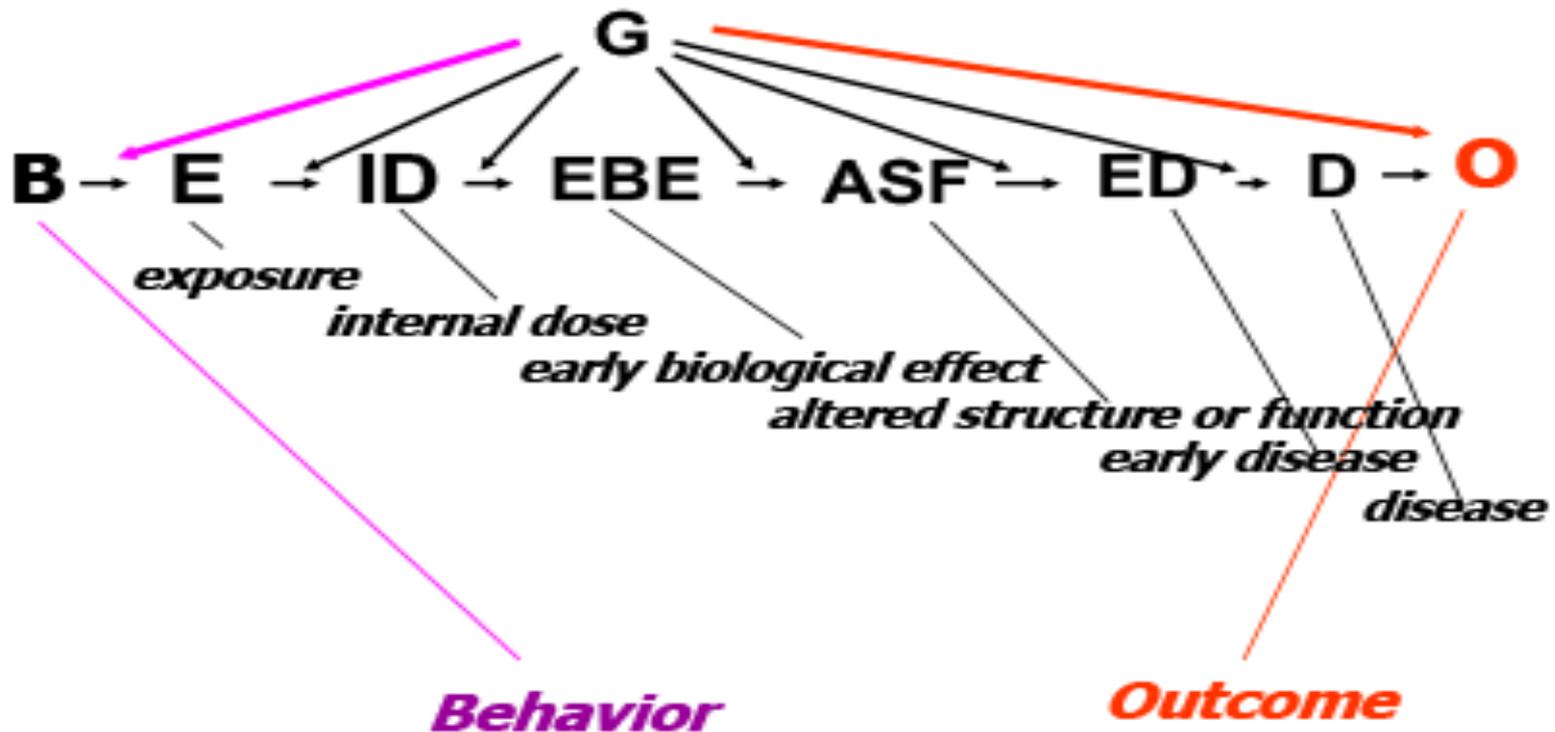
**Molecular** epidemiology



Adding **biomarkers** to investigate genes and mechanisms

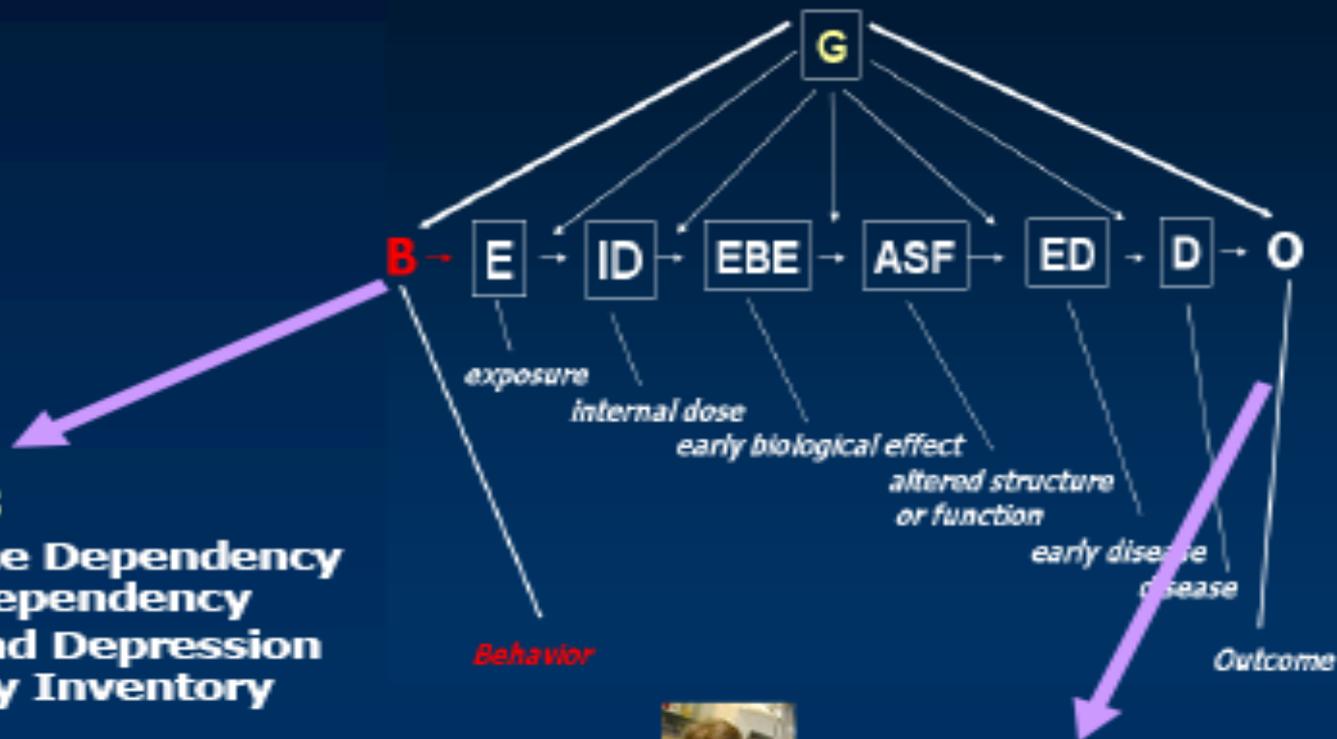
# Integrative epidemiology

Integrative epidemiology



# Integrative epidemiology

## Integrative epidemiology



### Instruments

- Fagerstrom Nicotine Dependency
- DSM-IV Nicotine Dependency
- Hospital Anxiety and Depression
- Eysenck Personality Inventory
- CESD- Depression
- Attention Deficit Inventory
- Attitudes and Knowledge about Smoking
- Intention to Quit Smoking



Treatment  
Survival  
Prognostic and Clinical

# Molecular epidemiology

EAGLE example: molecular epidemiology approach

Epidemiology  
'doneness module'

3.05 Se Lei mangia i seguenti tipi di carne, che grado di cottura hanno usualmente?

M. QUESTIONARIO

Tipi di carne	Ben cotta (quello dentro)	Media (rosa dentro)	Ai sangue (rosso dentro)
1. BISTECCA DI MANZO	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. HAMBURGER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. BRACIOLA DI MAIALE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. BRACIOLA O COSTOLETTA DI VITELLO	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. POLLO	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3.06 Se Lei mangia i seguenti tipi di carne, che grado di bruciocchiatura hanno di solito?

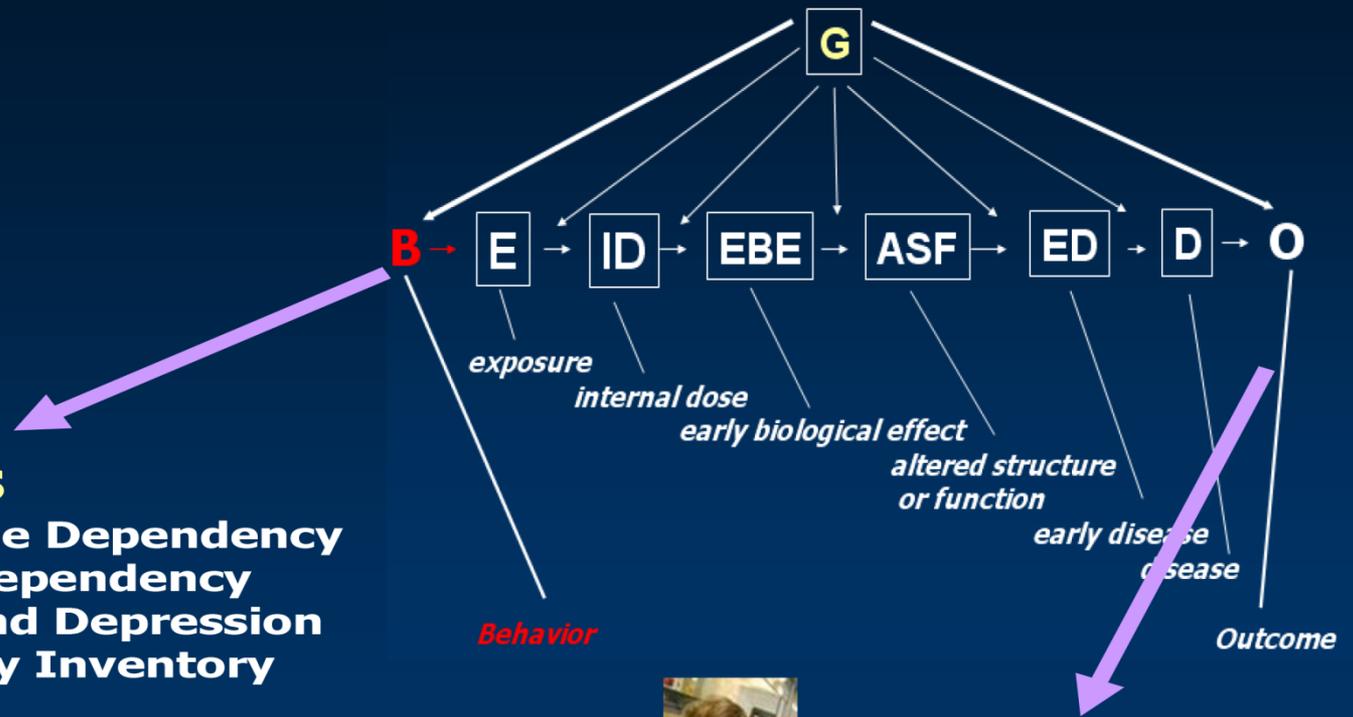
Per favore cerchi rispondendo ai seguenti quattro gruppi composti ciascuno da tre foto, per indicare il grado di bruciocchiatura di tutte le carni indicate qui sotto.

1. Bistecca di Manzo



# Integrative epidemiology

## Integrative epidemiology



## Instruments

**Fagerstrom Nicotine Dependency**  
**DSM-IV Nicotine Dependency**  
**Hospital Anxiety and Depression**  
**Eysenck Personality Inventory**  
**CESD- Depression**  
**Attention Deficit Inventory**  
**Attitudes and Knowledge about Smoking**  
**Intention to Quit Smoking**



**Treatment**  
**Survival**  
**Prognostic and Clinical**

# Molecular epidemiology

What has **molecular epidemiology** contributed?  
3 examples.....

- 1 HPV is the cause of 100% of cervical cancer  
- prevention is possible (vaccine)
- 2 'Cutting down' on smoking is ineffective  
- biomarker studies show levels of carcinogens don't decline
3. GWAS studies (100 + conditions) based on biospecimen collections...

# Consortia

## Consortia (selected examples)

- BPC3 (Breast and Prostate Cancer and Hormone-Related Gene Variant Study)
- CADISP (Cervical Artery Dissections and Ischemic Stroke Patients)
- CARE (Candidate-gene Association REsource)
- CGASP (Consortium of Genetic Association of Smoking Related Phenotypes)
- CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology)
- CKDGen Consortium
- COGENT (COlorectal cancer GENeTics)
- DentalSCORE (Dental Strategies Concentrating on Risk Evaluation)
- DGI (Diabetes Genetics Initiative)
- DIAGRAM (Diabetes Genetics Replication And Meta-analysis Consortium)
- eMERGE (Electronic Medical Records & Genomics)
- ENGAGE (European Network of Genomic and Genetic Epidemiology)
- EUROCRAN (European Collaboration on Craniofacial Anomalies)
- GAPPS (Global Alliance to Prevent Prematurity and Stillbirth)
- GARNET (Genomics and Randomized Trials Network)
- GEFOS (Genetic Factors of Osteoporosis Consortium)
- GENEVA (GENe EnVironment Association studies)
- GIANT (Genome-wide Investigation of ANthropometric measures)
- Global BPGen Consortium
- Global Lipid Genetics Consortium
- ILCCO (International Lung Cancer Consortium)
- INTERLYMPH Consortium
- International Type 2 Diabetes Consortium
- ISGC (International Stroke Genetics Consortium)
- MAGIC (The Meta-Analyses of Glucose and Insulin-related traits Consortium)
- NEIGHBOR (National Eye Institute Glaucoma Human Genetics CollaBORation)
- NGFN (German National Genome Research Network)
- P3G Consortium (Public Population Project in Genomics)
- PAGE (Population Architecture using Genomics and Epidemiology)
- PREGENIA (Preterm Birth and Genetics International Alliances)
- SHARe (SNP Health Association Research)
- SpiroMeta Consortium
- SUNLIGHT Consortium (Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits)
- TAG (The Tobacco, Alcohol and Genetics Consortium)
- WTCCC (Wellcome Trust Case-Control Consortium)

5+ million subjects followed in cohorts

# PhenX...approach to expand data collection and reduce misclassification



Web  Site  Search  
PhenX Toolkit

Home Project ▾ Steering Committee ▾ Working Groups ▾ PhenX Toolkit ▾ News ▾

## PhenX Toolkit

PhenX High-Priority Measures are available now in the PhenX Toolkit at:

<https://www.phenxtoolkit.org>

The PhenX Toolkit is a web-based catalog of high priority measures for consideration and inclusion in genome-wide association studies (GWAS) and other large-scale genomic research efforts. Investigators may want to visit the Toolkit to review and select PhenX measures when designing a new study or expanding an ongoing study.

# A Population Perspective on Cancer

What is epidemiology?

What has epidemiology accomplished?

What can go wrong?

What can really go wrong?

What next?

# A Population Perspective on Cancer

What is epidemiology?

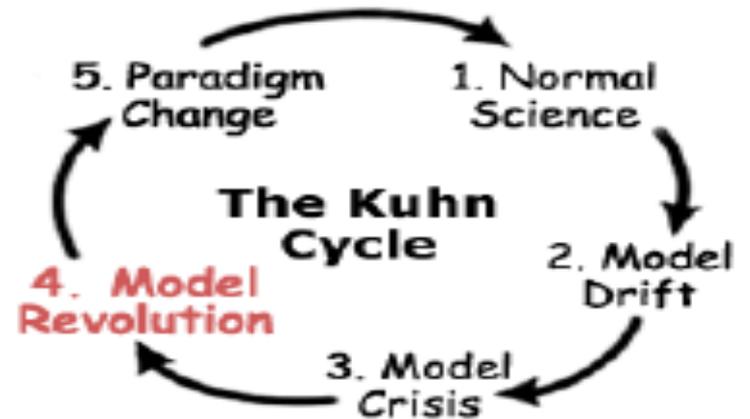
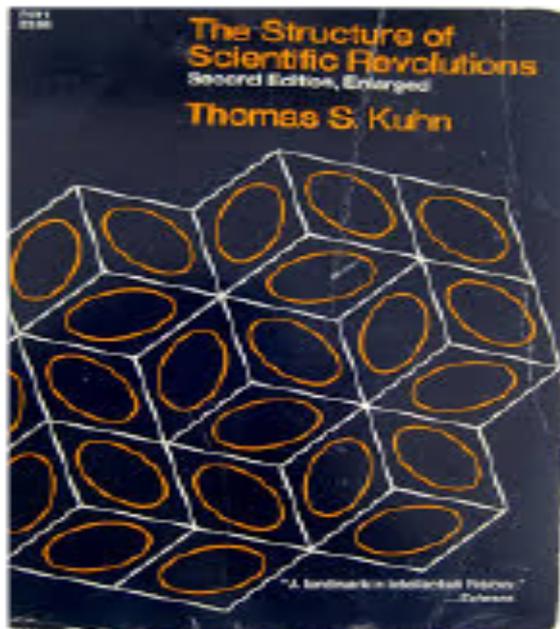
What has epidemiology accomplished?

What can go wrong?

What can really go wrong?

What next?

# Paradigm change



Paradigm change is hard....

# Paradigm shifting

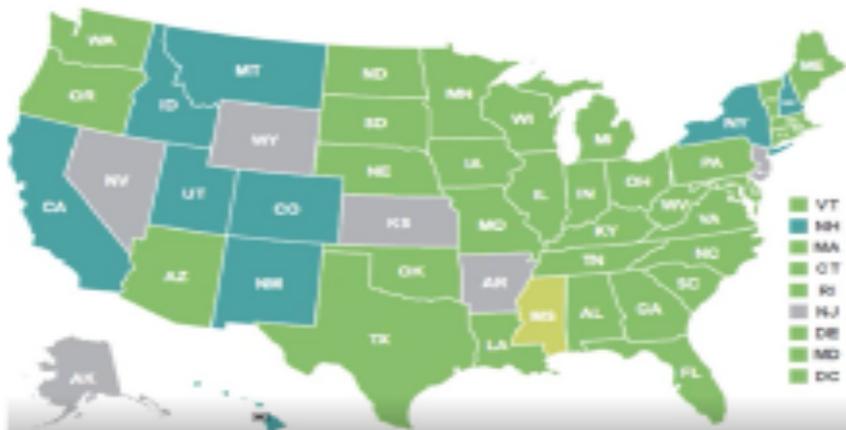
Examples of paradigm shifting  
'controversies'

1. Siegfried and metabolic theory of cancer
2. 'Herd immunity' and COVID-19.
3. **Relationships of diet and cancer**

# Obesity rates

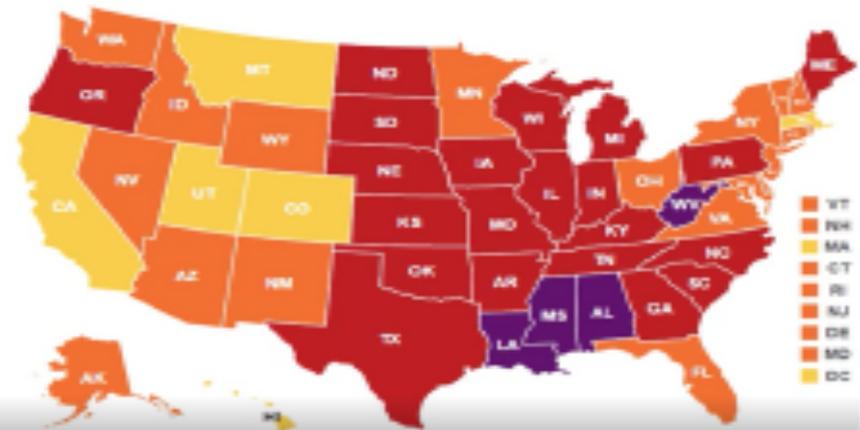
## CDC Obesity Rates

1990



No state > 20%

2015

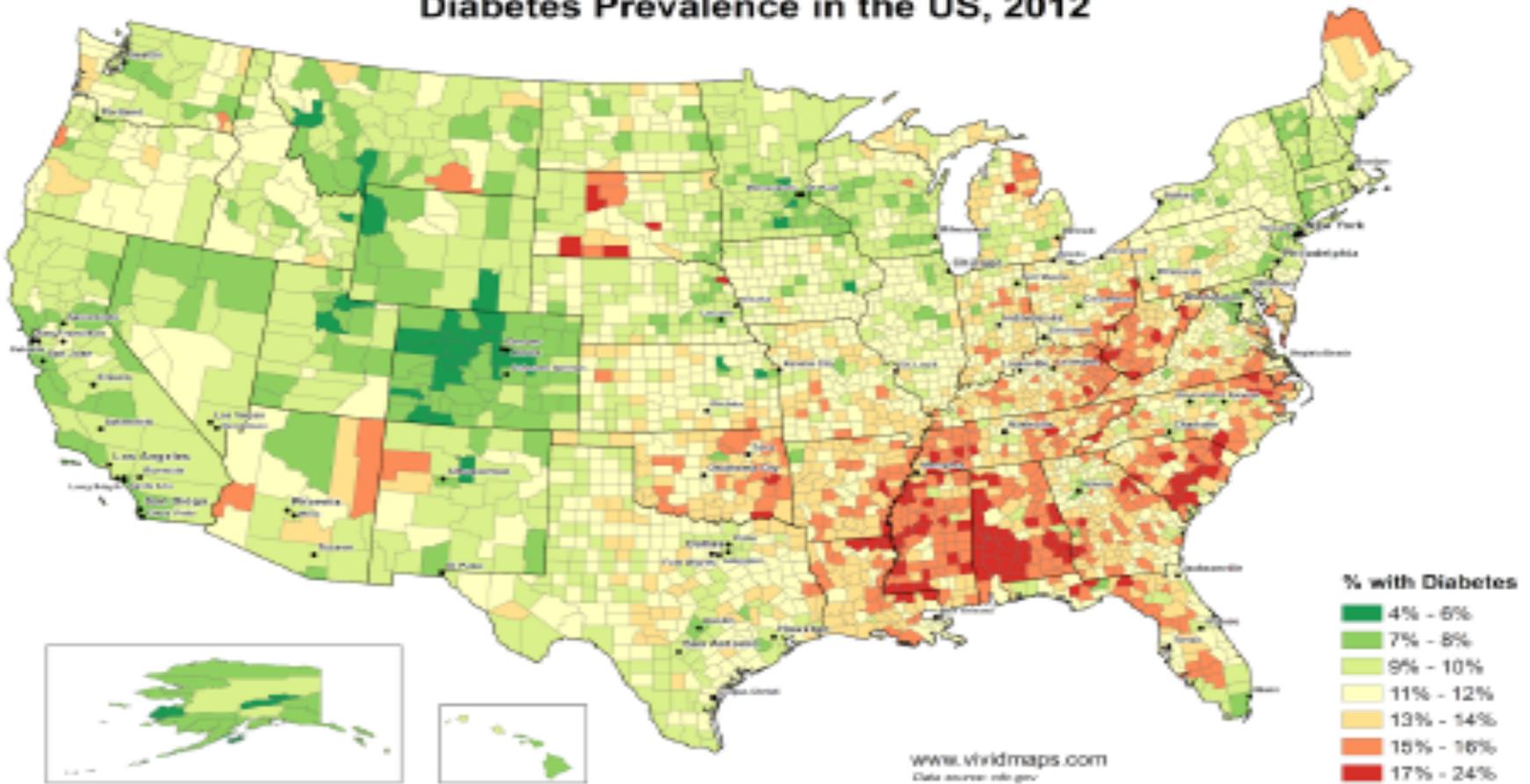


TODAY-

no state under 20%

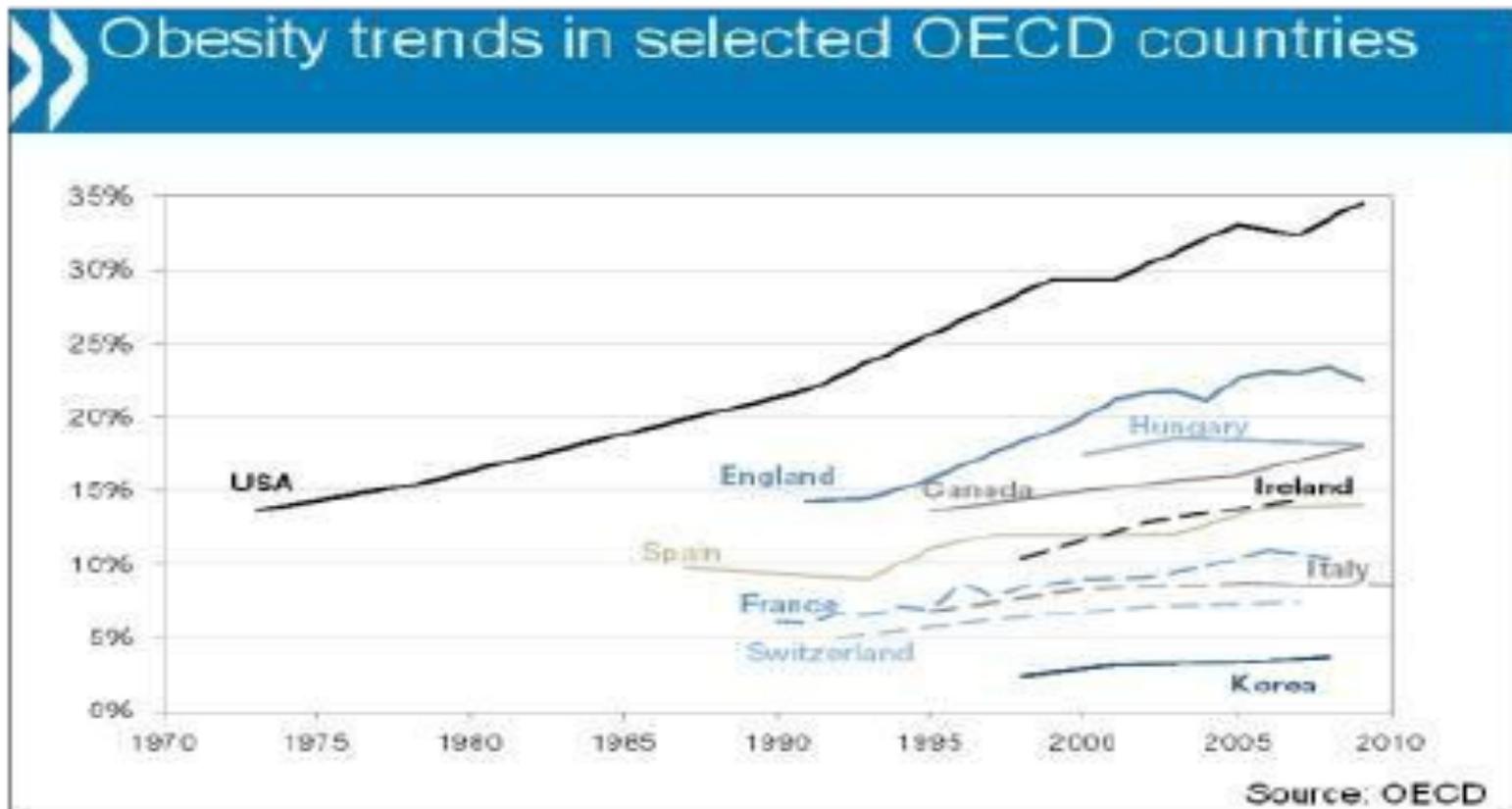
# Diabetes in US

Diabetes Prevalence in the US, 2012



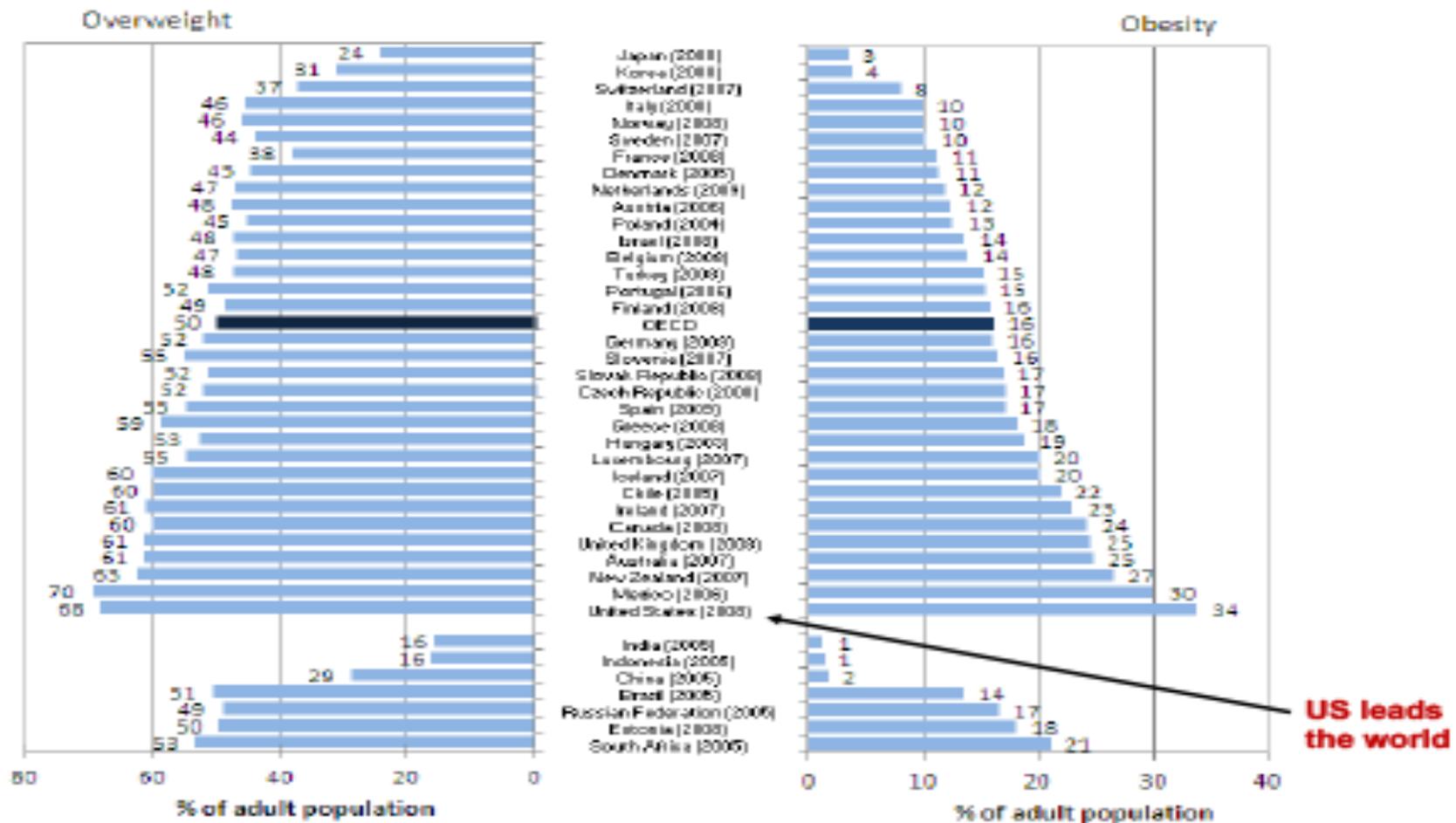
# Obesity

Obesity is an international problem



# Obesity worldwide

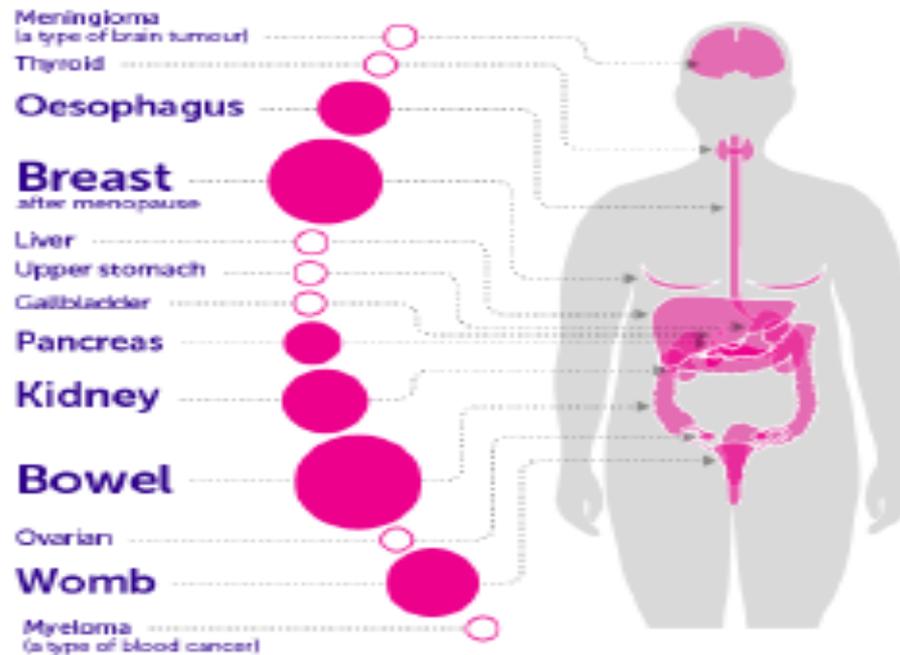
Staggering toll of overweight/obesity worldwide



# Being overweight

## BEING OVERWEIGHT CAN CAUSE 13 TYPES OF CANCER

- Larger circles indicate cancers with more UK cases linked to being overweight or obese
- Number of linked cases are currently being calculated and will be available in 2017



# Obesity causes

What is the **cause** of the obesity epidemic in the United States and worldwide?

## **Possible contributing factors**

### Changes in diet

- Macronutrients
- Quality of foods

### Obesogens in environment

- Toxins
- Endocrine disruptors

### Changes in activity levels

- Inactivity
- Screen time

### Changes in soil/enviroment

- Depletion of soil

### Circadian disruption/sleep fragmentation

- Light at night
- Artificial light during the day

# What causes obesity?

What caused the obesity epidemic?



DIETARY CHANGES

LESS Fat

MORE sugar/carbs

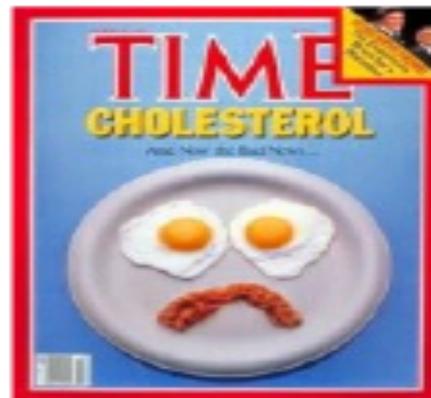
MORE processed veg oils

 **Why target meat, dairy, eggs?**

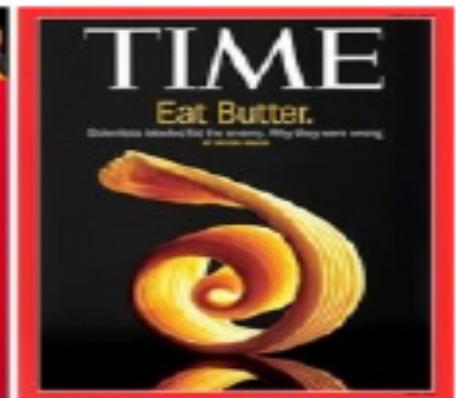
  
Sweet Keys, 1964

**Diet-Heart Hypothesis**

Saturated Fat and dietary cholesterol → Raised cholesterol (in the blood) → Heart Attack



1984

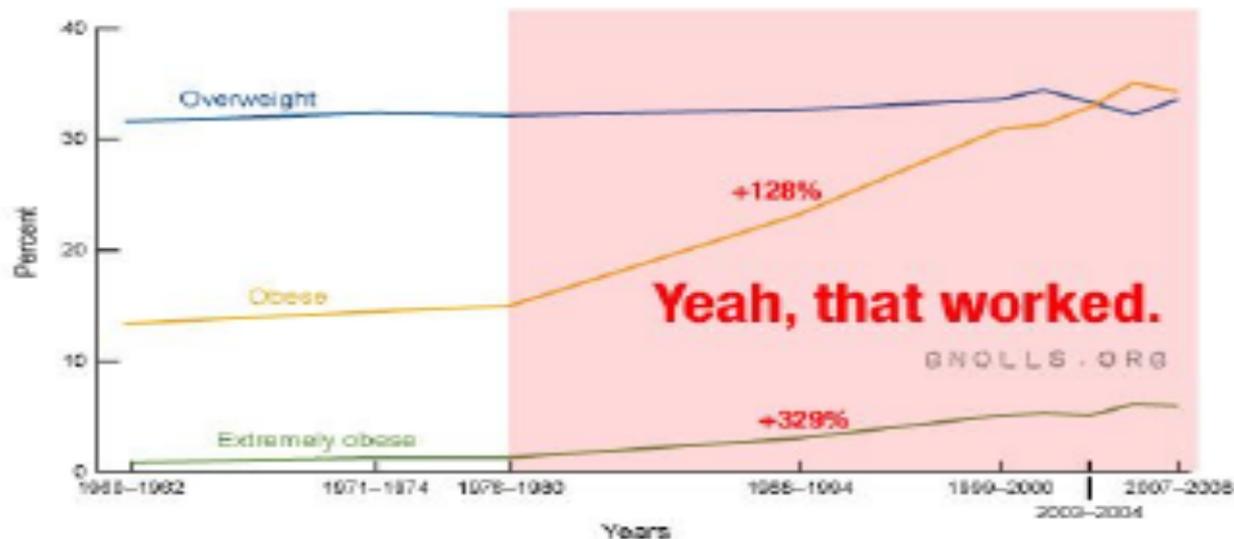


2014

# Eat less fat

In 1977, the US Government issued its first dietary recommendations: "Eat less fat and cholesterol, and more carbohydrates."

Figure 2. Trends in overweight, obesity, and extreme obesity among adults aged 20–74 years: United States, 1960–2008



NOTE: Age-adjusted by the direct method to the year 2000 U.S. Census Bureau estimates, using the age groups 20–39, 40–59, and 60–74 years. Pregnant females were excluded. Overweight is defined as a body mass index (BMI) of 25 or greater but less than 30; obesity is a BMI greater than or equal to 30; extreme obesity is a BMI greater than or equal to 40.  
SOURCE: CDC/NCHS, National Health Examination Survey cycle I (1960–1962); National Health and Nutrition Examination Survey I (1971–1974), II (1975–1980), and III (1988–1994), 1999–2000, 2001–2002, 2003–2004, 2005–2006, and 2007–2008.

Graph is from "Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1976–1980 Through 2007–2008." Cynthia L. Ogden, Ph.D., and Margaret D. Carroll, M.S.P.H. Available at [www.cdc.gov](http://www.cdc.gov)



# Food pyramid

**USDA says: eat more carbs, less fat**



# Institutional investment

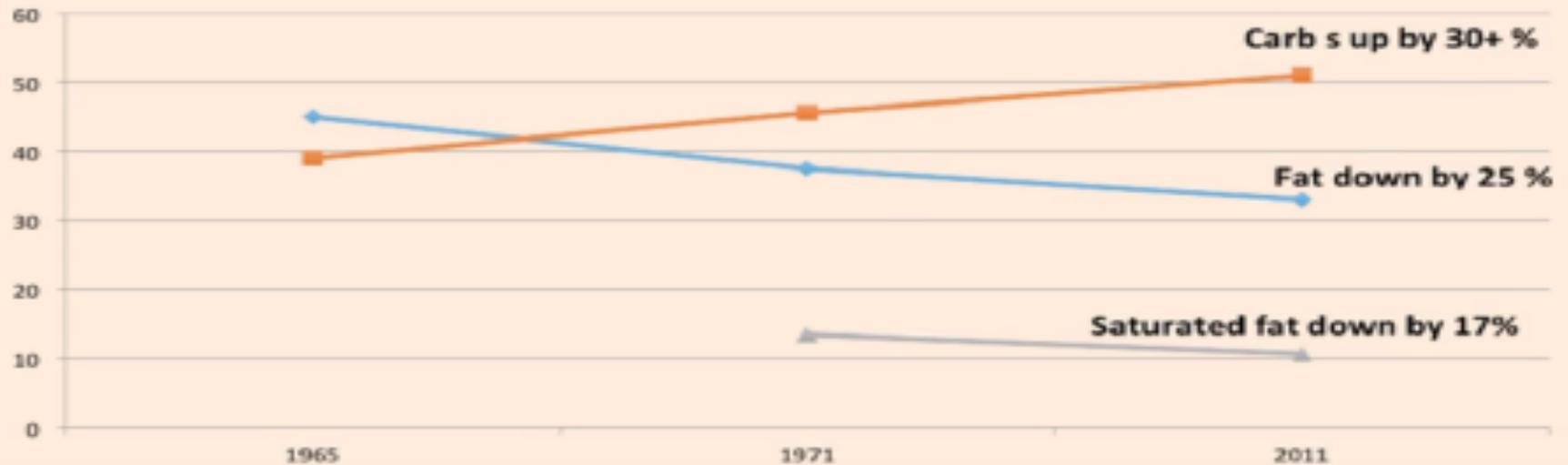
## Institutional investment



# Dietary habits

There has been a massive shift in US dietary habits...

## Major macronutrient shift in US 1965-2011



Source: Cohen et. al., *Nutrition*, 2015

# Low fat trials

## Summary: Randomized Clinical Trials and Cohort Studies of **LOW FAT**

**Table 1** Summary of meta-analyses of RCTs and prospective cohort studies

	Studies examined	Studies	People	Measure	Fat	Risk ratio	Conclusion
Stall and Miller (2009) <sup>13</sup>	Prospective cohort studies and RCTs	28	280 000	CHD mortality	Total fat	0.94 (0.74 to 1.18)	No significant difference
				CHD events	Total fat	0.92 (0.84 to 1.03)	No significant difference
Siri-Tarino et al (2010) <sup>17</sup>	Prospective cohort studies	21	347 747	CHD total and non-fatal	Saturated fat (extreme quintiles)	1.07 (0.96 to 1.19)	No significant difference
				CVD total and non-fatal	Saturated fat (extreme quintiles)	1.00 (0.89 to 1.11)	No significant difference
Mozaffarian et al (2010) <sup>11</sup>	RCTs	8	13 614	CHD events	Replacing SFA with PUFA	0.81 (0.70 to 0.95)	Significant difference
Hooper et al (2011) <sup>16</sup>	RCTs	21	71 790	Total mortality	All RCTs	0.98 (0.93 to 1.04)	No significant difference
					Modified fat	1.02 (0.88 to 1.18)	No significant difference
					Reduced fat	0.97 (0.90 to 1.04)	No significant difference
				CVD mortality	Reduced and modified fat	0.97 (0.76 to 1.23)	No significant difference
					All RCTs	0.94 (0.85 to 1.04)	No significant difference
					Modified fat	0.92 (0.72 to 1.15)	No significant difference
				CVD events	Reduced fat	0.96 (0.82 to 1.13)	No significant difference
					Reduced and modified fat	0.98 (0.76 to 1.27)	No significant difference
					All RCTs	0.86 (0.77 to 0.96)	Significant difference
Modified fat	0.82 (0.66 to 1.02)	No significant difference					
Reduced fat	0.97 (0.87 to 1.08)	No significant difference					
Reduced and modified fat	0.77 (0.57 to 1.00)	No significant difference					
Chowdhury et al (2014) <sup>14</sup>	Prospective cohort studies and RCTs	32	530 525	Coronary disease (All top vs bottom third)	Saturated fat	1.02 (0.97 to 1.07)	No significant difference
					Monounsaturated fat	0.99 (0.89 to 1.09)	No significant difference
					Polysaturated fat	0.93 (0.84 to 1.02)	No significant difference
					Trans fat	1.10 (1.06 to 1.27)	Significant difference
Schwingshackl and Hoffmann (2014) <sup>15</sup>	RCTs	12	7150	All-cause mortality	Modified fat intake	0.92 (0.68 to 1.25)	No significant difference
				CVD mortality	Modified fat intake	0.96 (0.65 to 1.42)	No significant difference
				CVD events	Modified fat intake	0.85 (0.63 to 1.15)	No significant difference
				MI	Modified fat intake	0.76 (0.54 to 1.09)	No significant difference
				All-cause mortality	Reduced fat intake	0.79 (0.42 to 1.48)	No significant difference
				CVD mortality	Reduced fat intake	0.93 (0.66 to 1.31)	No significant difference
				CVD events	Reduced fat intake	0.93 (0.65 to 1.34)	No significant difference
				MI	Reduced fat intake	1.18 (0.88 to 1.59)	No significant difference
				Reduced or modified fat	0.99 (0.87 to 1.15)	No significant difference	
Harcombe et al (2015) <sup>15</sup>	RCTs to 1977/1983	6	2467	All-cause mortality	Reduced or modified fat	0.99 (0.78 to 1.25)	No significant difference
				CHD mortality	Reduced or modified fat	0.99 (0.78 to 1.25)	No significant difference
Hooper et al (2015) <sup>16</sup>	RCTs	12	55 898	Total mortality	Reduced saturated fat	0.97 (0.90 to 1.05)	No significant difference
				CHD mortality	Reduced saturated fat	0.95 (0.80 to 1.12)	No significant difference
				CVD events	Reduced saturated fat	0.83 (0.72 to 0.96)	Significant difference
				MI	Reduced saturated fat	0.90 (0.80 to 1.01)	No significant difference
				Non-fatal MI	Reduced saturated fat	0.95 (0.80 to 1.13)	No significant difference
				Stroke	Reduced saturated fat	1.00 (0.89 to 1.12)	No significant difference
				CHD mortality	Reduced saturated fat	0.98 (0.84 to 1.15)	No significant difference
				CHD events	Reduced saturated fat	0.87 (0.74 to 1.03)	No significant difference

All studies examined data available at the time of the meta-analysis other than Harcombe et al, which examined data available to the dietary committees. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; PUFA, polyunsaturated fatty acids; RCT, randomised controlled trial; SFA, saturated fatty acids.

# Standard American diet

## SAD (**S**tandard **A**merican **D**iet)

### Obesogenic Rodent Chow

Protein: 15%

Fat: 45%

Carbohydrate: 40%



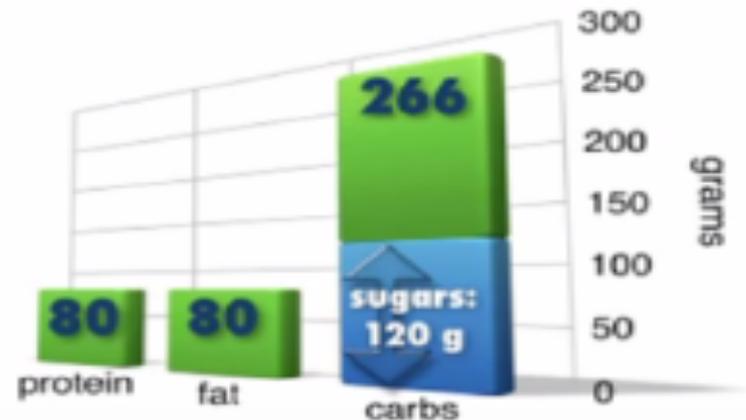
### American Daily Intake

protein: 80 grams

fat: 80 grams

carbohydrates: 266 grams

(sugars: 120 grams)



# Obesity food



40% Refined Carbs  
(sugar/starch)

+



40% Vegetable  
Oil

=



=



**Specially designed  
obesogenic rat chow**

40% Refined Carbs  
(sugar/starch)



+

40% Vegetable  
Oil



=

**Doughnut**



# Nutritional epidemiology

## Raging debate in nutritional epidemiology

### **Perspective: Limiting Dependence on Nonrandomized Studies and Improving Randomized Trials in Human Nutrition Research: Why and How**

John F Trepanowski<sup>1</sup> and John PA Ioannidis<sup>1,2,3,4,5,6</sup>

<sup>1</sup>Stanford Prevention Research Center; <sup>2</sup>Meta-Research Association Center of Stanford (METRICS); and <sup>3</sup>Departments of <sup>4</sup>Medicine, <sup>5</sup>Health Research and Policy, <sup>6</sup>Biomedical Data Science, and <sup>7</sup>Statistics, Stanford University, Stanford, CA

Cancer Causes & Control  
<https://doi.org/10.1007/s10552-018-1088-y>

COMMENTARY

### **Nutritional epidemiology and cancer: A Tale of Two Cities**

Edward Giovannucci<sup>1</sup> 

# Questionnaire

Issues with meat in epidemiological studies.....

## Questionnaire vs reality



**Meat consumption** is associated with many other potentially adverse dietary and non-dietary exposures.....

# Food questionnaire

## Food Questionnaires have limitations



### COHORT STUDIES RELIANT UPON FOOD QUESTIONNAIRES

SO WAS IT THE MEAT OR NITRATES IN THE HOT DOG  
THAT CAUSED THE ASSOCIATION WITH CANCER?

OR MAYBE MAYBE IT WAS THE SUGAR OR HIGH FRUCTOSE  
CORN SYRUP IN THE SODA AND KETCHUP

OR MAYBE THE HFCS OR OTHER FILLERS ADDED TO THE HOT DOG?

OR MAYBE IT WAS THE FREE RADICALS, TRANSFATS AND  
OMEGA 6'S FROM THE SOY COOKING OIL

OR MAYBE THE ANTIBIOTICS IN THE MEAT ADVERSELY  
IMPACTING GUT BACTERIA IN ONE'S MICROBIOME

OR MAYBE MUTAGENIC WHEAT  
IN THE BUN

OR THE CARBS FROM THE POTATOES  
OR THE WHEAT IN THE BUN THAT WAS  
DESICCATED WITH GLYPHOSATE SEVEN  
DAYS BEFORE BEING HARVESTED

PLUS MAYBE THE PERSON WHO ATE  
THIS MEAL WASN'T EXACTLY THE MOST  
HEALTH CONSCIOUS PERSON TO  
BEGIN WITH IN THE FIRST PLACE

Actual food intake ??= food diary ??????= Food Frequency Questionnaire

# Challenges

Some general **challenges** in applying epidemiological findings to prevention

1. Short term focus of most research
2. Interventions deployed late in life
3. Treatment focus (prevention ignored)
4. Controversies: are results credible
5. Social factors (poverty, lack of education)
6. Lack of transdisciplinary approaches

# Obesity rates

What is the cause of increasing rates of **obesity** in the USA?

1. Dietary changes

2. 'Light at night'

3. Many others...



# Sugar

reasons.....

1. Western diet
  - Sugar
  - Processed vegetable oils
  - Hyperpalatable
  
2. 'Engineered' (processed) foods
  - High carbs
  - High fat
  - High salt
  
- **SECONDARY FACTORS**
  - Bad advice ('low fat')
  - Less active
  - Obesogenic toxins
  - Economic pressure\_ food desserts
  - Less home cooking/more fast food



# Late at night

## **‘Light at night’ hypothesis**

Light exposure at night disrupts sleep, inhibits melatonin.....



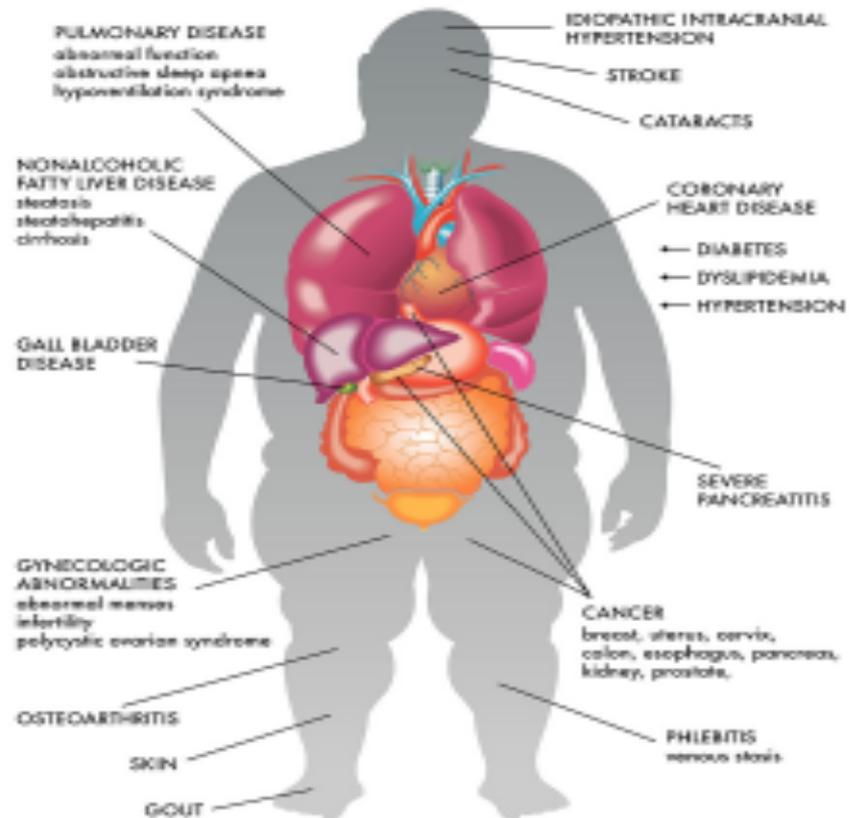
Stevens, 1987

# Insulin resistance

**Before we develop diabetes.....**

**Insulin resistance**  
**Is present for many years and does damage**

## Conditions Associated with Insulin Resistance



# Insulin resistance

ARTICLES

## Insulin resistance is associated with the pathology of Alzheimer disease

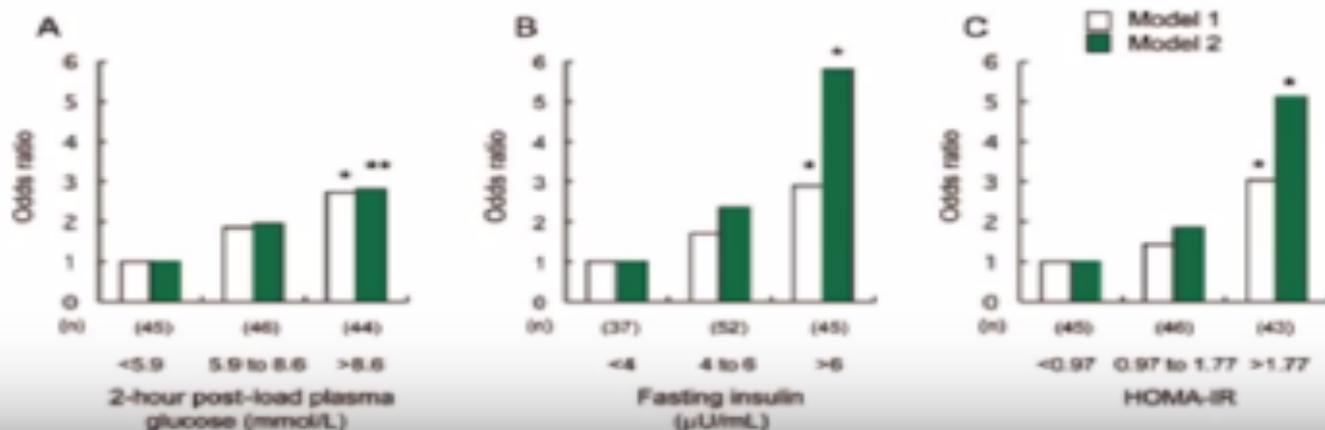
The Hisayama Study

T. Matsuzaki, MD  
K. Sasaki, MD, PhD  
Y. Tanigaki, MD, PhD

### ABSTRACT

**Objective:** We examined the association between diabetes-related factors and pathology of Alzheimer disease (AD) to evaluate how diabetes affects the pathogenic process of AD.

Figure 1 Odds ratios for each tertile of glucose (A), insulin (B), and HOMA-IR (C) vs the lowest tertile for the presence of neuritic plaques



# Insulin resistance

## Insulin Resistance Predicts Mortality in Nondiabetic Individuals in the U.S.

KARLEE J. AUSK, MD<sup>1</sup>  
EDWARD J. BOYKO, MD, MPH<sup>2</sup>  
GEORGE N. EMANOUIL, MBChB, MS<sup>1,3</sup>

**OBJECTIVE** — Insulin resistance is a suspected causative factor in a wide variety of diseases. We aimed to determine whether insulin resistance, estimated by the homeostasis model assessment for insulin resistance (HOMA-IR), is associated with all-cause or disease-specific mortality among nondiabetic persons in the U.S.

**RESEARCH DESIGN AND METHODS** — We determined the association between HOMA-IR and death certificate–based mortality among 5,511 nondiabetic, adult participants of the third U.S. National Health and Nutrition Examination Survey (1988–1994) during up to 12 years of follow-up, after adjustment for potential confounders (age, sex, BMI, waist-to-hip ratio, alcohol consumption, race/ethnicity, educational attainment, smoking status, physical activity, C-reactive protein, systolic and diastolic blood pressure, plasma total and HDL cholesterol, and triglycerides).

**RESULTS** — HOMA-IR was significantly associated with all-cause mortality (adjusted hazard ratio 1.16 [95% CI 1.01–1.3], comparing successive quartiles of HOMA-IR in a linear model and 1.64 [1.1–2.5], comparing the top [HOMA-IR >2.8] to the bottom [HOMA-IR ≤1.4] quartile). HOMA-IR was significantly associated with all-cause mortality only in subjects with BMI <25.2 kg/m<sup>2</sup> (the median value) but not in subjects with BMI ≥25.2 kg/m<sup>2</sup>. Subjects in the second, third, and fourth quartile of HOMA-IR appeared to have higher cardiovascular mortality than subjects in the lowest quartile of HOMA-IR. HOMA-IR was not associated with cancer-related mortality.

insulin resistance, such as race, sex, physical activity, and genetic factors, while as-yet-unknown causes of insulin resistance also likely exist.

The homeostasis model assessment for insulin resistance (HOMA-IR) estimates insulin resistance from fasting plasma glucose and serum insulin levels (11). There is good correlation between values of insulin resistance obtained using HOMA-IR and the euglycemic-hyperinsulinemic clamp method (12), the gold-standard test that is too costly and technically demanding to be used in epidemiologic studies or clinical practice. Given the combination of accuracy and ease of testing, HOMA-IR is considered an appropriate method for measurement of insulin resistance in epidemiologic studies (12).

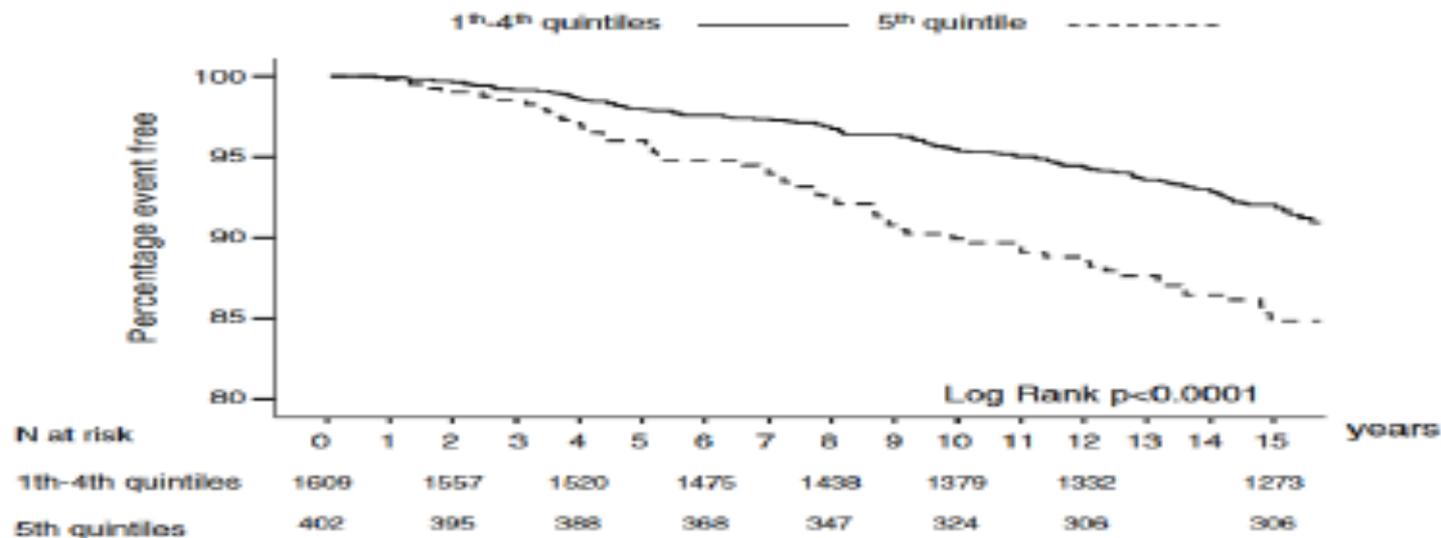
Our aim was to determine the association between HOMA-IR and mortality in nondiabetic people in the U.S. independently of other important predictors of mortality. This finding would be impor-



**CONCLUSIONS** — HOMA-IR is associated with all-cause mortality in the nondiabetic U.S. population but only among persons with normal BMI. HOMA-IR is a readily available measure it can be used in the future to predict mortality in clinical or epidemiological settings.

# Metabolic factors

**Metabolic factors** are relatively unstudied but related to overall **cancer mortality** in cohort settings.....



Acta Diabetol (2012) 49:421–428  
DOI 10.1007/s00592-011-0361-2

ORIGINAL ARTICLE

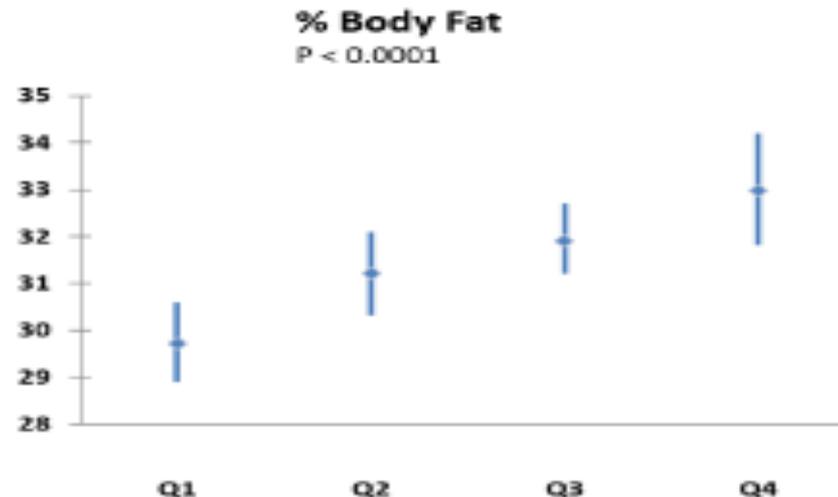
**Insulin resistance/hyperinsulinemia and cancer mortality:  
the Cremona study at the 15th year of follow-up**

# Hyperinsulinemia

**Hyperinsulinemia** is a likely culprit: shown here, relation to **Obesity**, also related to inflammation, liver function, hypertension, general health, hematologic parameters, adverse lipid profiles, vitamin levels....

HOMA-IR (Insulin) quartiles, adjusted\*, both prediabetics and diabetics are excluded, Q1=2064, Q2=2181, Q3=2391, Q4=2588

## Anthropometry



\*Adjusted: age (continuous), age-squared, ethnicity/race, alcohol, SES, Smoking (ever/never/current), pack years, BMI

# Population perspective

## A Population Perspective on Cancer

- *What is epidemiology?*
- *What has epidemiology accomplished?*
- *What can go wrong?*
- *What can go really wrong?*
- *What next?*

# Population perspective

## A Population Perspective on Cancer

- *What is epidemiology?*
- *What has epidemiology accomplished?*
- *What can go wrong?*
- *What can go really wrong?*
- ***What next?***

# Technology features

## Features of 'technology'



- Capture previously inaccessible exposures
- More extensive data than traditional
- Improve misclassification
- Data validation critical
- Examples: activity, sleep, location....

# Lung cancer

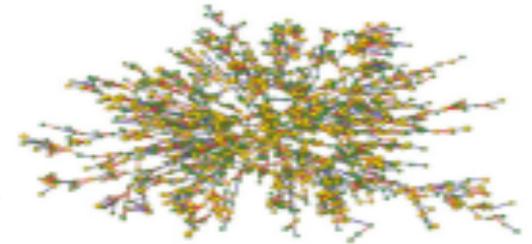
Traditional lung cancer risk factors used to assess utility of screening

- Age
- Gender
- Smoking History
- Occupation
- Family Hx lung cancer
- COPD

# Lung cancer risk factors

Examples of lung cancer risk factors that can be assessed by technology:

1. Sleep
2. Physical activity/inactivity
3. Vital signs- heart rate
4. Circadian variation
5. Social factors
6. Location
7. Pulse oximetry



# Sleep

## Sleep

Sleep quantity  
Sleep quality  
Sleep interruptions  
Stages of sleep  
REM sleep  
Wakefulness  
Avg. time in bed



# Sleep and obesity/smoking

## Sleep and obesity/smoking

### Data from NHANES

	Sleep duration			
	<6 hr	6h	7h	8h
Current smokers	<b>35%</b>	25%	18%	19%
Alcohol (> 1d/day)	15%	14%	13%	15%
Diabetes	<b>8%</b>	5%	4%	6%

# Physical Activity

## Physical activity/inactivity

Type and quality of exercise

Timing of movement

Periods of inactivity

Calories

Steps

Climbing

Distance

Indices of fitness:

- Body fat
- Breathing rate
- Heart rate
- Pulse ox



Many Apps: RunKeeper, S Health, MyFitnessPal

# Vital Signs

## Vital signs

Heart rate  
Heart rate variability  
Arrhythmias  
Max and min  
Relation to diet/exercise

### Examples:

- Polar line of 'watches'
- FitBit
- Adidas, Nike, etc.
- newer Apple, Samsung



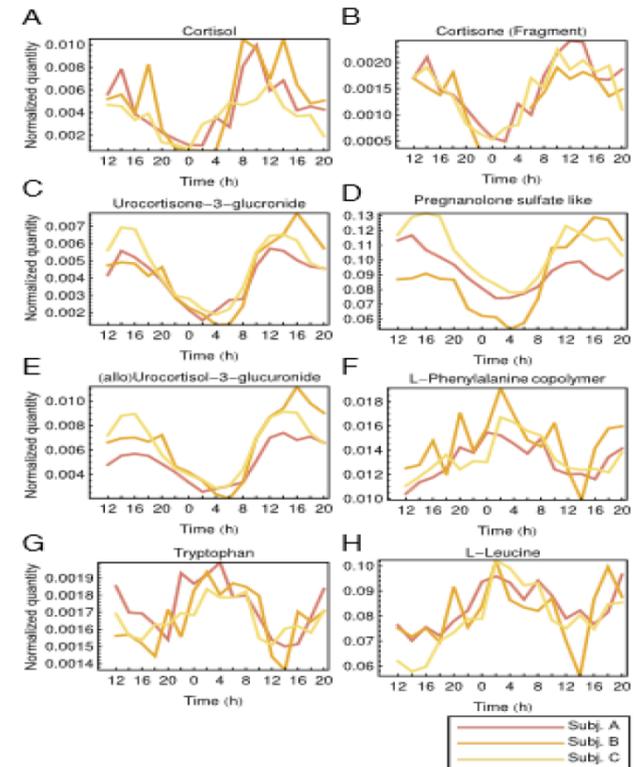
# Circadian variation

## Circadian variation

Internal body time is related to:  
disease susceptibility  
chronotherapy

Internal body time determined by 2 blood samples

Also can be determined by **activity/sleep/food** cycles



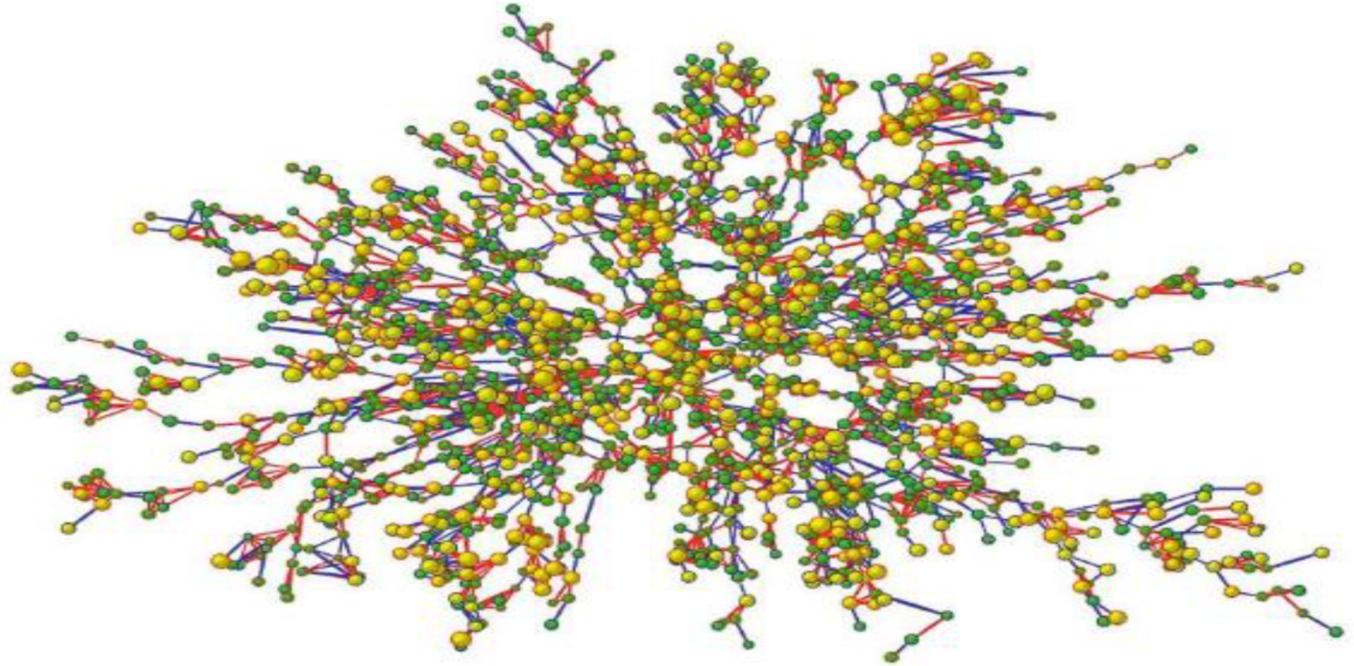
# Social data

## Social data

Data on social factors often absent from epidemiologic study designs

Can quantitate:  
contacts,  
'friends',  
indices of interaction,  
relationships,  
frequency of contact

## Social networks



The Spread of Obesity in a large social network over 32 years.  
New Eng J Med 26jul, 2007, Christakis NA et al.

# Oxygen saturation and mortality

## Oxygenation saturation and mortality

- monitor noninvasively with a cheap finger device
- SpO2 categories related to **all-cause mortality** after adjustment for age, sex, smoking, BMI, CRP, spirometry, medical illness and respiratory Sxs

SpO2 < 92%	1.99 (1.33-2.96)
SpO2 93-95%	1.36 (1.15-1.60)
Ref SpO2 > 96%	

Sponsored

 Covidien Nellcor PM 10... Master Mo... ▼ \$483.00	 Finger fingertip Pulse Oximet... Walmart ▼ \$16.98	 Pulse Oximeter Blood Oxyge... Walmart ▼ \$15.80	 FaceLake FL-400 Finge... Walmart ▼ \$13.50
 Finger tip Pulse Oximeter CM... Clinical Ox... ▼ \$14.99	 Finger tip Pulse Oximeter Pin... Walmart ▼ \$13.50	 FaceLake FL-350 Finge... Walmart ▼ \$14.90	 Delos Pulse Oximeter - M... Quill ▼ \$38.99

EMC Pulm Med. 2015 Feb 12;15(9). doi: 10.1186/s12890-015-0003-5.

Low oxygen saturation and mortality in an adult cohort: the Tromsø study.

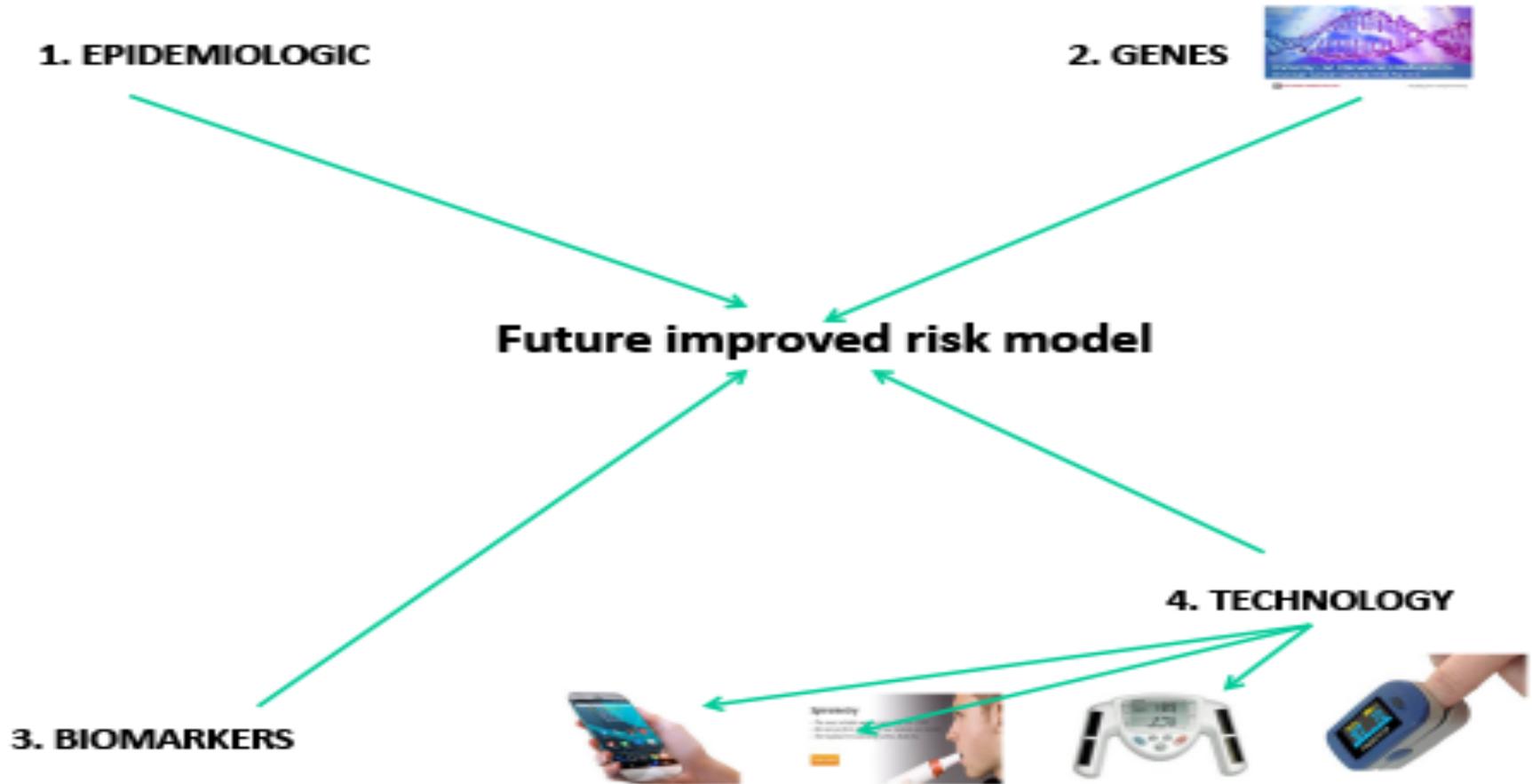
Vold ML<sup>1,2</sup>, Aasebo U<sup>3,4</sup>, Wilsgaard T<sup>5</sup>, Melbye H<sup>6</sup>

Read free full text at  
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# Future applications

## Future Applications: Screening



# Virtual cohort

Next step: **'virtual' cohort**

1. Sign up in diverse locations: hospital/healthy
2. Regional biorepository with tissue access
3. Link to pathology/medical records
4. Database
5. Consent, security, privacy protection
6. Disease ascertainment
7. Lifestyle, habits, hobbies, home, workplace
8. Regular electronic follow-up

# Retiring

## Retiring! Nov 2020

1980's

Include biomarkers in epidemiologic studies

1990's

Genetics plays a role in common cancers: lung

2000's

Common leukemia is preceded by precursor (MBL)

2010's

Genetics plays a role in exposures

2020

Insulin resistance is common and bad

Sleep is good

Any exposure to tobacco is bad