Epidemiology

Epidemiology

Translational Research in Clinical Oncology

October, 2016

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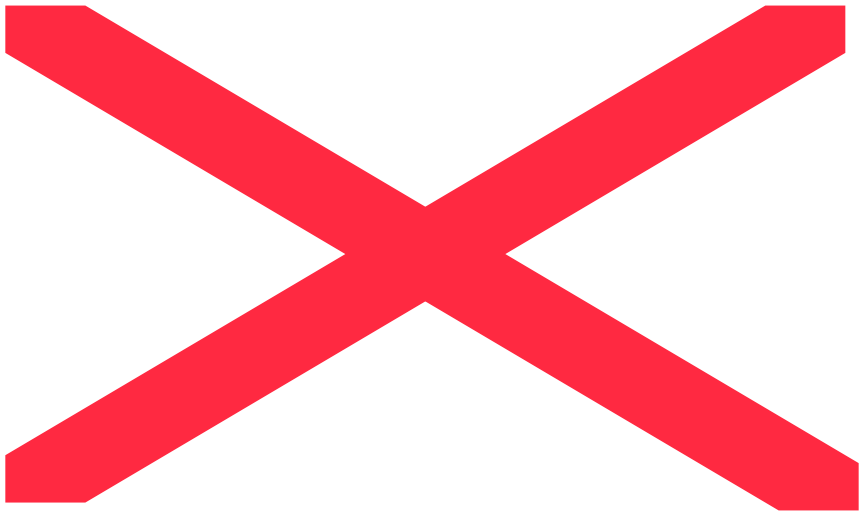
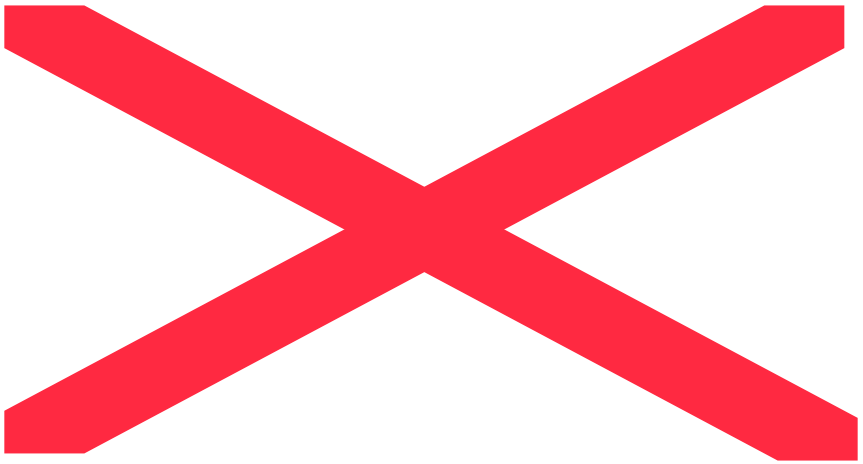
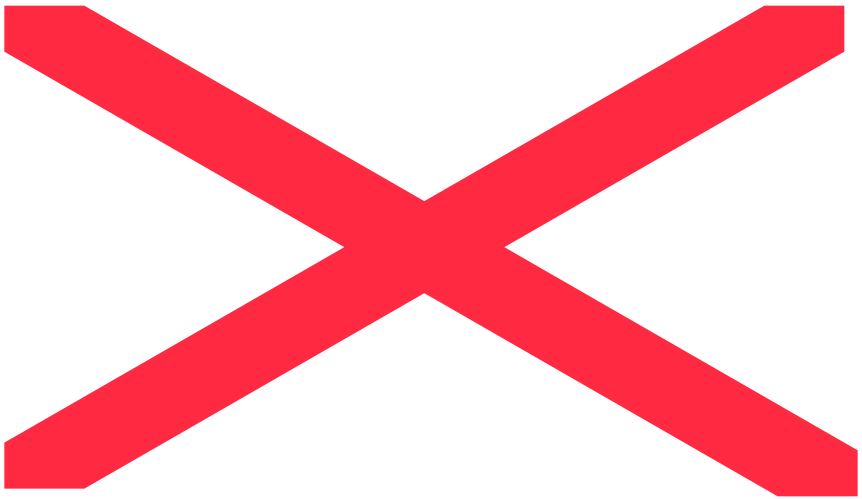
A Population Perspective



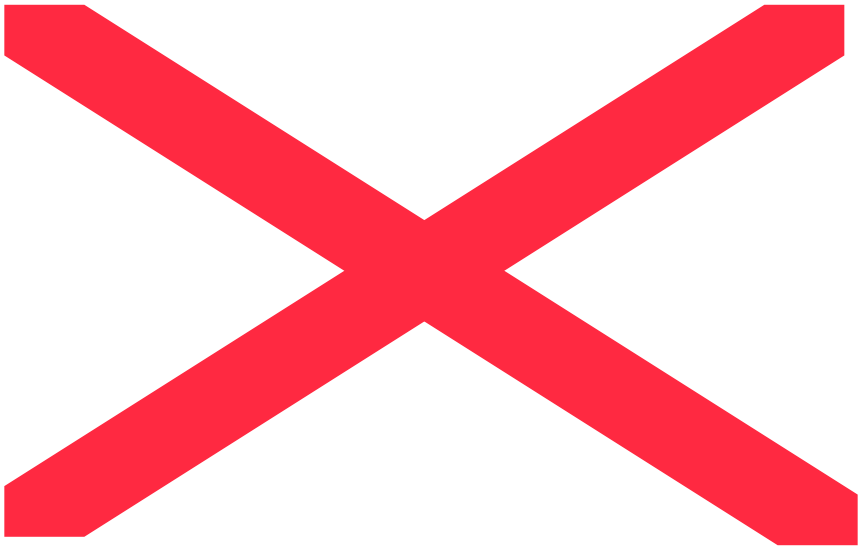
Cigarettes and culture



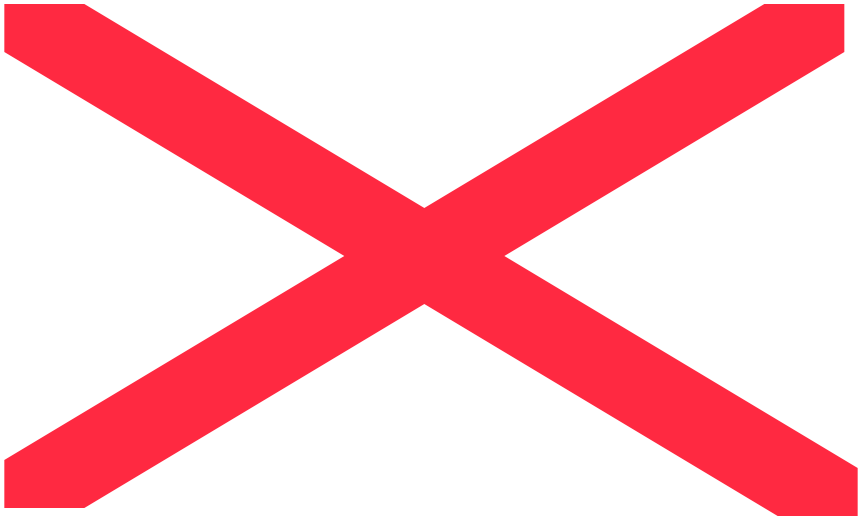
Decades of change



Epidemiology



DCEG



NIH epidemiology

National Cancer Institute → We are **INTRAMURAL**
~ 85% $$ are extramural

Division of Cancer Epidemiology and Genetics → Cancer **ETIOLOGY**

Genetic Epidemiology Branch

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

Division of Cancer Epidemiology and Genetics (DCEG)

- Identify the environmental and genetic causes of cancer in the population
- High quality, high impact, value-added research
- National and international in scope
- Scientific partnerships in molecular epidemiology across NCI and beyond

Major public health advances

Major public health advances

Regulatory changes

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

Clinical practice

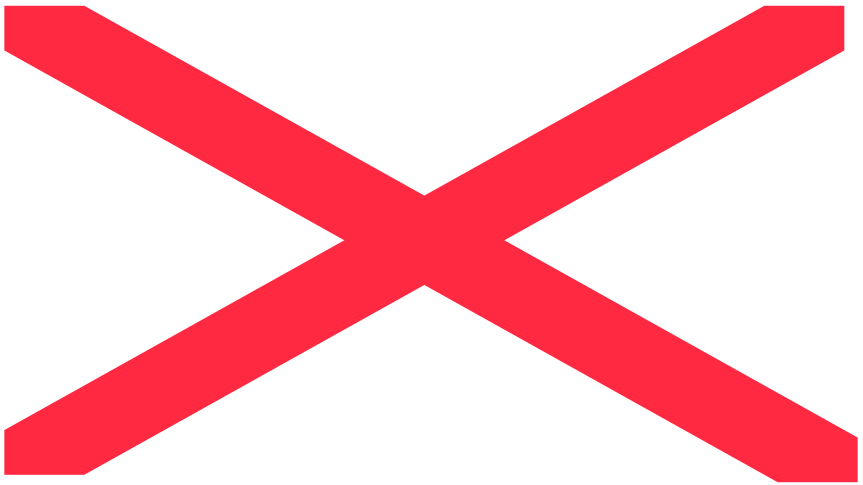
- Cancer susceptibility syndromes
- Second cancers among cancer survivors

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

Collaborations

DCEG



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

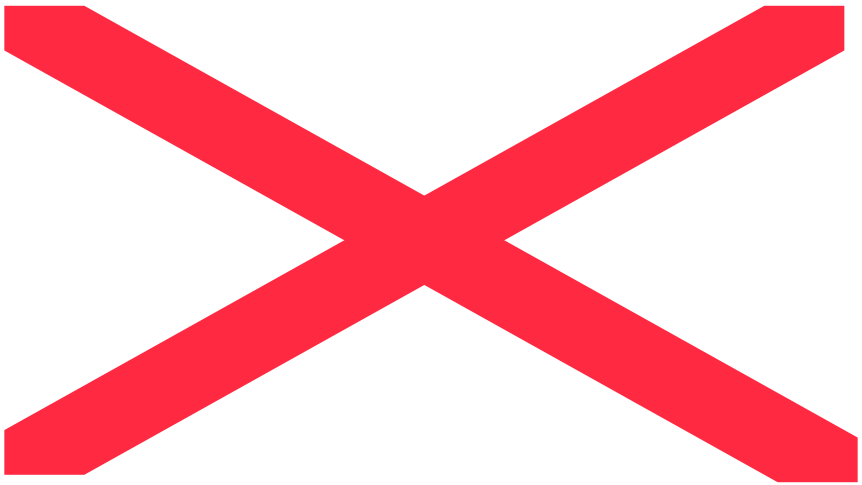
Observational vs. Experimental

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……

Hierarchy of studies



Goals of Epidemiology

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

Epidemiologists emphasize prevention

Rationale:
Effective (think polio, smallpox, smoking cessation, clean water, HPV…)
Cheaper (compared to late stage interventions)
Public health orientation
Eliminate disease at the source
Downsides
Requires time to demonstrate effectiveness
Less dramatic than treatment
Can't see disease you have prevented
Lives saved appear in statistics- not grateful patients
Less positive political impact (= funding)
Political opposition from powerful groups (Tobacco, Soft Drink Companies, Polluters, etc.)
No Nobel Prizes

Primary = directed to susceptibility stage
Example: Needle exchange to prevent AIDS, HPV vaccine
Secondary = directed to subclinical stage
Example: Screen for cervical cancer with Pap Smear
Tertiary = directed to clinical stage

Example: Treat diabetic retinopathy to prevent blindness

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

Participation rate

Pilot studies: participation rate

30%	49%	73%
• Phone Survey	• Invitation letter • Follow-up by phone • In hospital • Advertisements • Cash award • Physicians' letter • Home/hospital	• **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%

Controls for epidemiologists

Epidemiologists worry about controls

Population controls

- Expensive
- Most representative (section bias still possible)
- Calculate ABSOLUTE risks (contract 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….

Gerstman, 2003

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.)

Can you explain

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 buttered toast for breakfast…
she drank shots on her 90th birthday

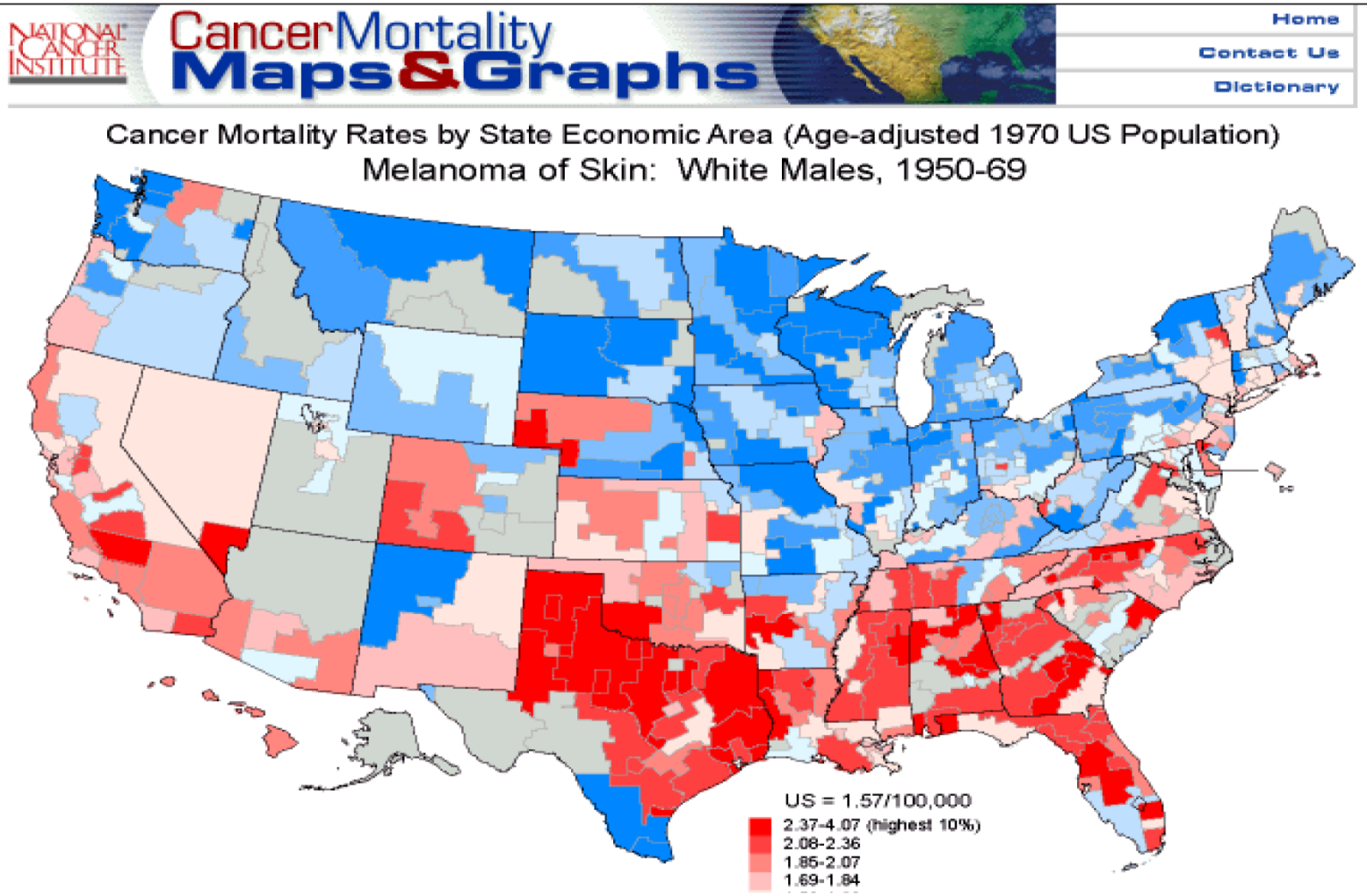
she outlived all her doctors…..

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)

Deterministic vs. Probabilistic

Cancer Maps

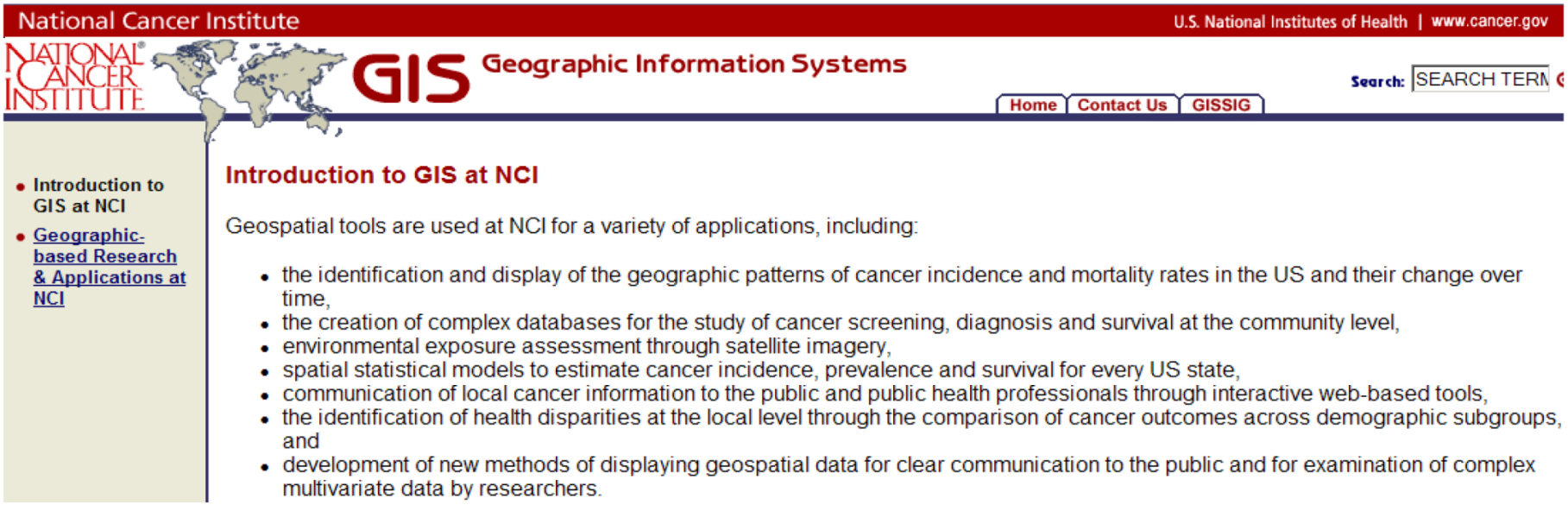
MAPS 1



Geographic Information Systems

GIS

Geographic patterns of disease and exposure via satellite
Examples, used to estimate nitrate, pesticide levels (see, Ward et al., 2000)



SEER

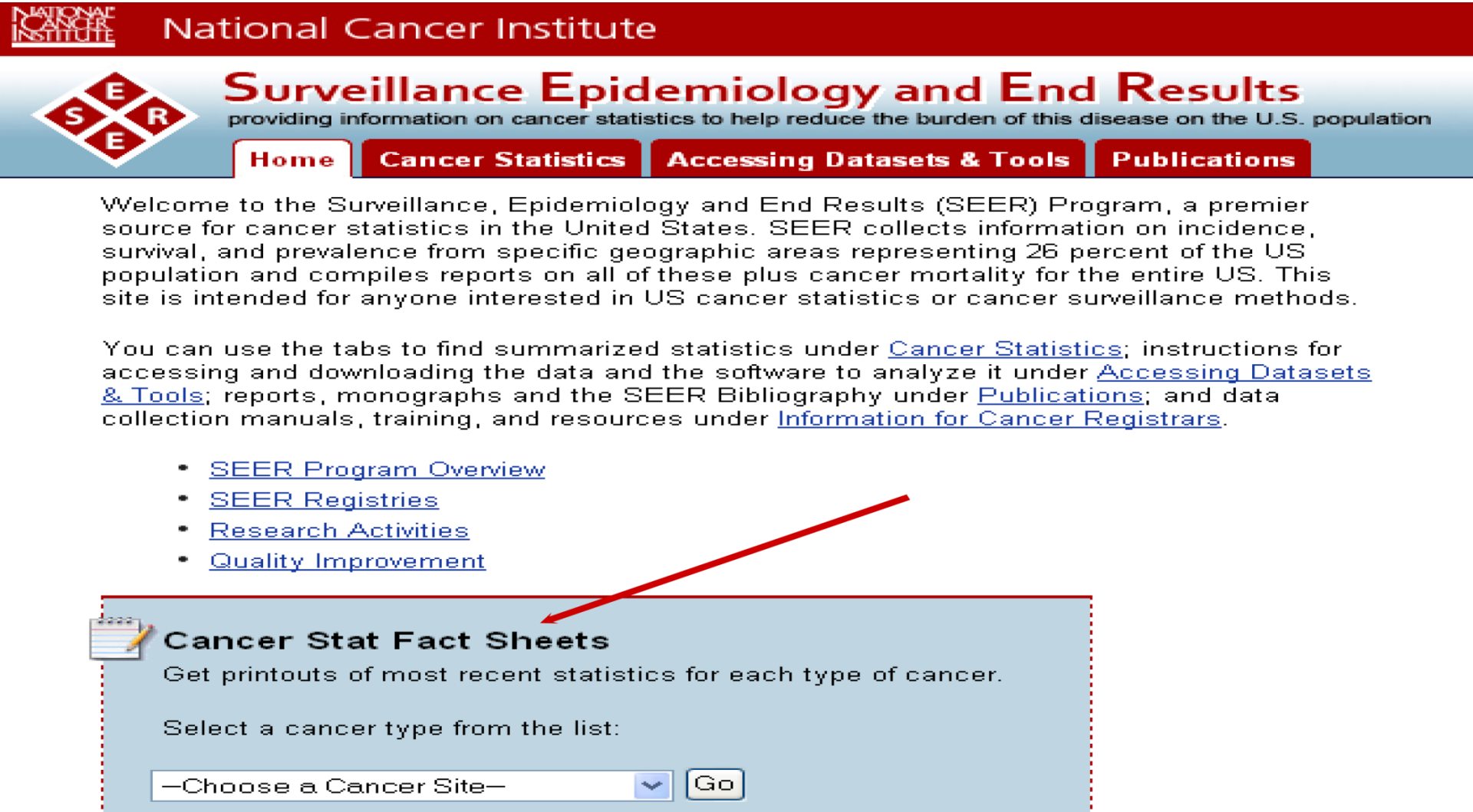
Surveillance, Epidemiology, and End Results (SEER) Program

26% of US population

incidence and survival, patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status

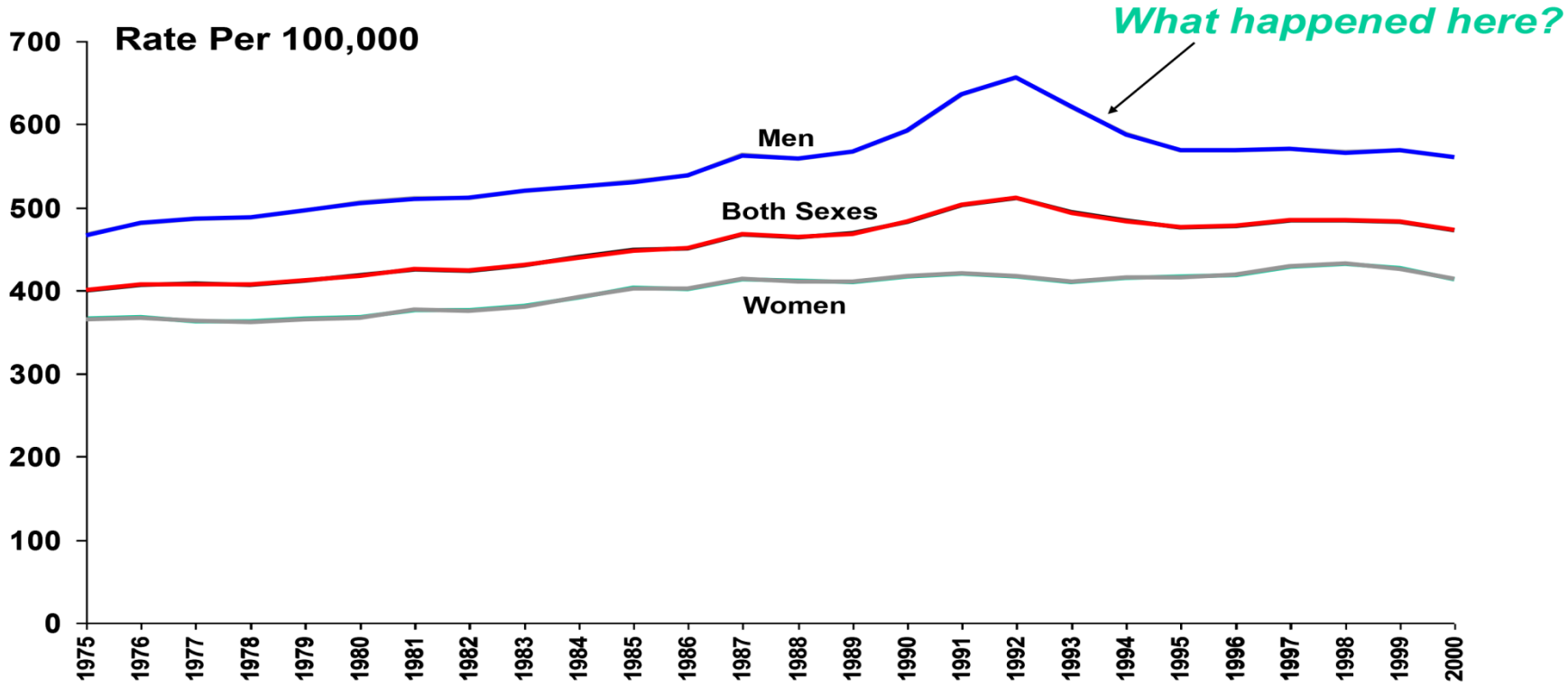
comprehensive source of population-based information

SEER


National Cancer Institute
Surveillance Epidemiology and End Results
providing information on cancer statistics to help reduce the burden of this disease on the U.S. population
Home
Cancer Statistics
Accessing Datasets & Tools
Publications
Welcome to the Surveillance, Epidemiology and End Results (SEER) Program, a premier source for cancer statistics in the United States. SEER collects information on incidence, survival, and prevalence from specific geographic areas representing 26 percent of the US population and compiles reports on all of these plus cancer mortality for the entire US. This site is intended for anyone interested in US cancer statistics or cancer surveillance methods.
You can use the tabs to find summarized statistics under Cancer Statistics; instructions for accessing and downloading the data and the software to analyze it under Accessing Datasets & Tools; reports, monographs and the SEER Bibliography under Publications; and data collection manuals, training, and resources under Information for Cancer Registrars.
SEER Program Overview
SEER Registries
Research Activities
Quality Improvement
Cancer Stat Fact Sheets
Get printouts of most recent statistics for each type of cancer.
Select a cancer type from the list:
—Choose a Cancer Site—
Go

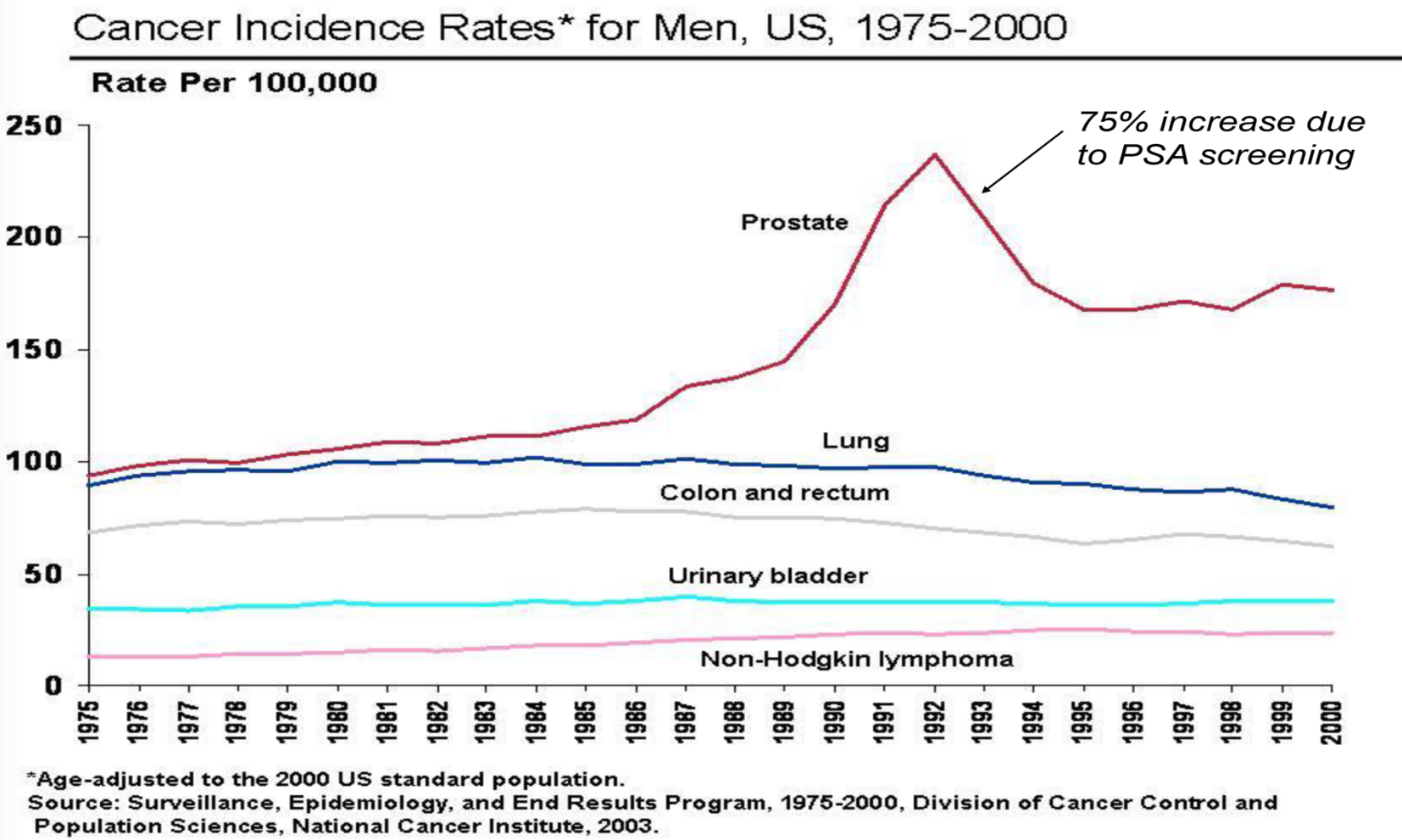
Cancer Incidence Rates

Cancer Incidence Rates*, All Sites Combined, All Races, 1975-2000

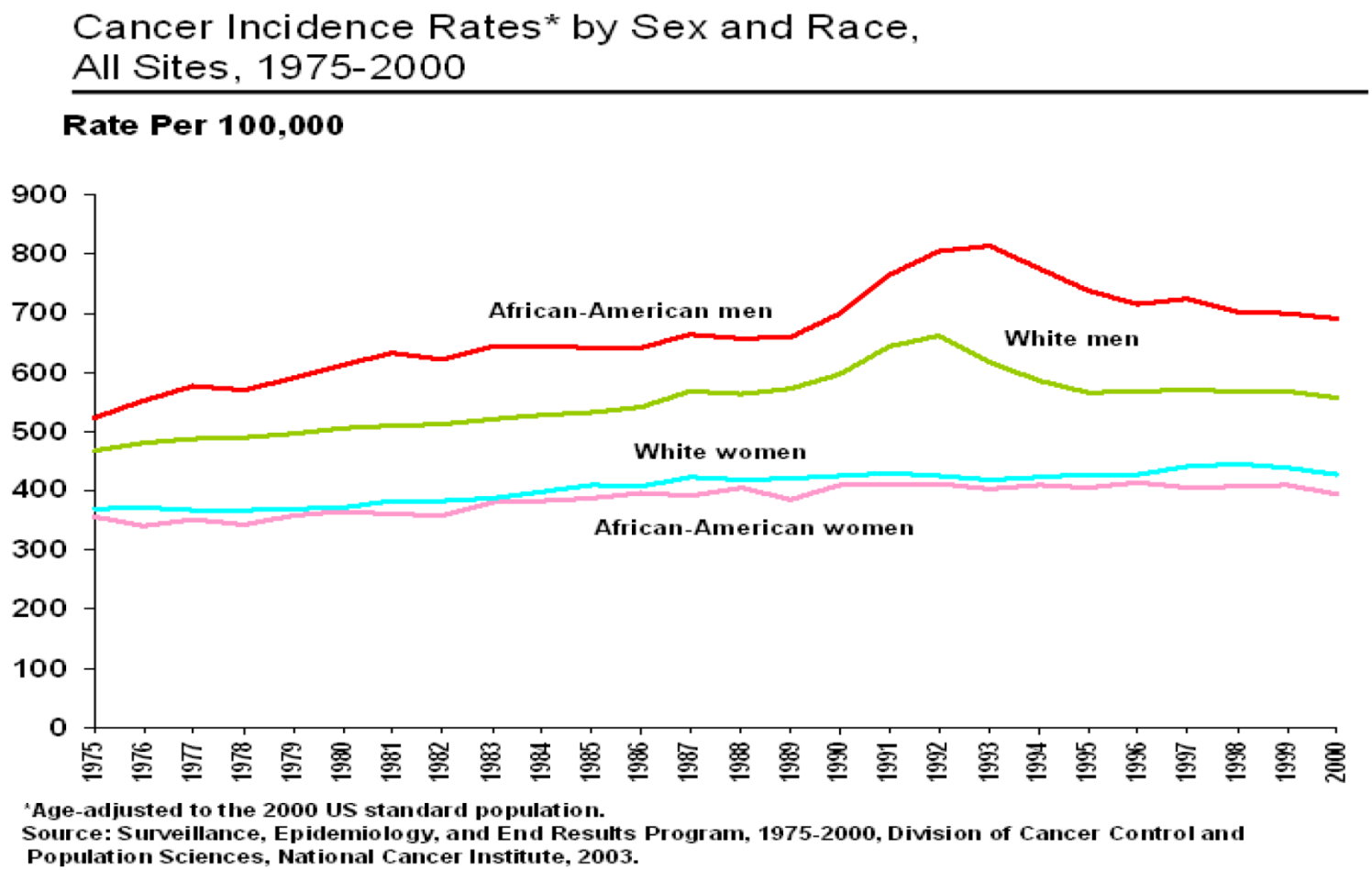


*Age-adjusted to the 2000 US standard population.
Source: Surveillance, Epidemiology, and End Results Program, 1973-1999, Division of Cancer Control and Population Sciences, National Cancer Institute, 2003.

Cancer Rates for Men

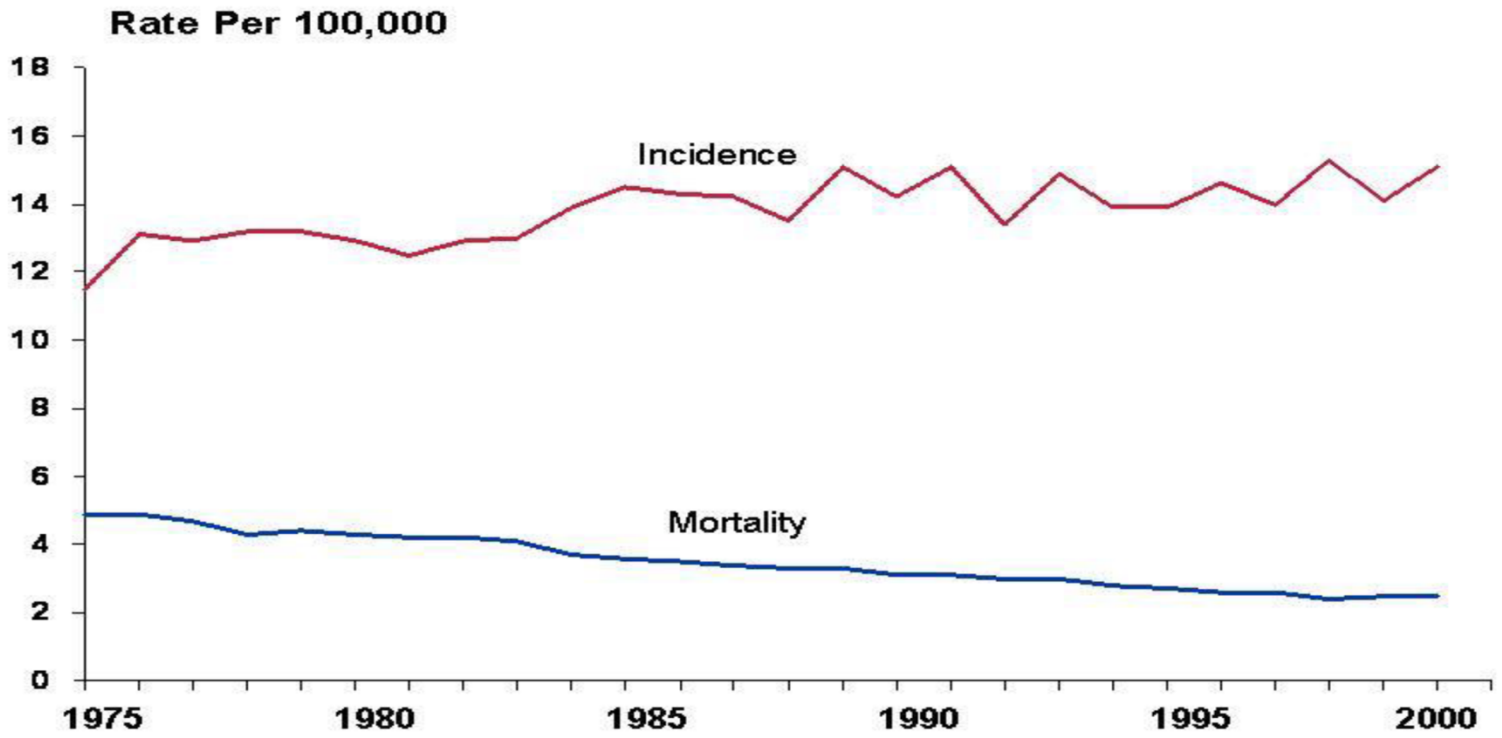


Cancer by sex and race



Cancer and Children

Cancer Incidence & Death Rates* in Children 0-14 Years, 1975-2000



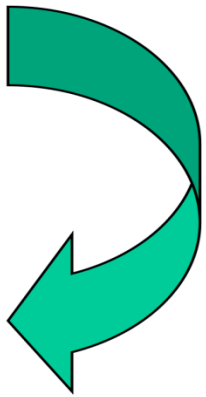
*Age-adjusted to the 2000 Standard population.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2000, Division of Cancer Control and Population Sciences, National Cancer Institute, 2003.

Childhood Cancers

Childhood Cancers (< 14 ys)

* **Incidence**
  - **8,600 new cases/yr**
  - **12,400 (0 – 19 ys)**

* **Mortality**
  - **1,500 deaths/yr**
  - **2,300 (0 – 19 ys)**
  - **rates ↓ 50% since 1973**



Treatment Effective !

* **Etiology -- poorly understood**

How do you prove a cause?

(CLASSICAL)

1. It should confer high risk

2. It should be consistent

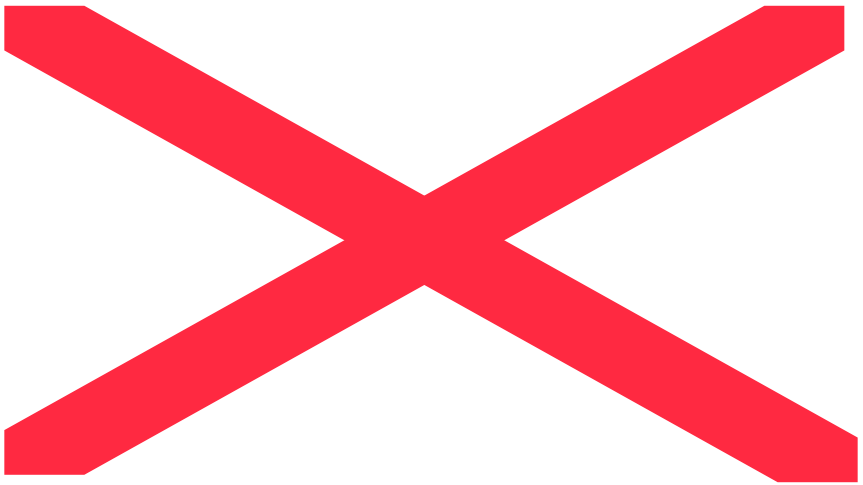
3. Dose response

4. Cause occurs first!

5. Biology makes sense

How do you prove a cause?

Causation



How do you prove a cause?

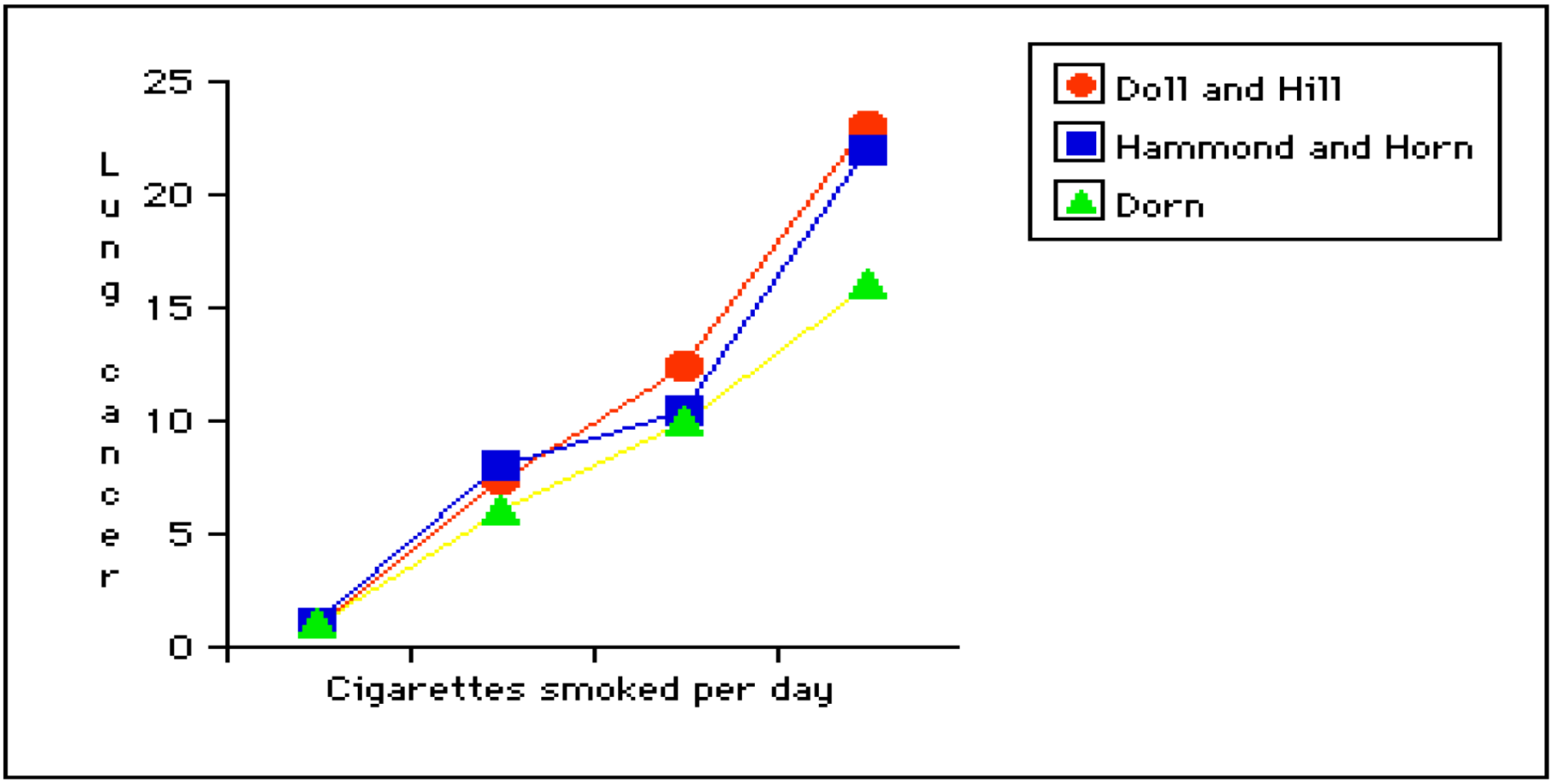
(TODAY)

1. Mendelian Randomization

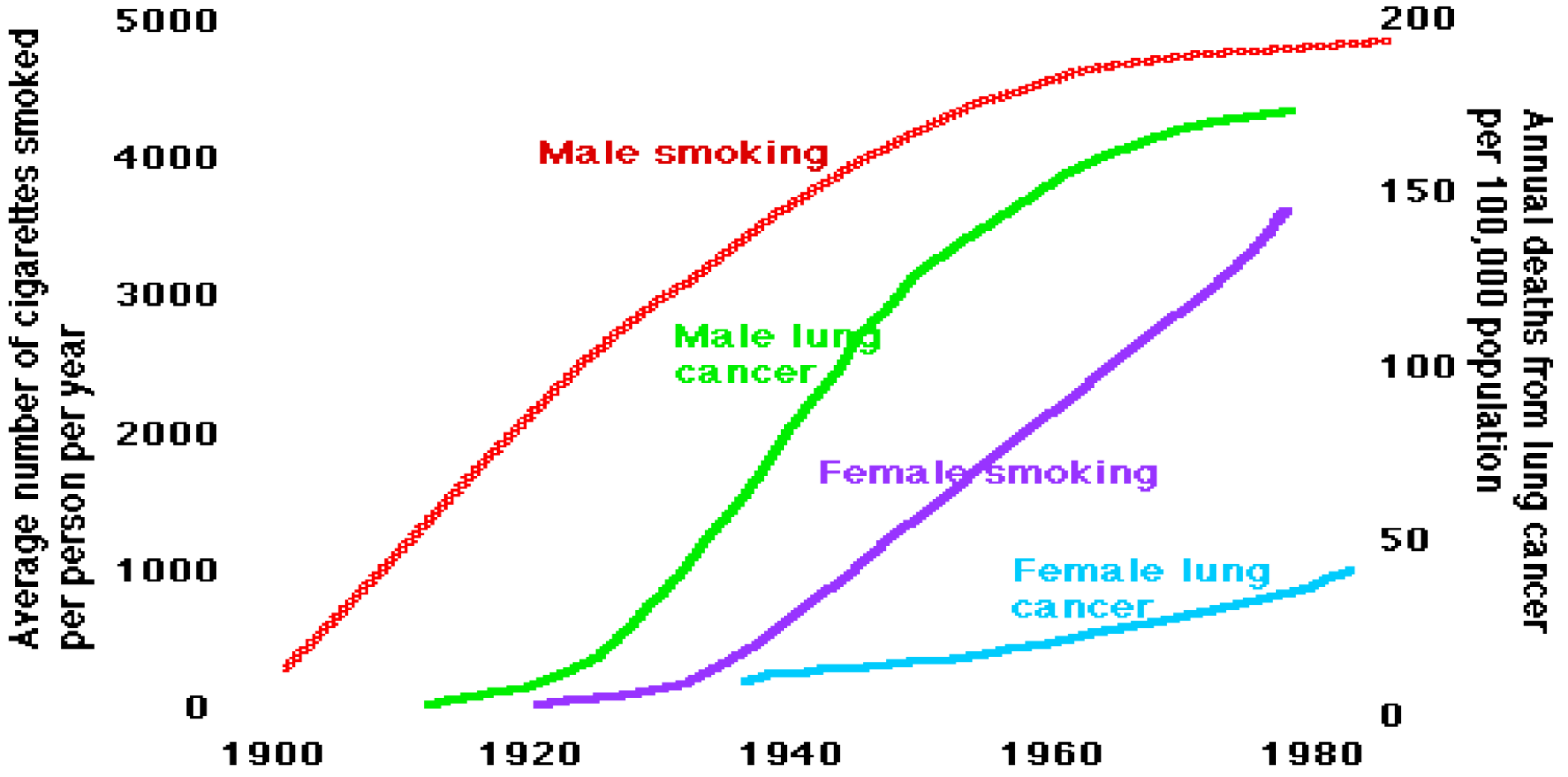
2. Molecular Epidemiology

3. Mediation analysis

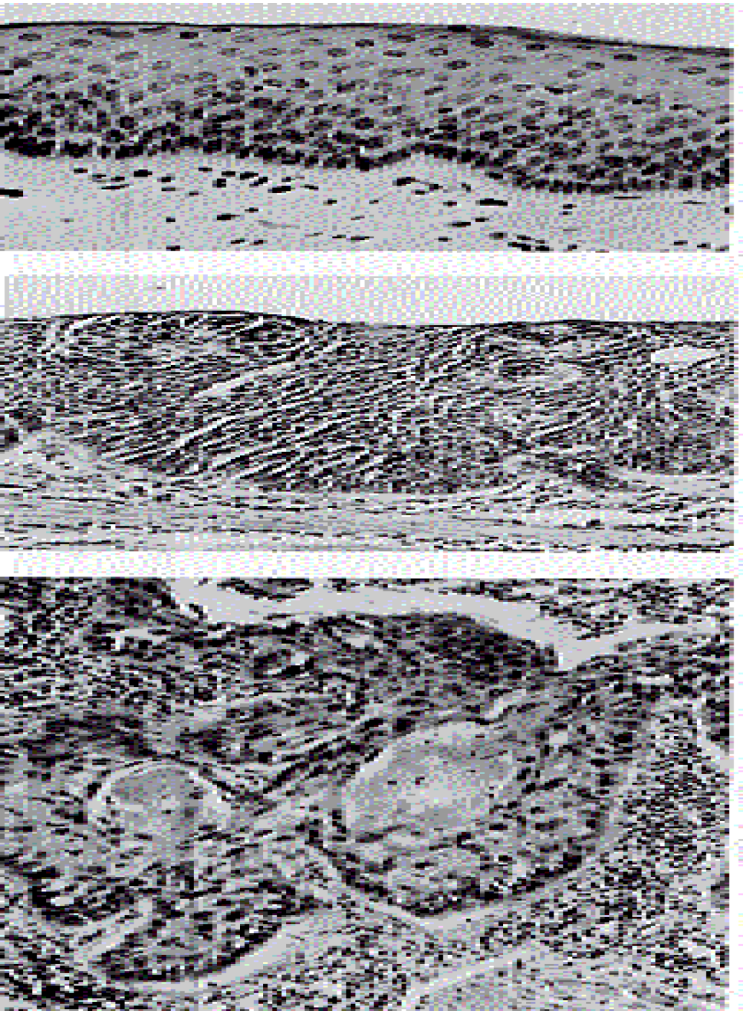
Lung Cancer and smoking

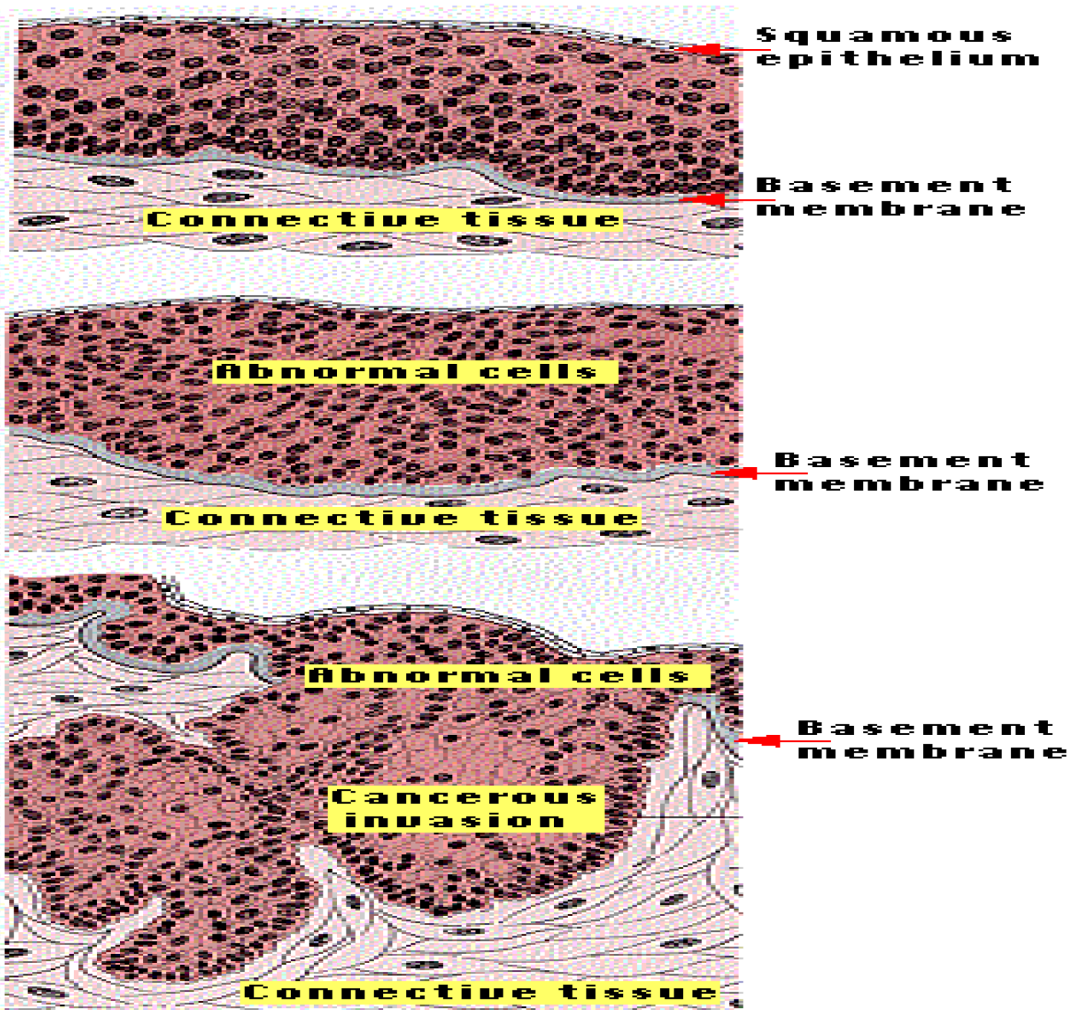


Lung cancer

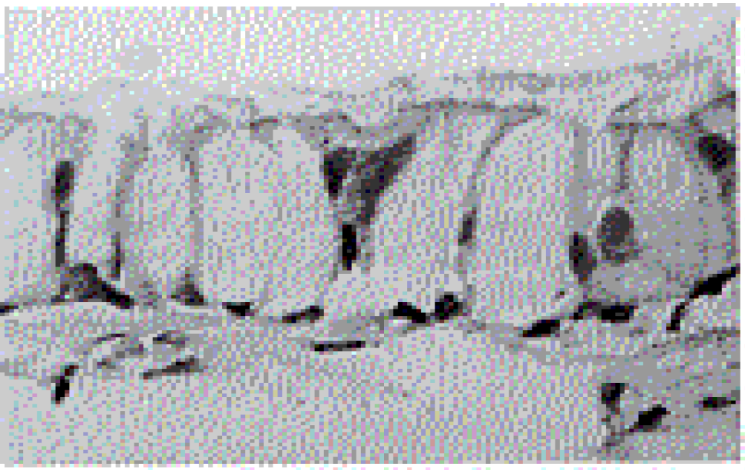

Average number of cigarettes smoked per person per year
5000
4000
3000
2000
1000
0
1900
1920
1940
1960
1980
200
150
100
50
0
Annual deaths from lung cancer per 100,000 population
Male smoking
Male lung cancer
Female smoking
Female lung cancer

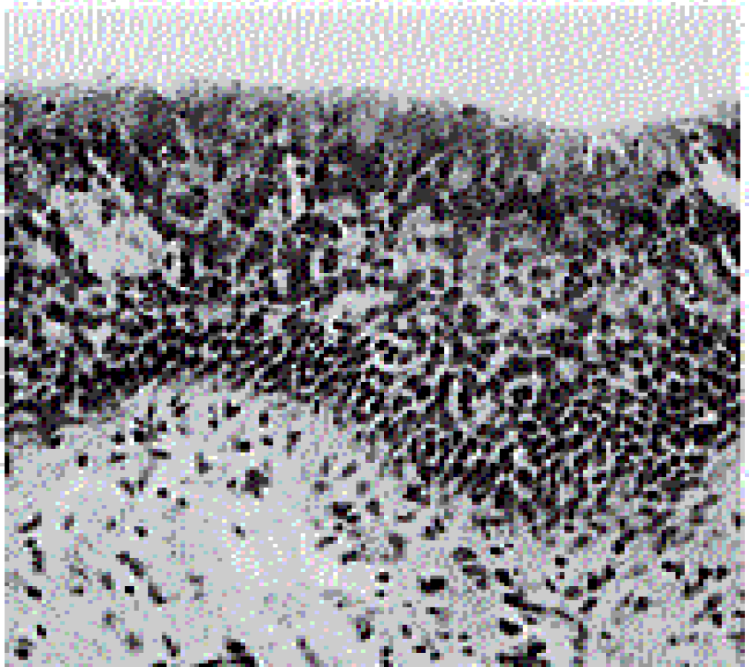
Lung cancer

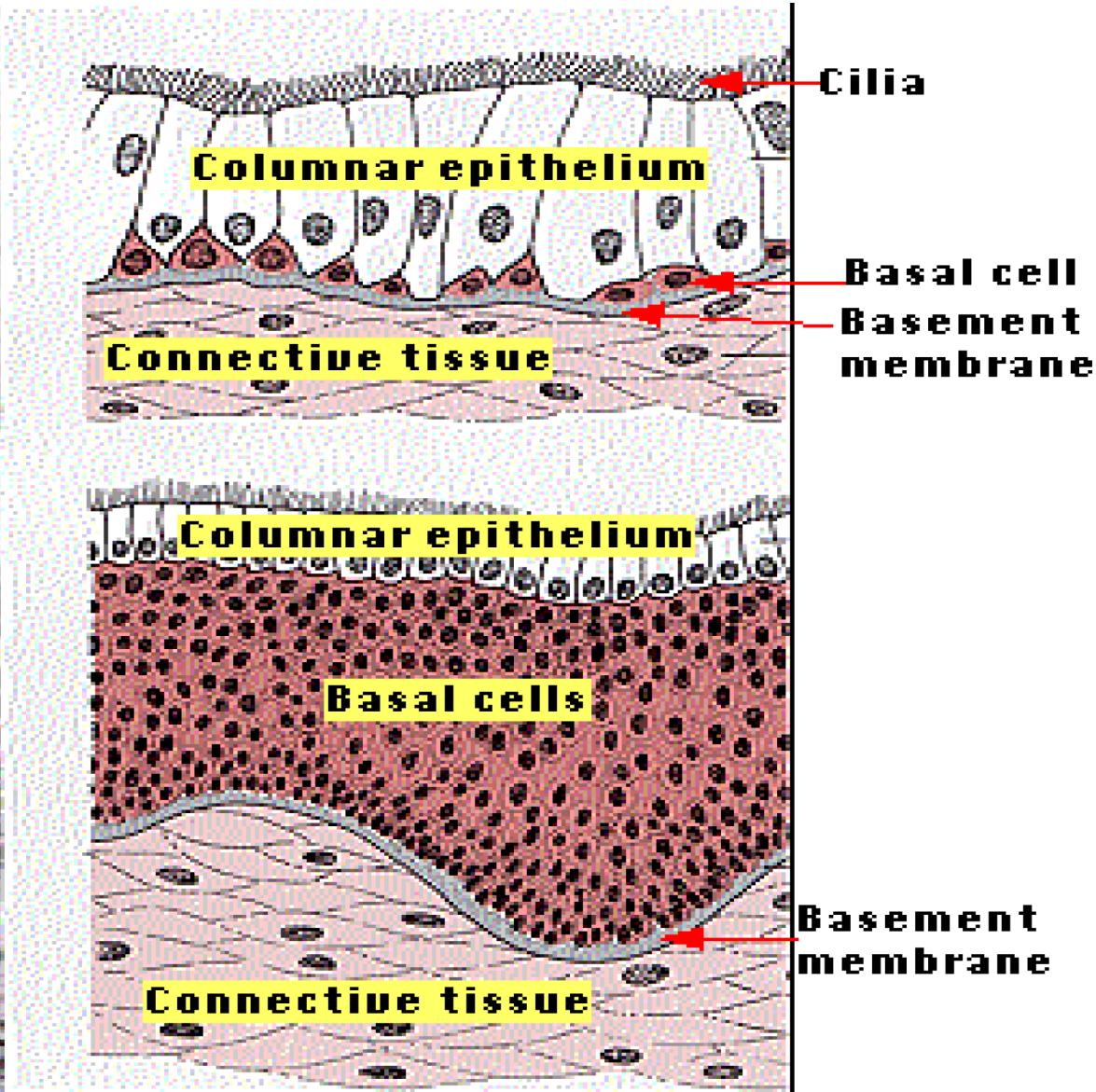



Squamous epithelium
Basement membrane
Connective tissue
Abnormal cells
Basement membrane
Connective tissue
Abnormal cells
Basement membrane
Cancerous invasion
Connective tissue

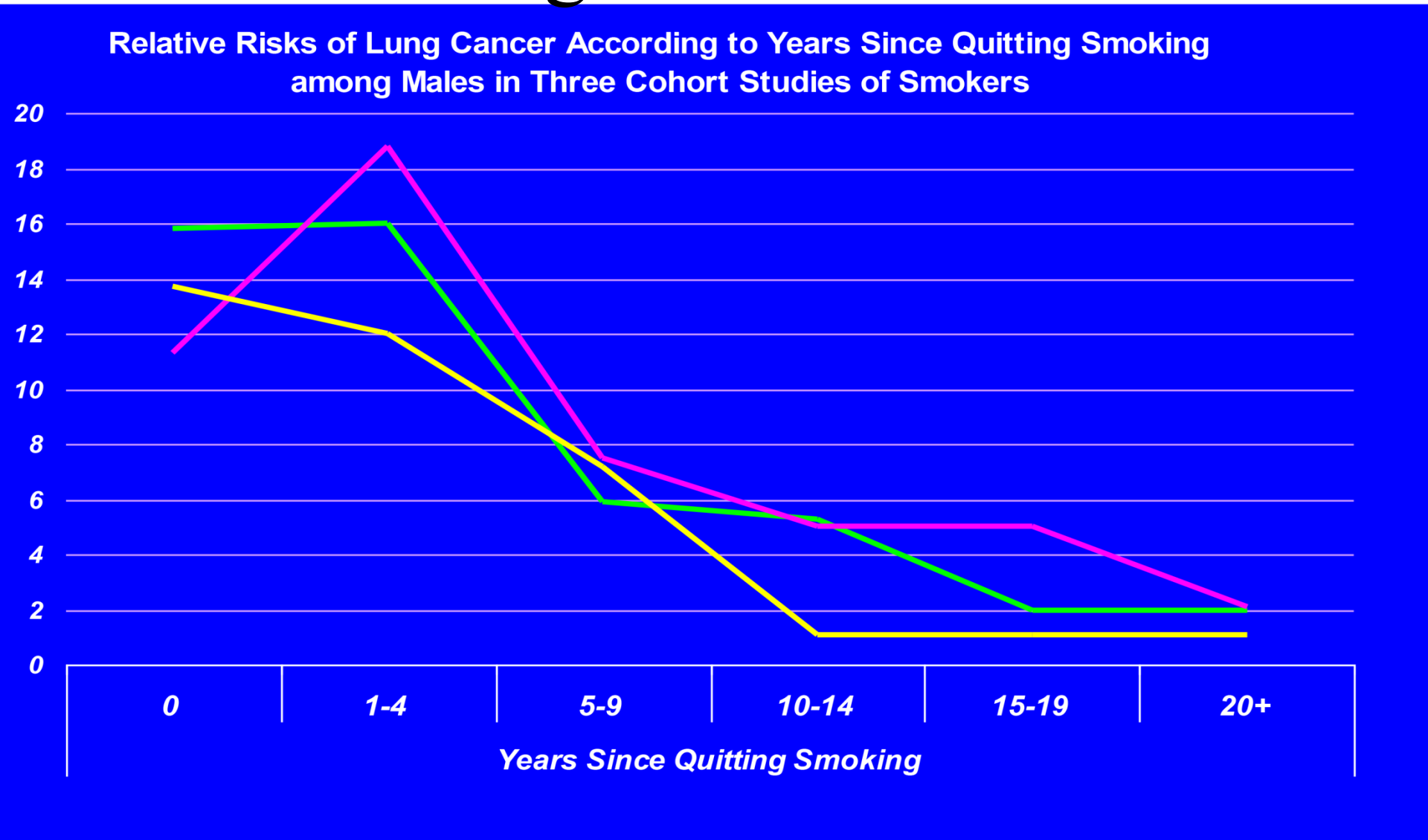
Lung cancer



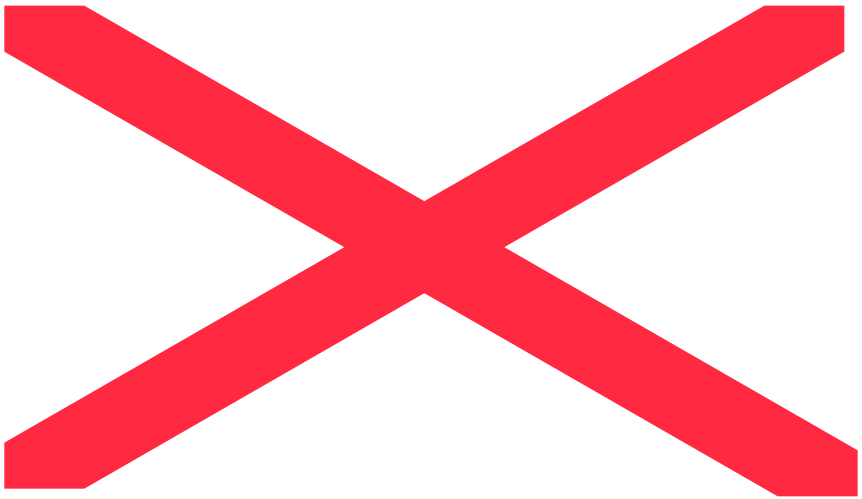



Cilia
Columnar epithelium
Basal cell
Basement membrane
Connective tissue
Columnar epithelium
Basal cells
Basement membrane
Connective tissue

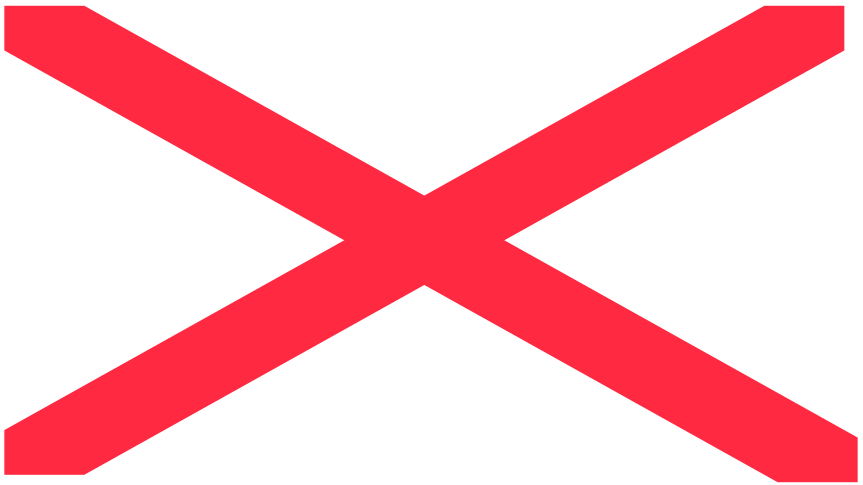
Lung cancer risks



Population Perspective



Accomplishments



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

What are the general risk factors for cancer?

Increasing age

Environmental factors

Genetic factors

Combinations of the above!

Most Cancer is due to the Environment

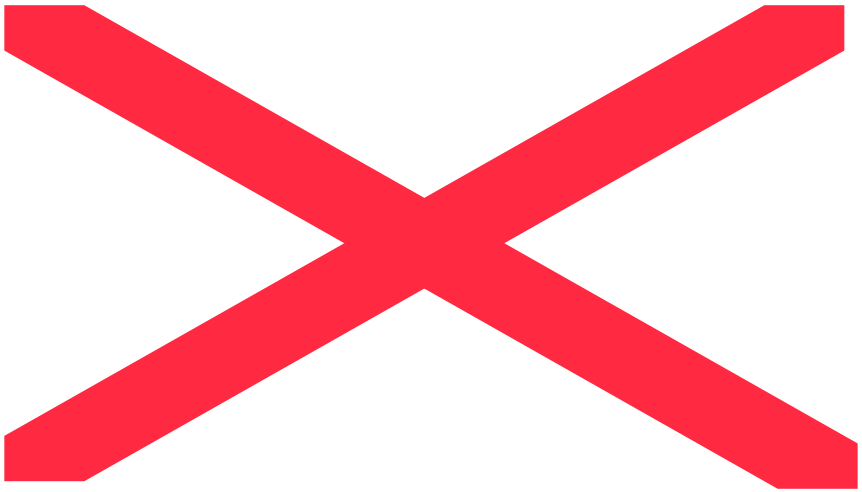
Dramatic differences in cancer rates by geography and over time are only compatible with extrinsic environmental causes

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

International Variation in Cancer Rates

Type of cancer	*H/L*	*highest*	*lowest*
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

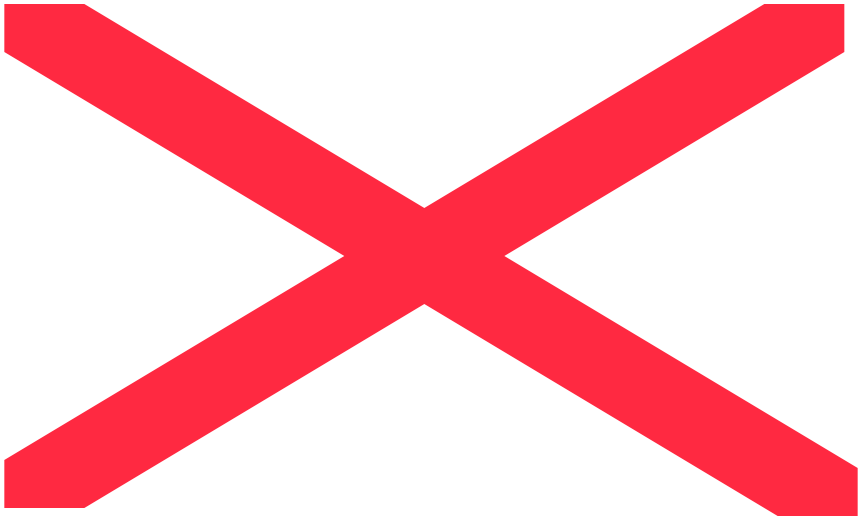


Lung cancer mortality

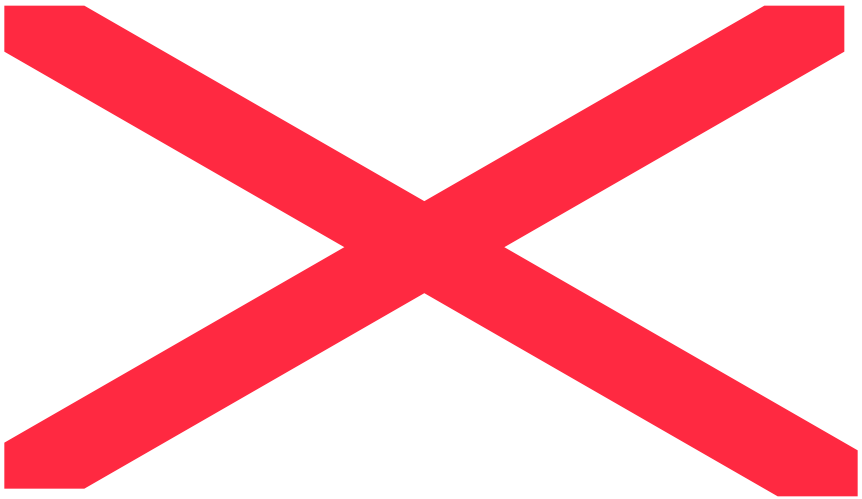
Lung cancer mortality rate in Xuan Wei is among the highest in China

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

Cancer and prevention



Skull with cigarette



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

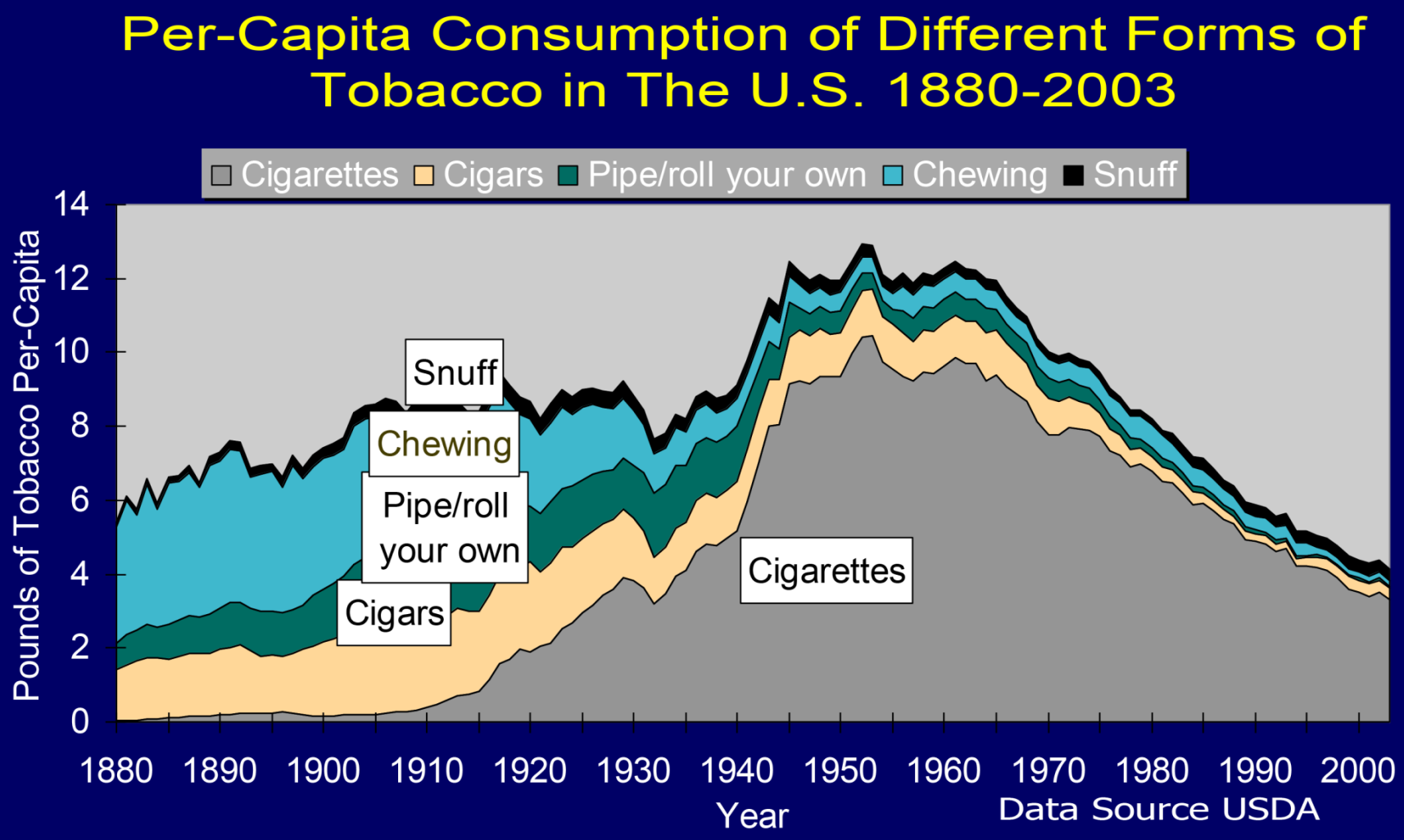
Medicare/ Medicaid > $10B/yr each

In spite of widespread knowledge of the health consequences of smoking

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

- *individual smoking cessation very difficult*

Tobacco consumption



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)

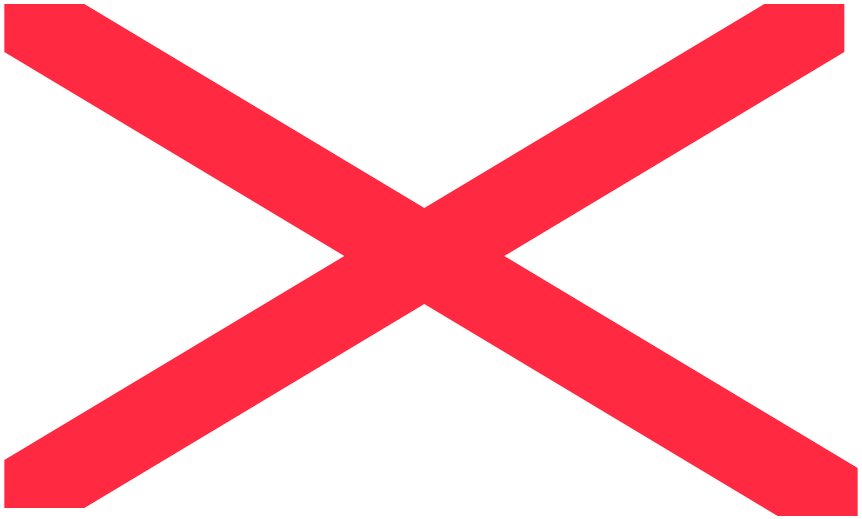
Metanalyses conclude that ETS (both workplace and at home) is a significant risk factor, e.g. *Law, 1997*

Summary:

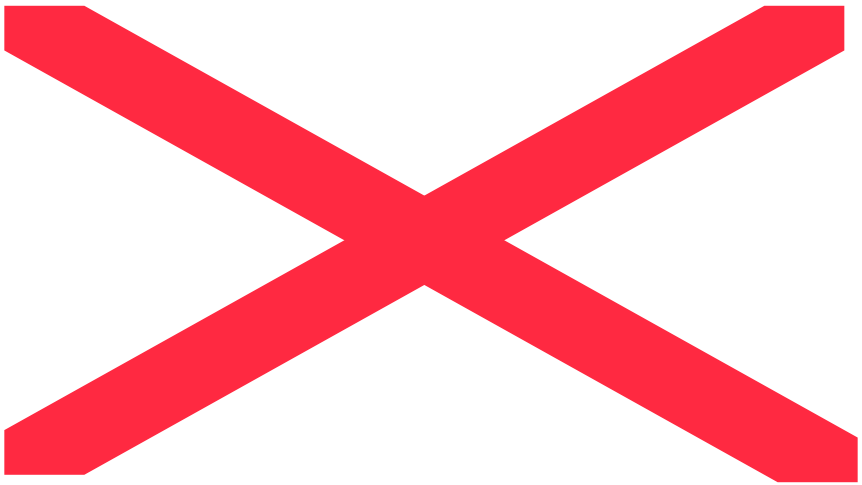
Evidence implicating ETS suggests dose-response

extends to lowest exposures, i.e. no threshold

LITS



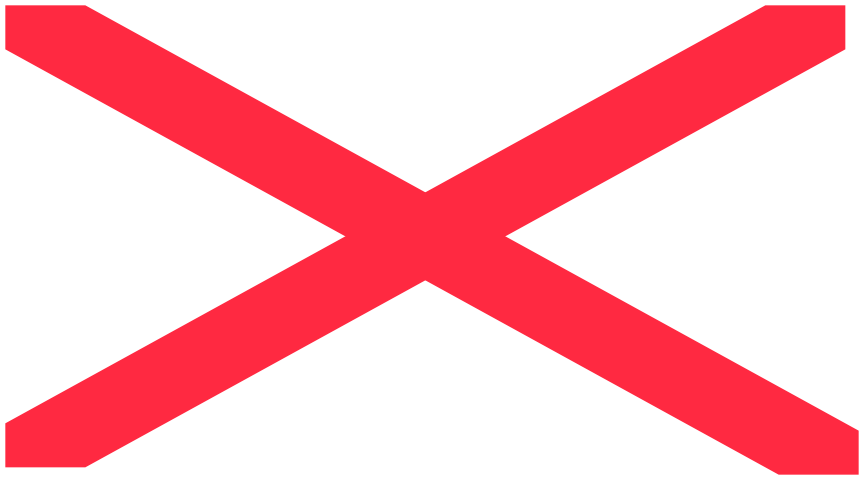
Smoking increases mortality



What are alcohol-associated cancers?

Oral
Pharynx
Esophagus
Larynx
Liver

Coffee drinking



Ionizing Radiation

Leukemia (AML, but not CLL*)

Breast

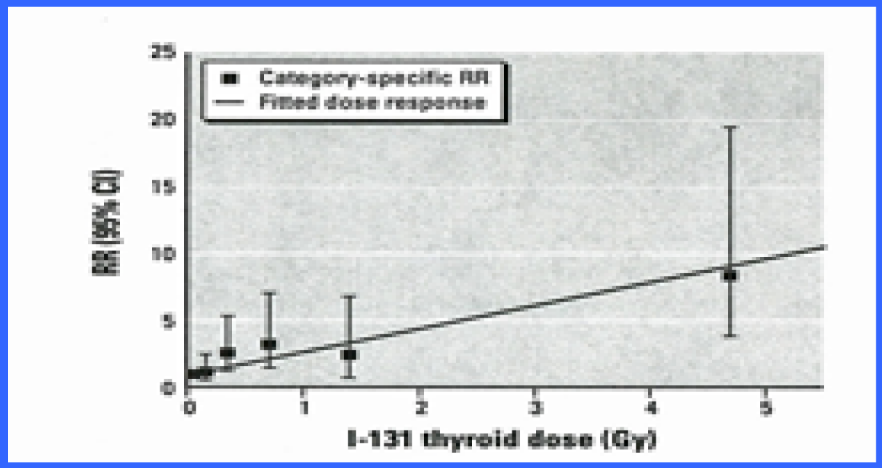
Lung

Thyroid

Head and neck cancer

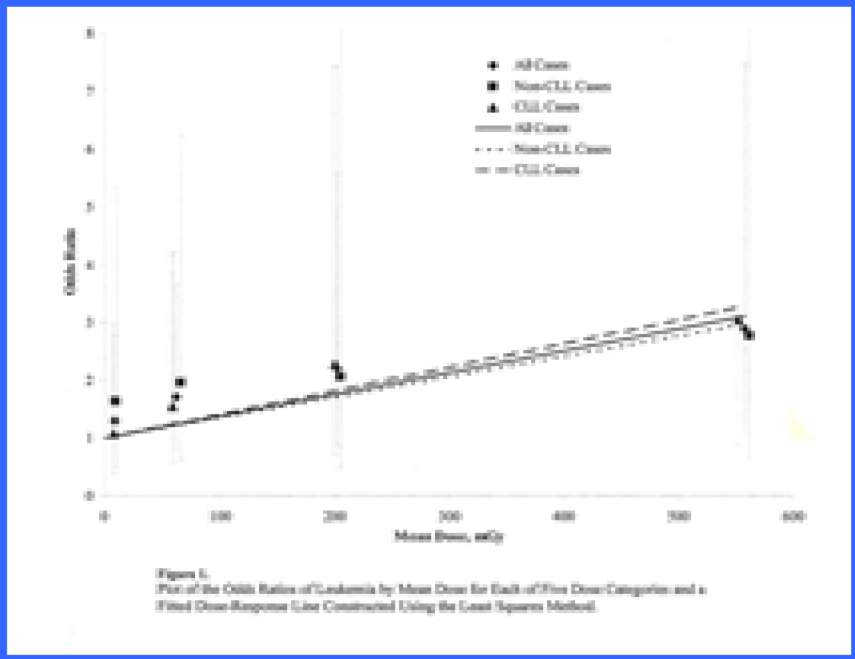
Cancer risk

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	Japan	Breast, Leuk, Gastric, Thy
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	Spondylytis	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


© J&J 1981
THE SUN YOU GET TODAY
MAY NOT LOOK SO BEAUTIFUL
TOMORROW.

Infections and Cancer

Infections and Cancer

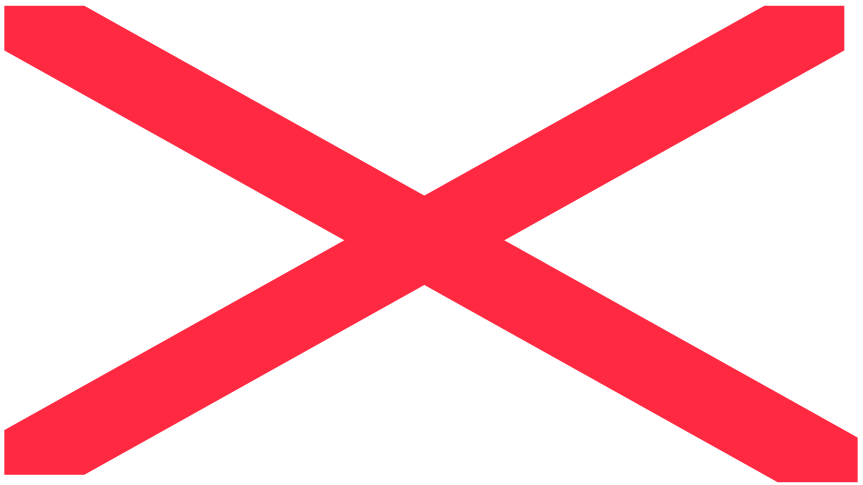
Human papillomavirus	Cervical cancer Vulvar/vaginal cancer Anal cancer Penile cancer Oropharyngeal cancer
Hepatitis B & C virus	Hepatocellular Non-Hodgkin's lymphoma
Helicobacter pylori	Gastric cancer
Liver flukes	Cholangiocarcinoma

Newer infections

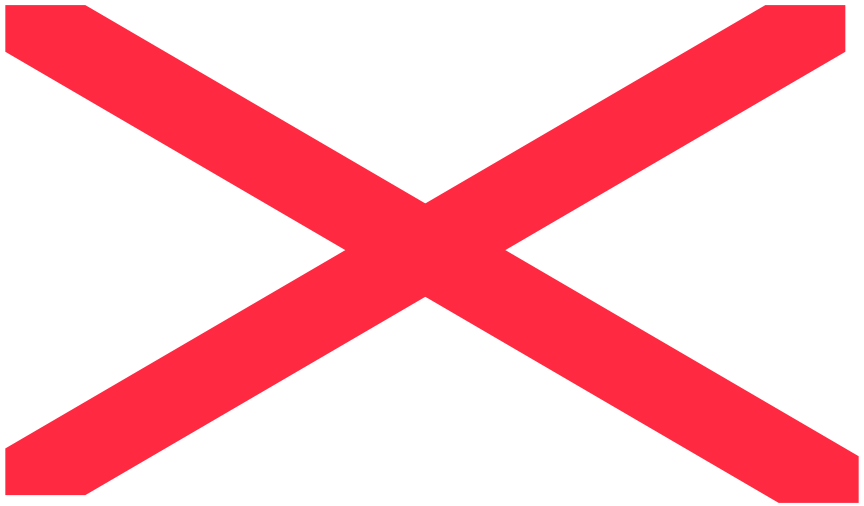
Newer infectious hypotheses

VIRUS	Human Cancer (hypothesized)
HCV	hepatocellular cancer
	NHL
EBV	NPC
	Hodgkin's lymphoma
	leiomyosarcoma
KSHV (HHV8)	Kaposi's sarcoma
HPV-16, -18, -33, -39	Vulvo-vaginal cancer
	Anal cancer
	Penile cancer
	Oropharyngeal cancer
Polyomavirus	Merkel cell virus/ **CLL?**
HIV	NHL

Fusobacterium and colorectal carcinoma



Oropharynx cancers



Occupational exposures

OCCUPATIONAL EXPOSURES -- HUMAN CARCINOGENS

EXPOSURE	SITE OF CANCER
4-Aminobiphenyl	Bladder
Arsenic	Lung, skin
Asbestos	Lung, pleura, peritoneum
Benzene	Leukemia
Benzidine	Bladder
beta-Naphthylamine	Bladder
Coal tars and pitches	Lung, skin
Mineral oils	Skin
Mustard gas	Pharynx, lung
Radon	Lung
Soot, tars, and oils (polycyclic hydrocarbons)	Lung, skin
Vinyl chloride	Liver
Wood dusts (furniture)	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

A Population Perspective on Cancer

What is epidemiology?

What has epidemiology accomplished?

What can go wrong?

What can really go wrong?

What next?

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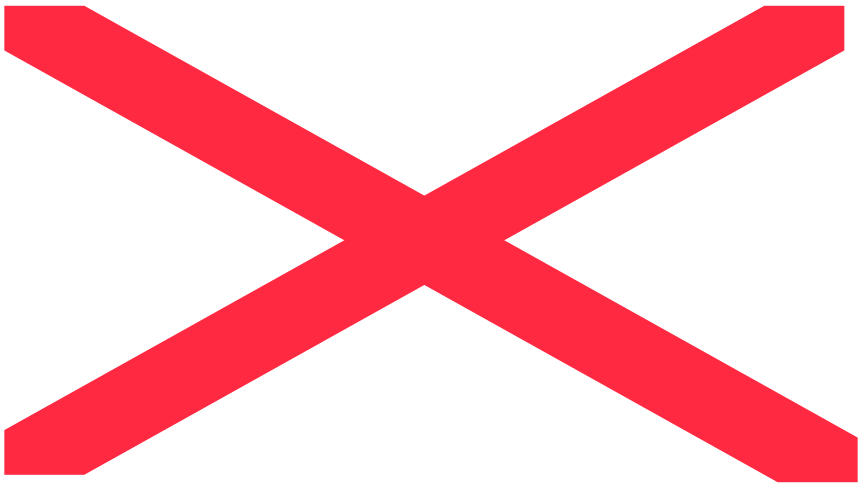
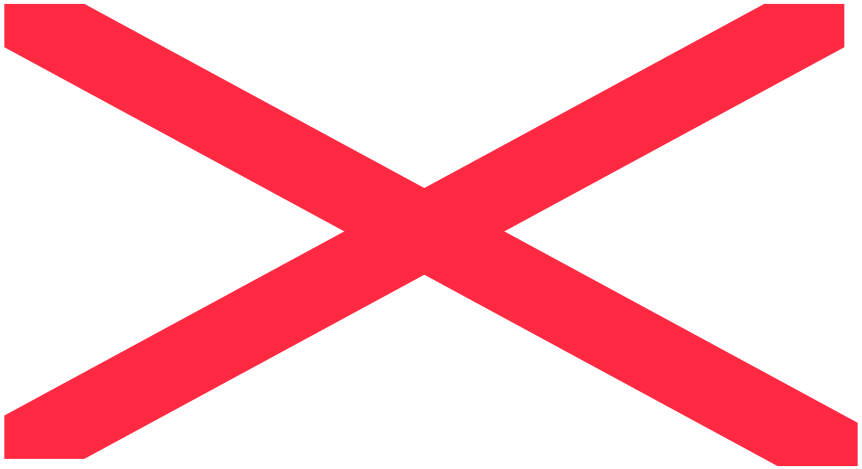
Gaps in understanding



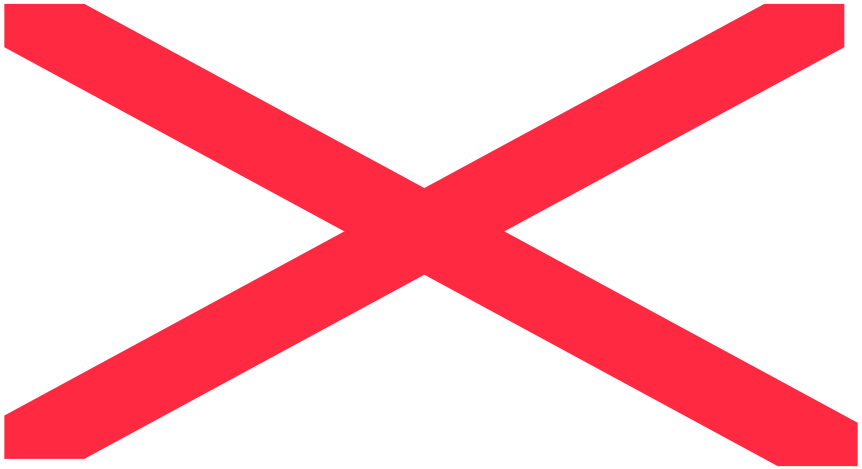
Chronic Lymphocytic Leukemia

- 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

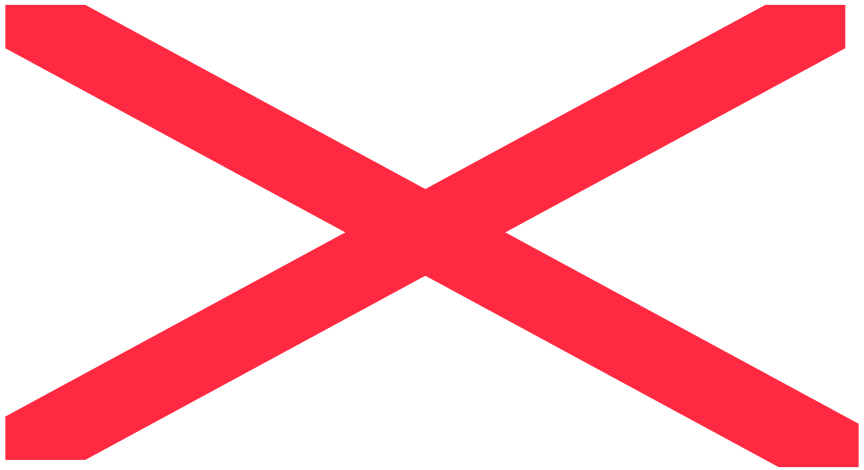
Gaps



Cancer and genetic changes



Genetic distinctions



gaps on the GENETIC side

New technologies have accelerated gene discovery but…

- *Genes associated with common cancers confer minimal risk*
- *and explain only a small portion of the variation*
- *and do not help much with risk models*
- *How G and E work in concert is poorly understood*

- *Many cancer families- genes remain obscure*

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’

GETTING ORIENTED

1. Germline or Somatic

   (inherited or in the tumor)

2. Family or Population

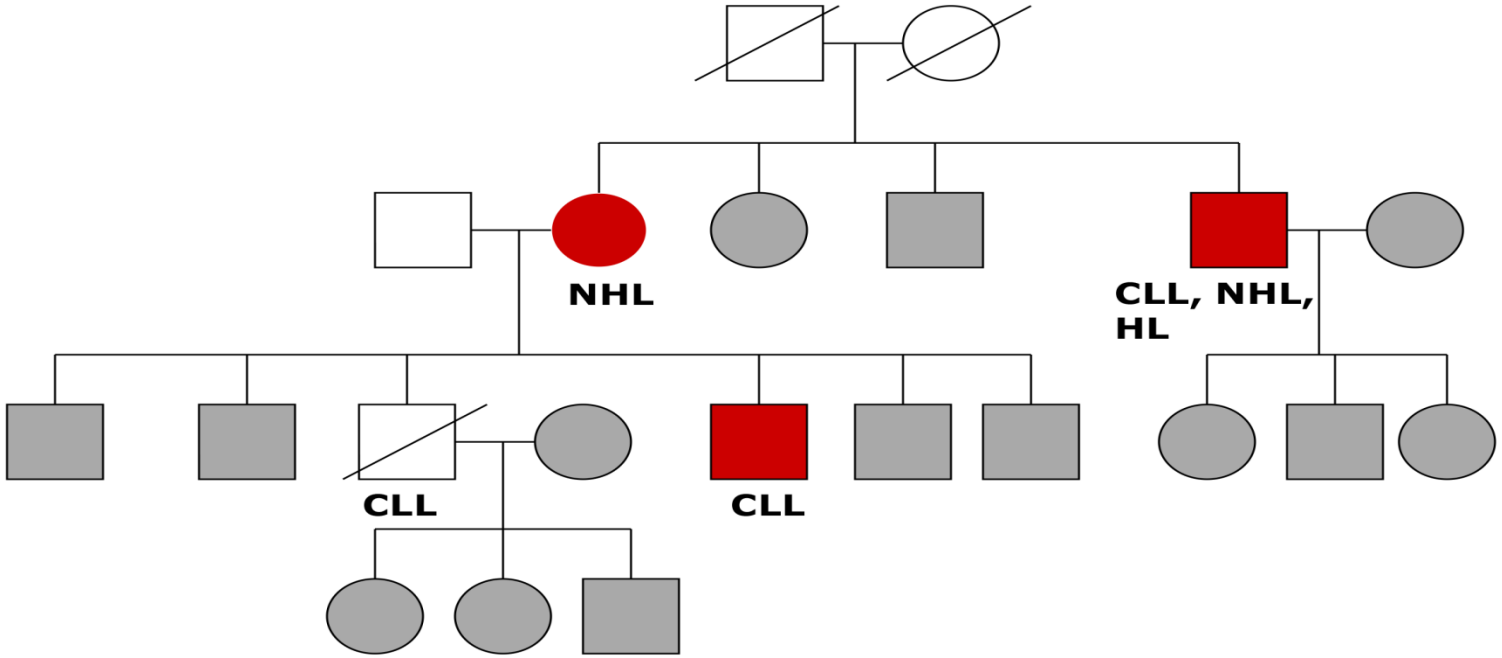
   (rare or common)

3. Candidate or Agnostic

   (candidate gene study or GWAS)

Rare Genes

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



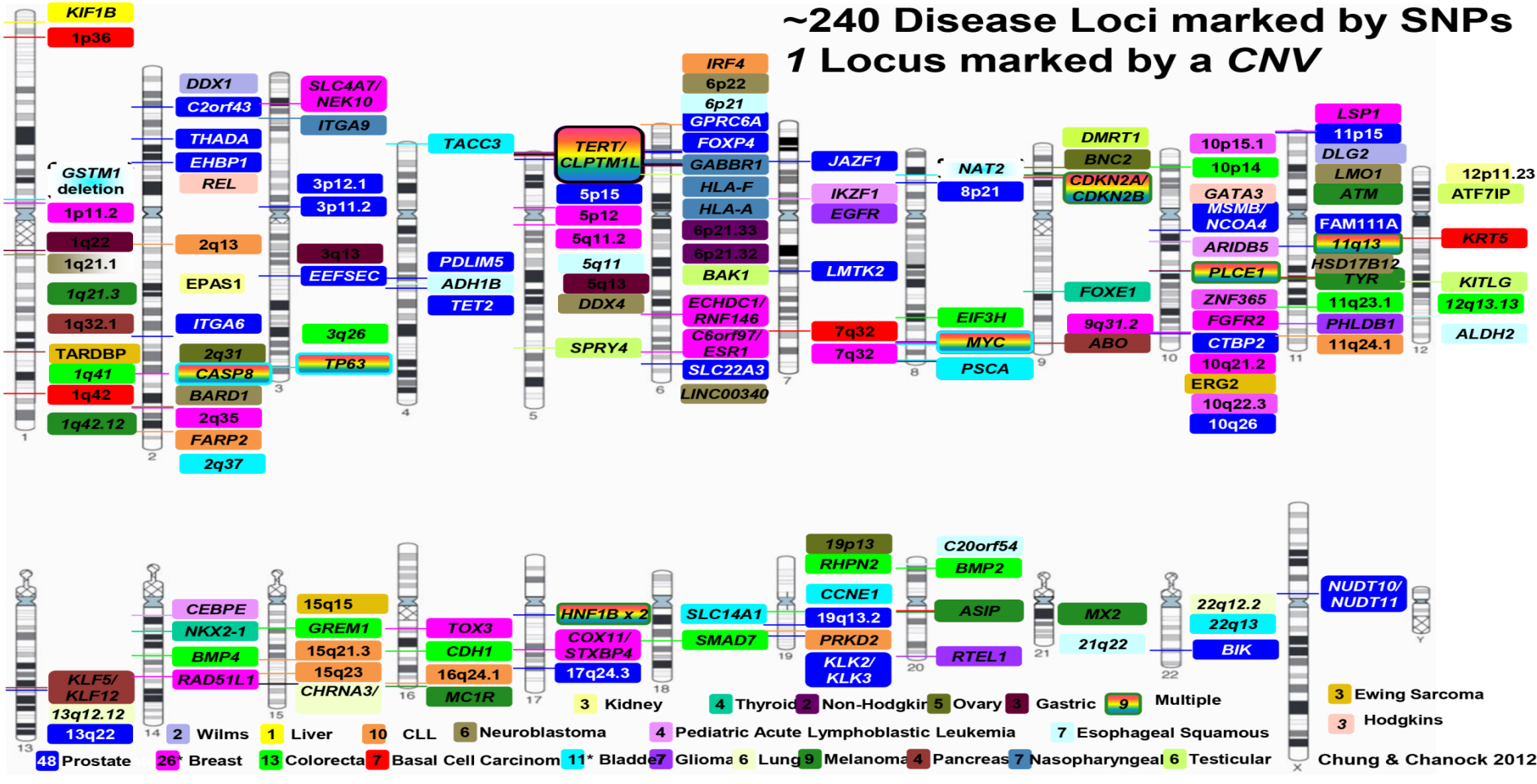
High risk kindreds like this likely harbor rare genes that confer high risk- if we knew what were they would be clinically important....

Cloned familiar 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



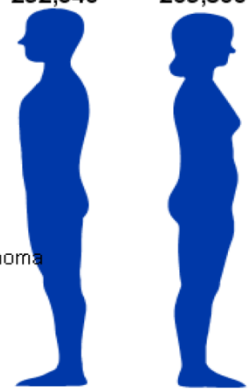
Lung cancer challenge

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*

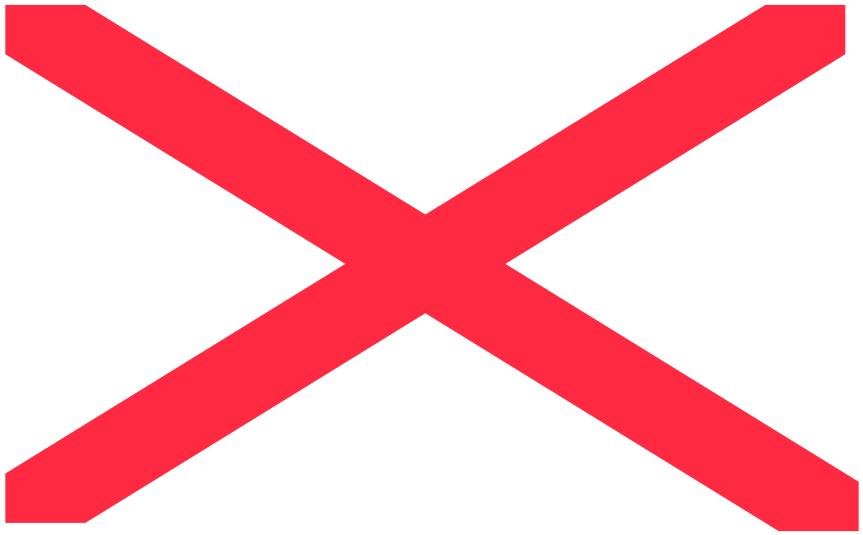
Men 292,540		Women 269,800	
Lung & bronchus	30%	26%	Lung & bronchus
Prostate	9%	15%	Breast
Colon & rectum	9%	9%	Colon & rectum
Pancreas	6%	6%	Pancreas
Leukemia	4%	5%	Ovary
Liver & intrahepatic bile duct	4%	4%	Non-Hodgkin lymphoma
Esophagus	4%	3%	Leukemia
Urinary bladder	3%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain/ONS
All other sites	25%	25%	All other sites



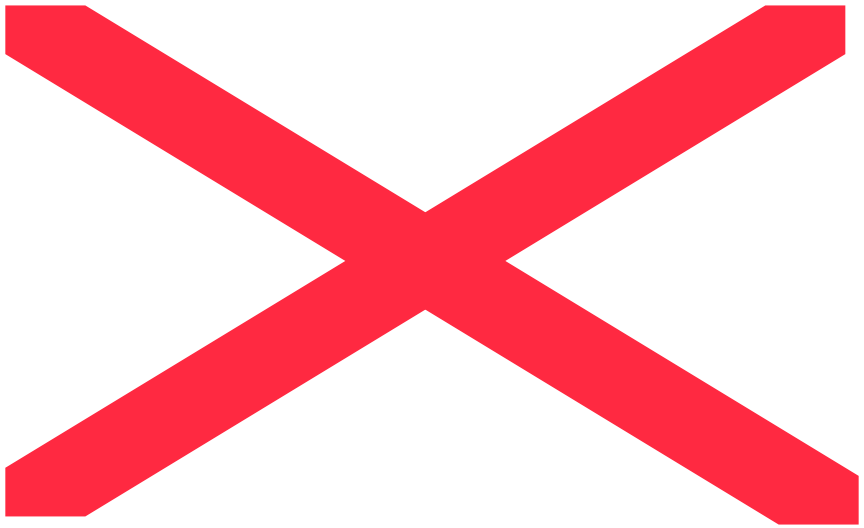
Trends in Five-year Relative Survival (%)* Rates, US, 1975-2004

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

Molecular epidemiology



Integrative epidemiology



Traditional epidemiology

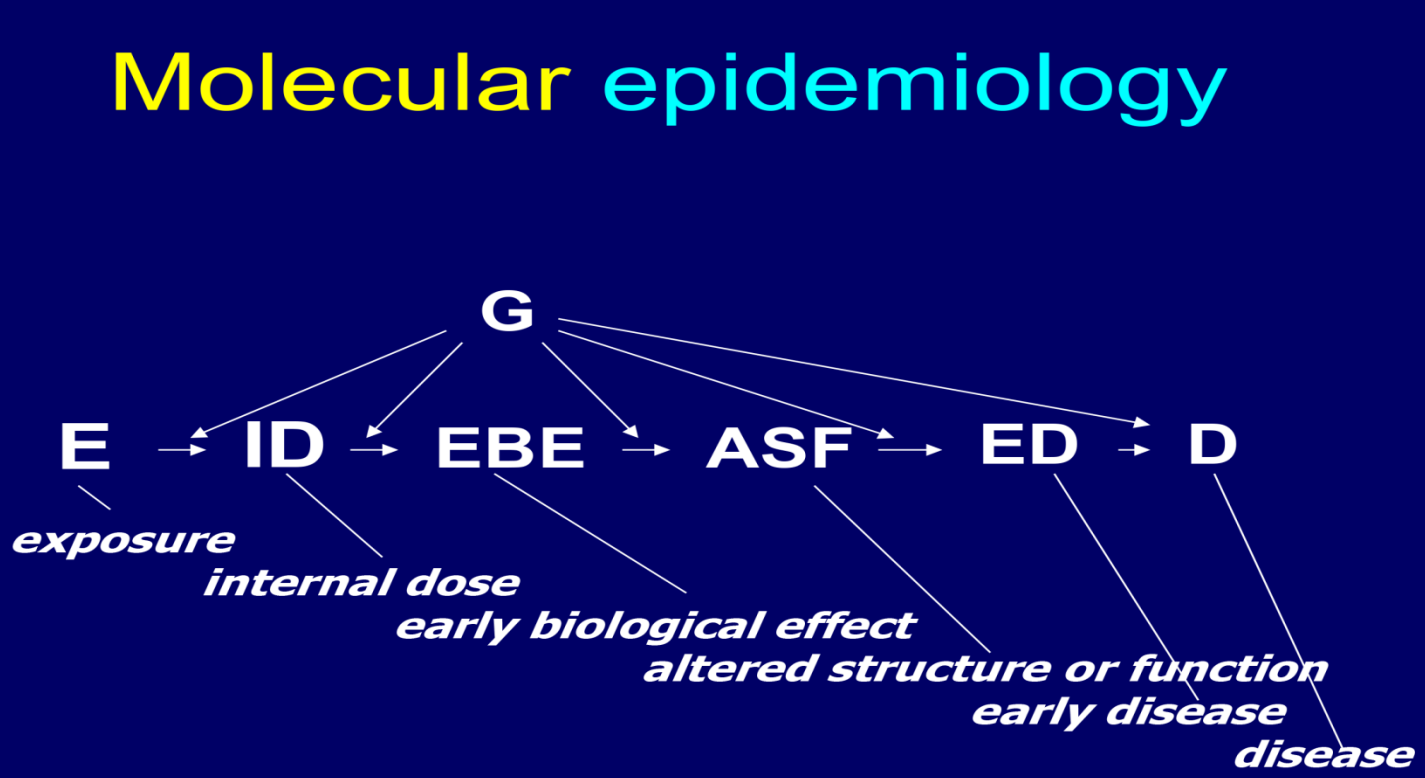
Traditional epidemiology

E → D

Exposure — Disease

Tobacco — Lung Cancer

Molecular epidemiology



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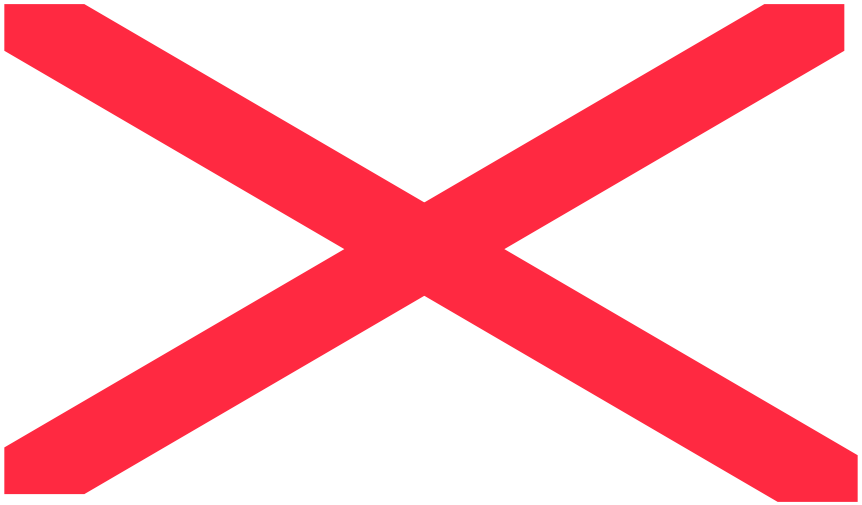
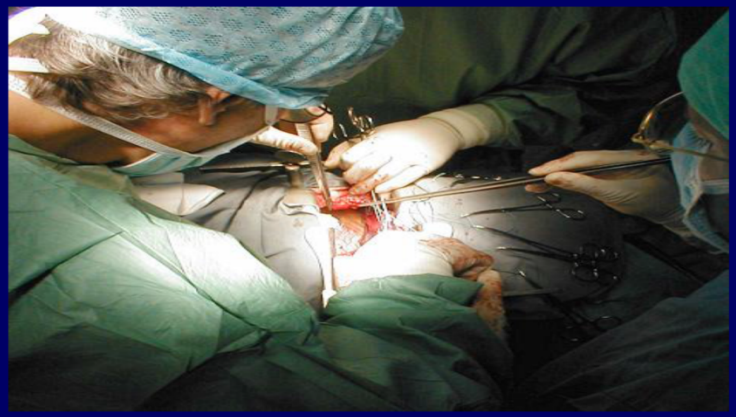


Lung cancer case control

Lung Cancer Case Control



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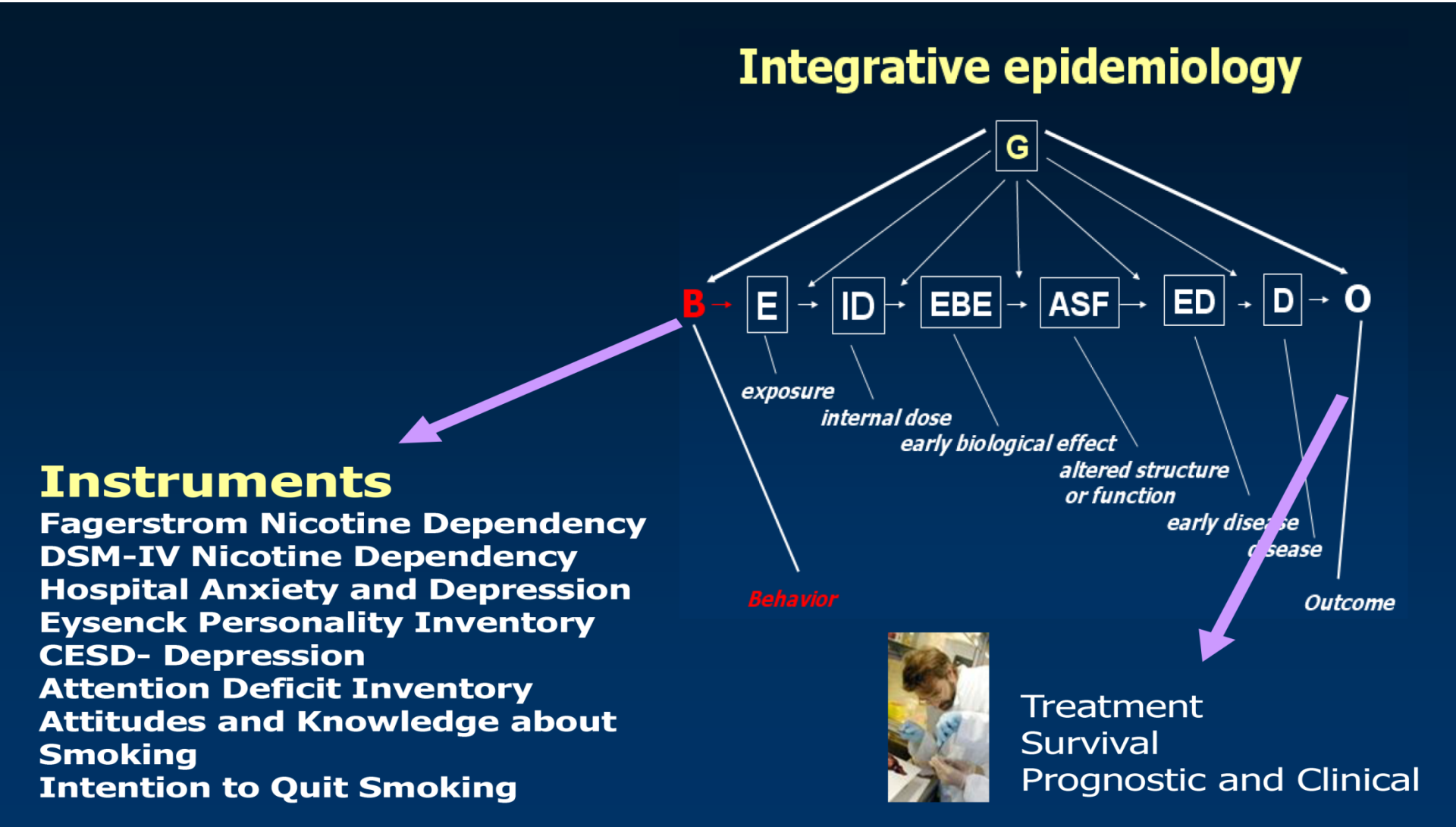
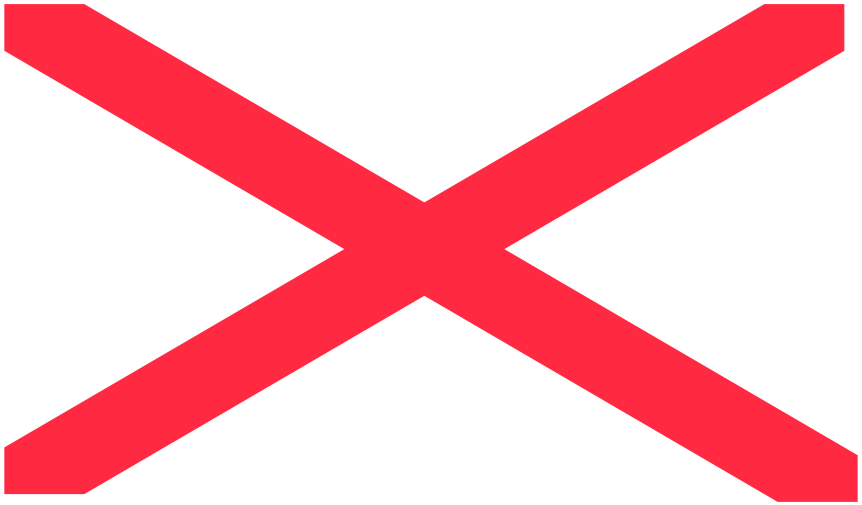


Population perspective



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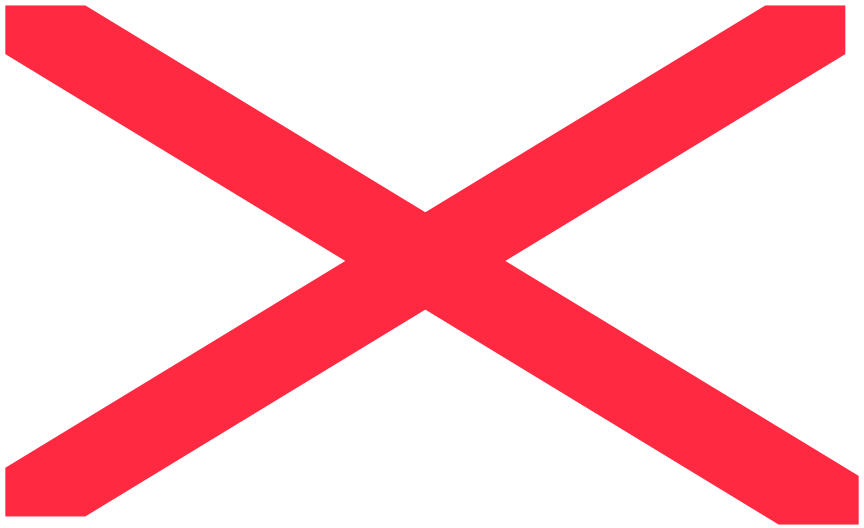
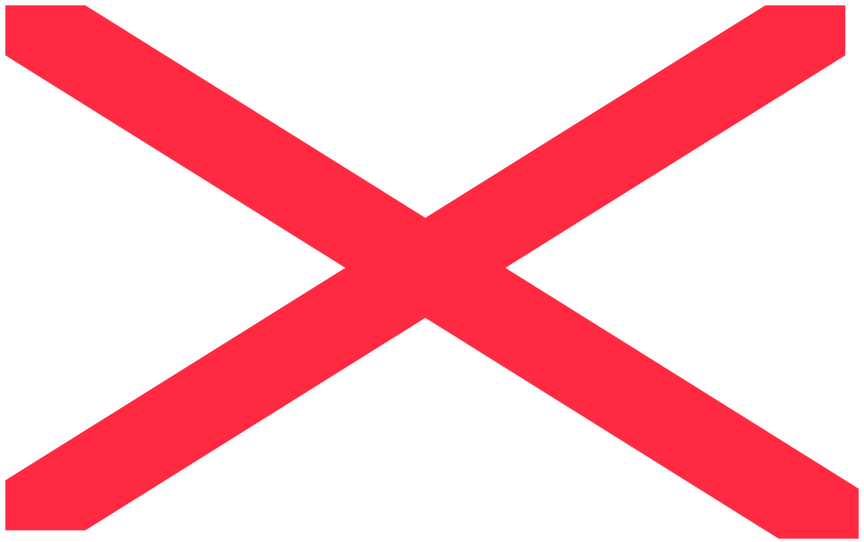
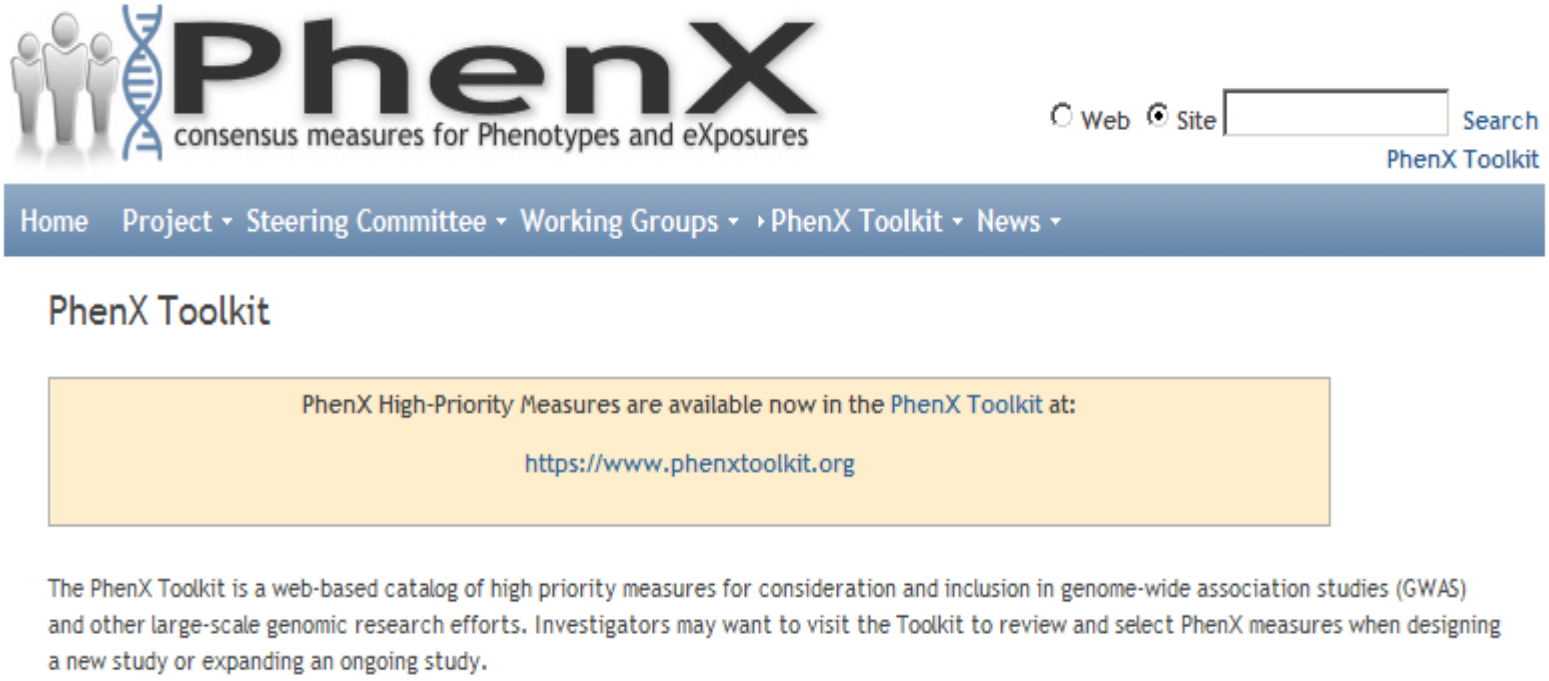


Consortia



PhenX…approach to expand data collection and reduce misclassification



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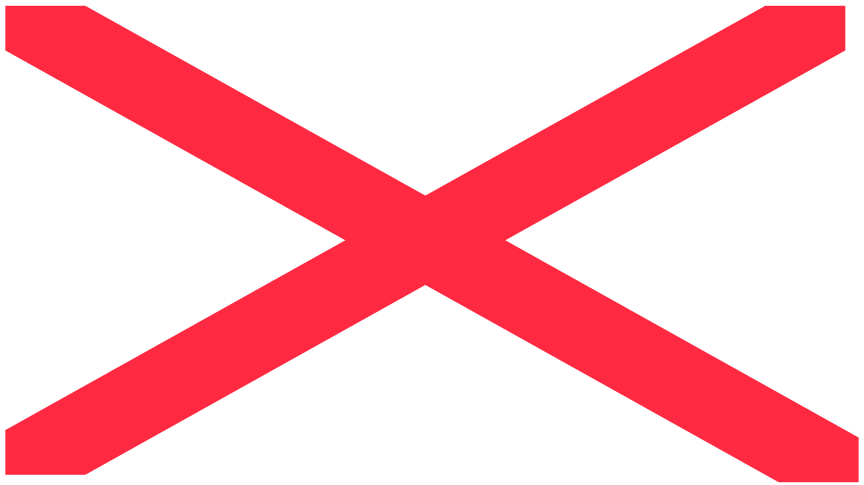
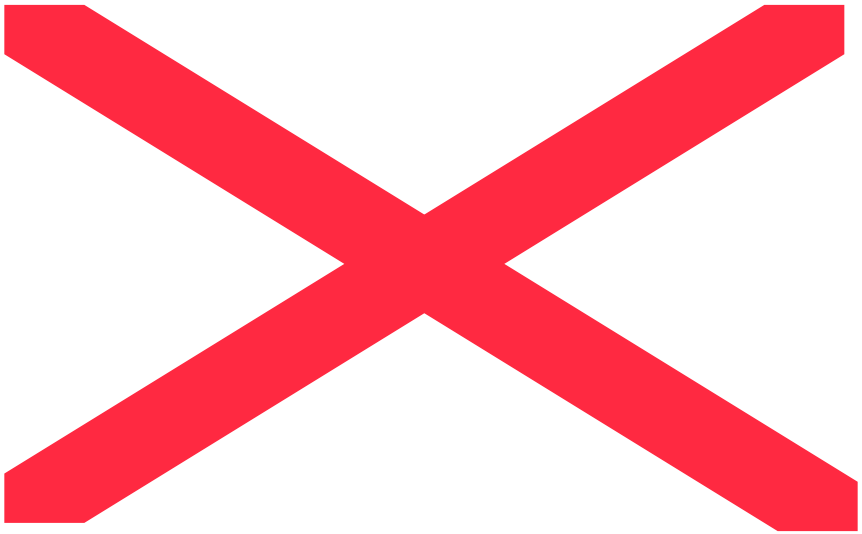
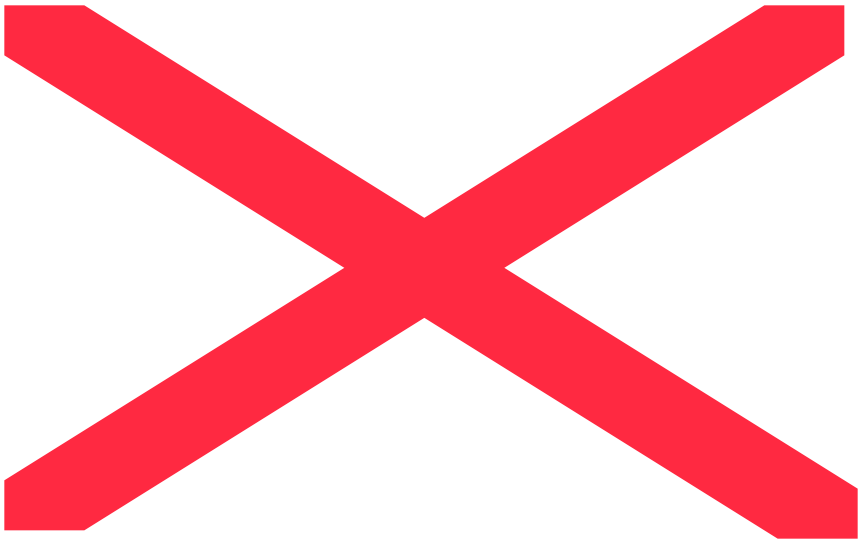
Paradigm change



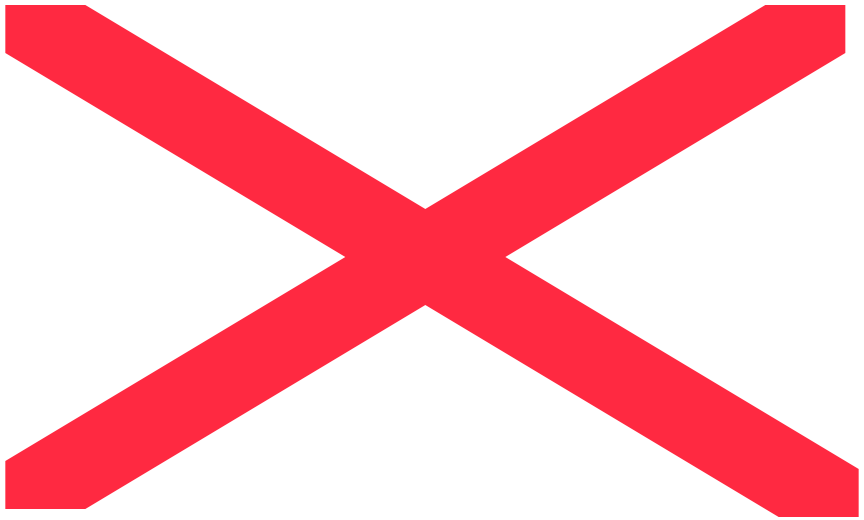
Obesity rates



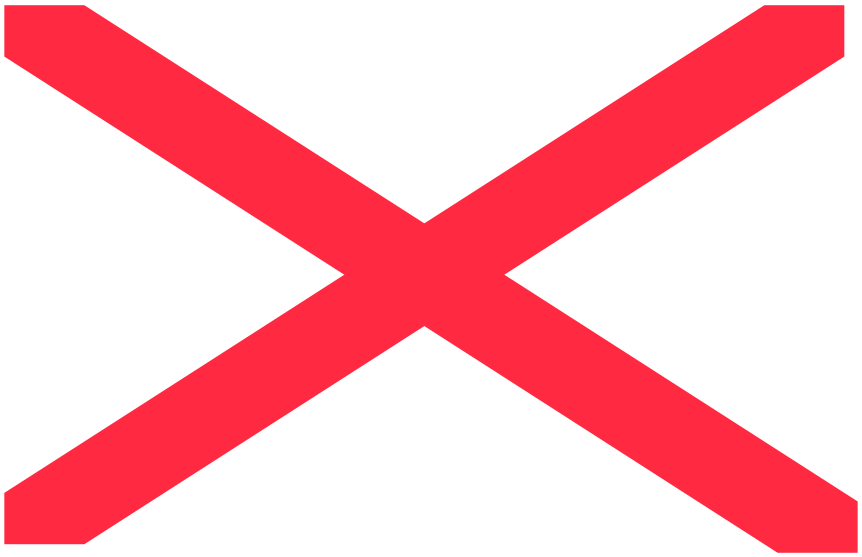
Obesity in the world and US



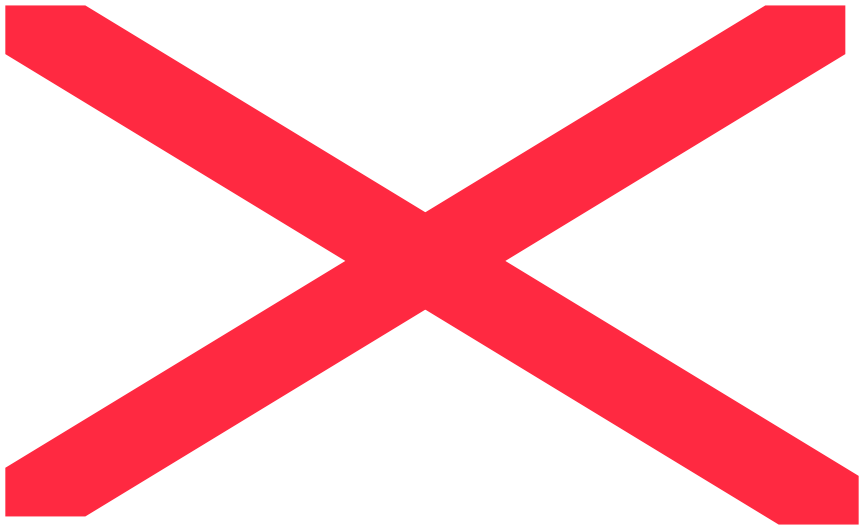
Diabetes trends



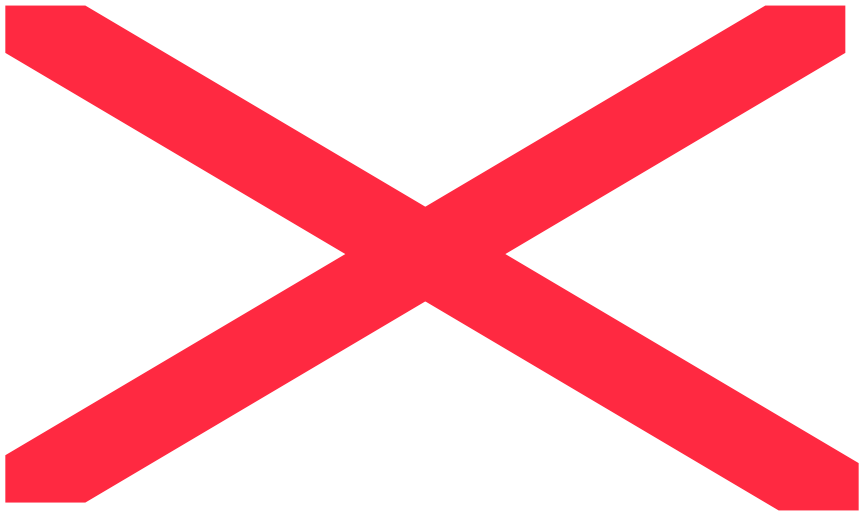
Diabetes in US



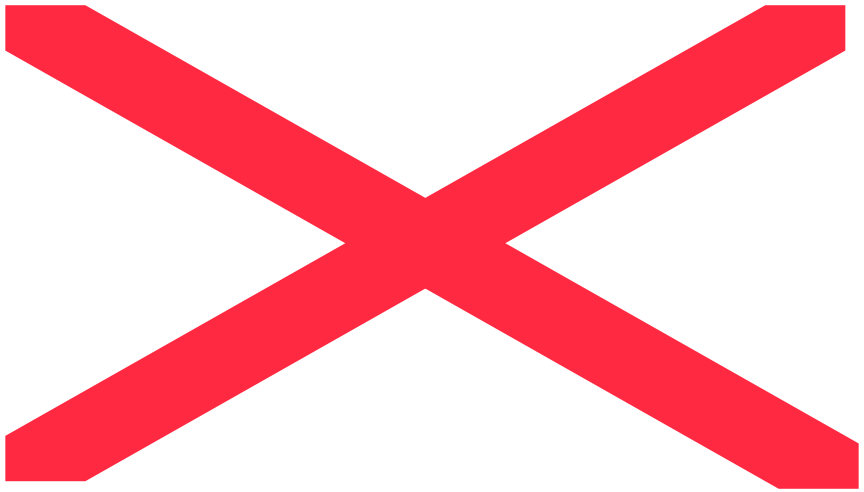
Obesity



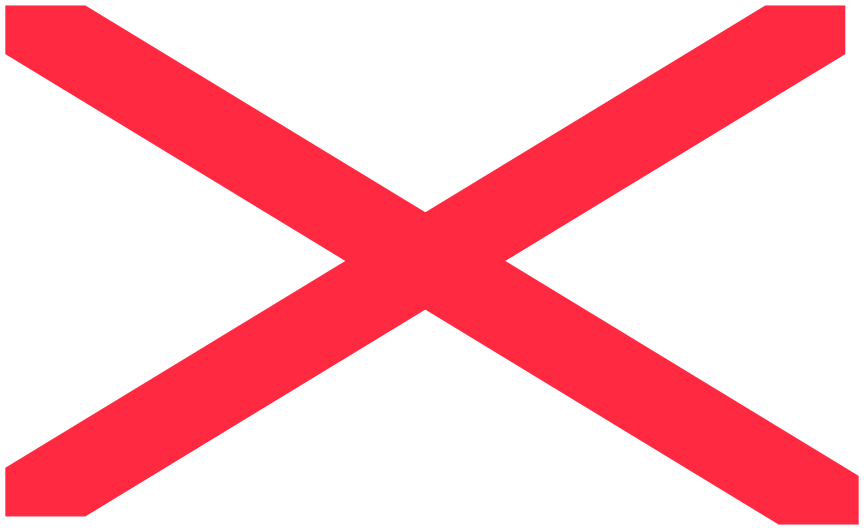
Obesity worldwide



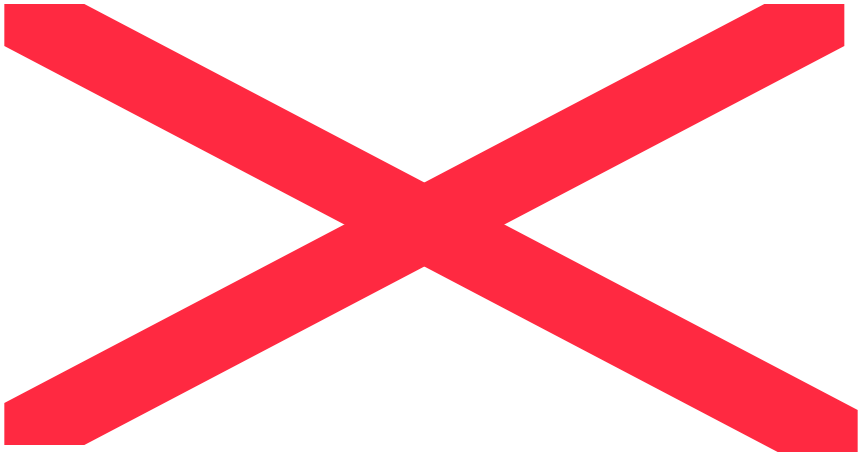
Being overweight



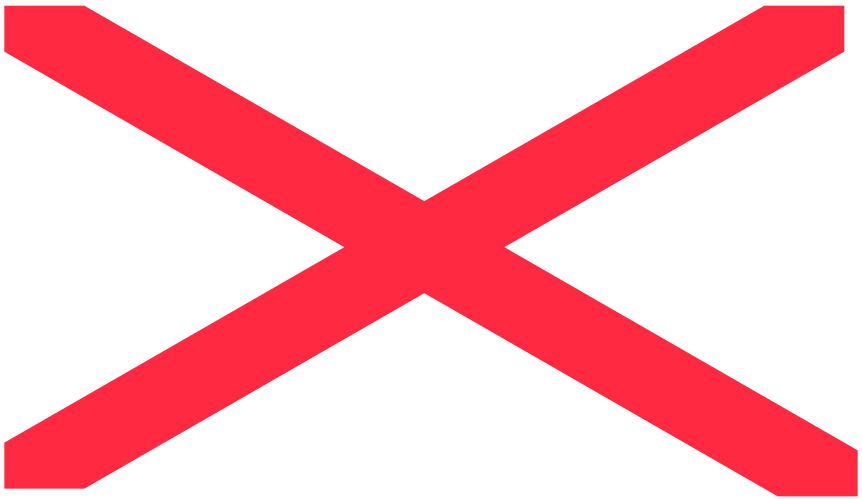
Obesity causes



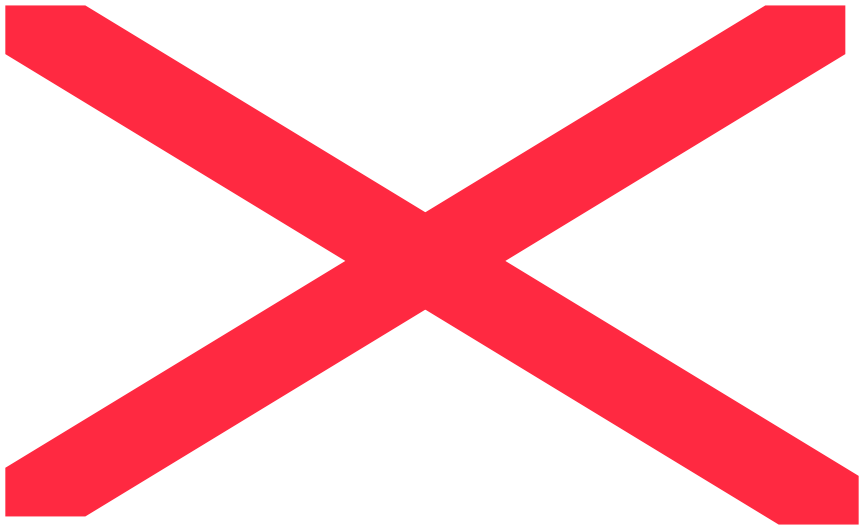
What causes obesity?



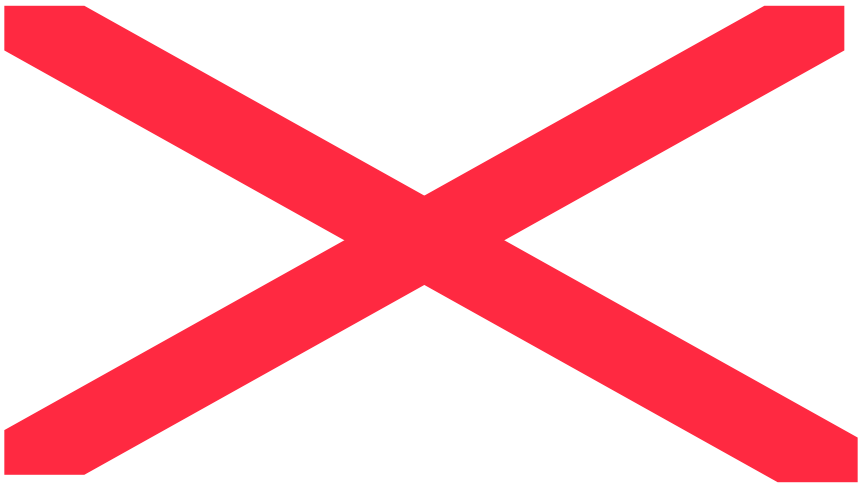
Dietary habits



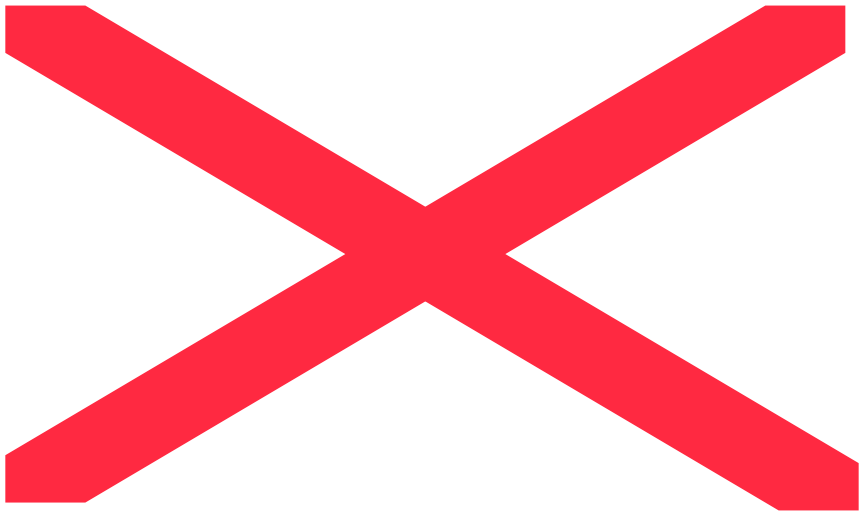
Food pyramid



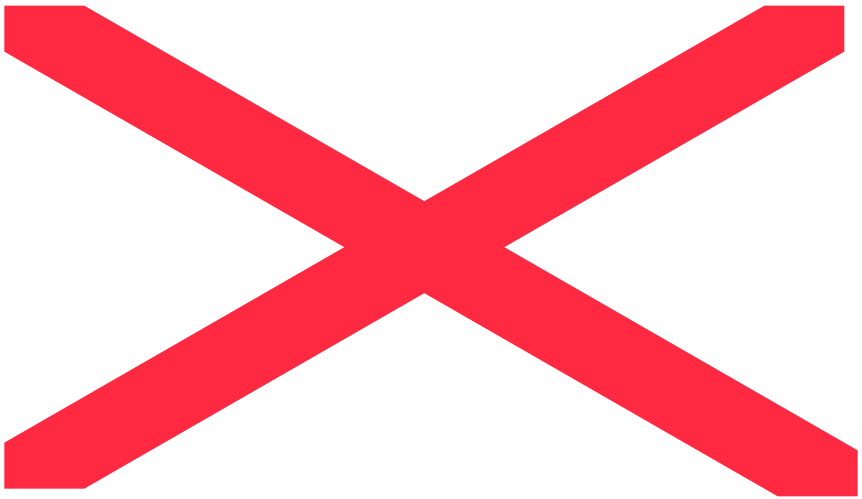
Institutional investment



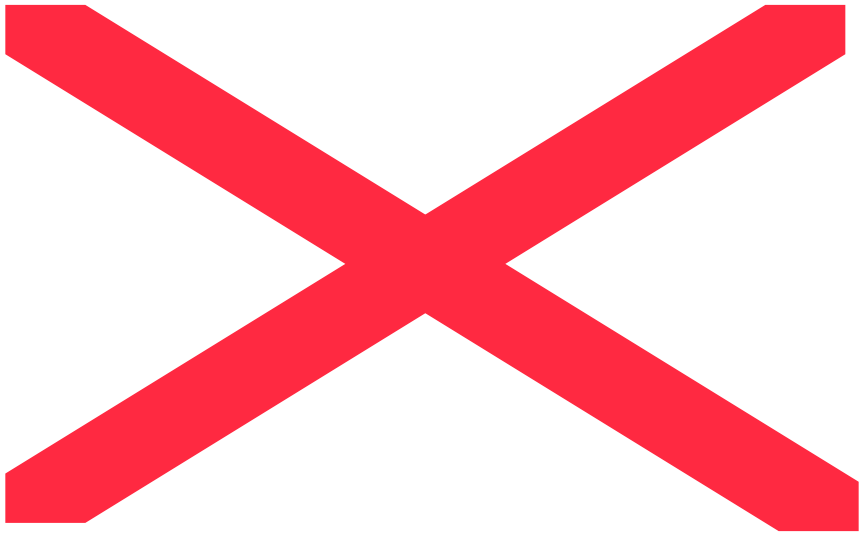
Standard American diet



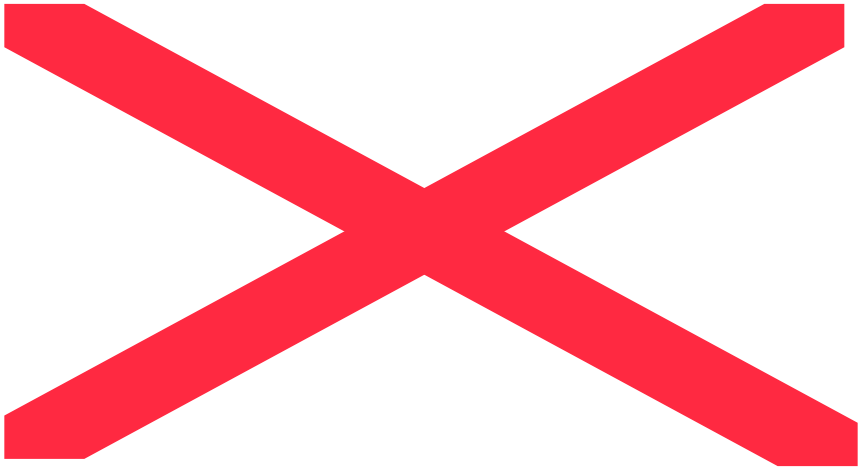
Obesity food



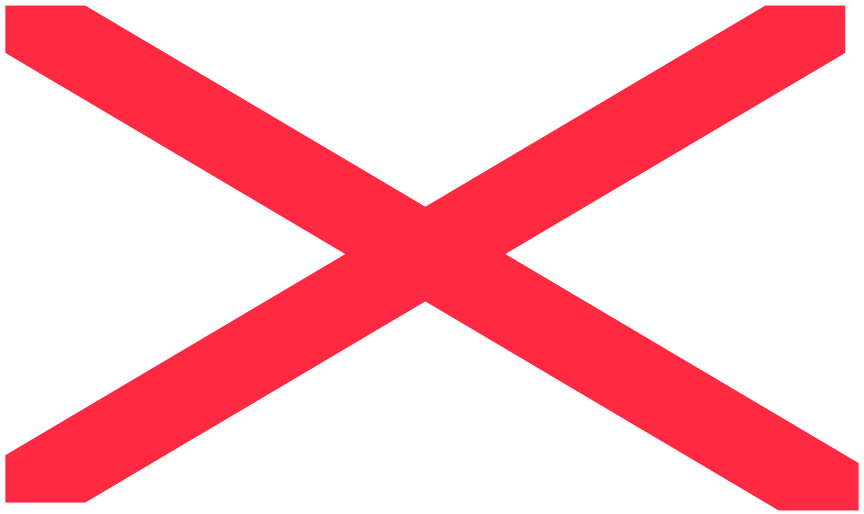
Dietary recommendations



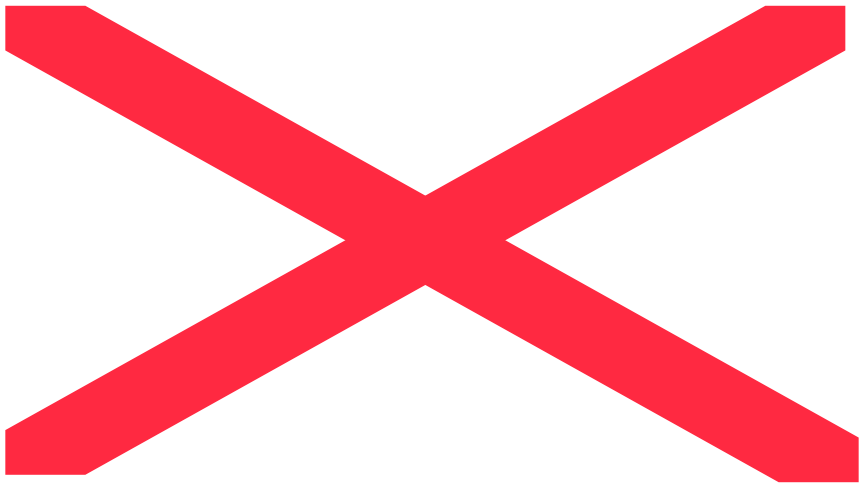
Nutritional epidemiology



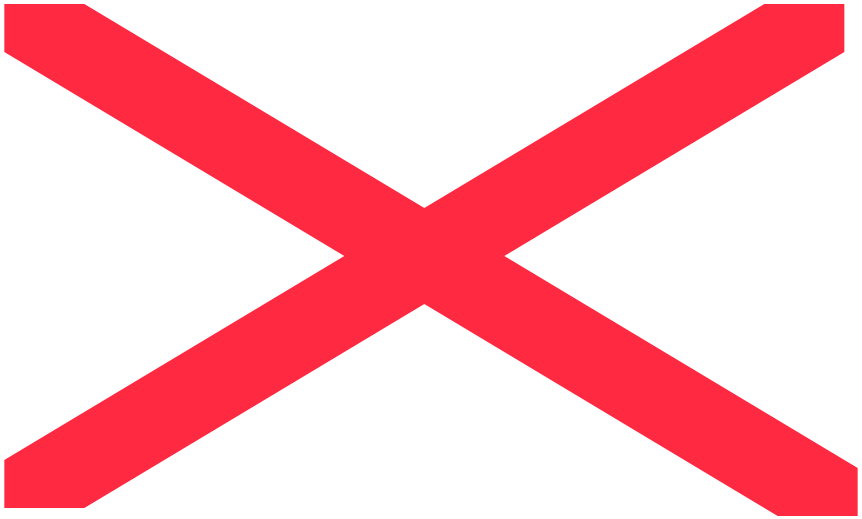
Questionnaire



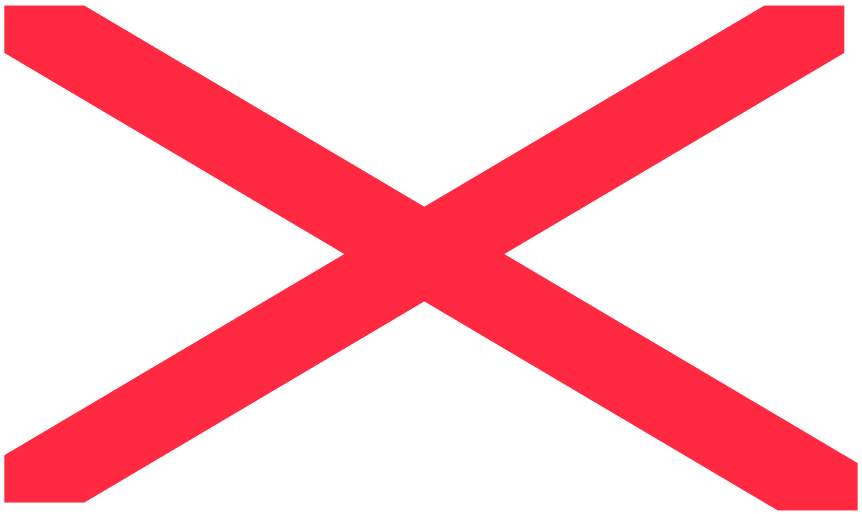
Food questionaire



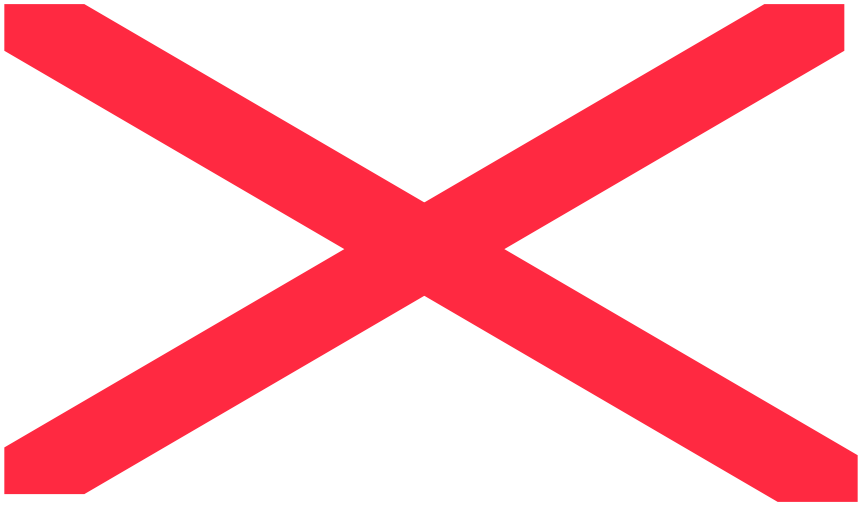
Challenges



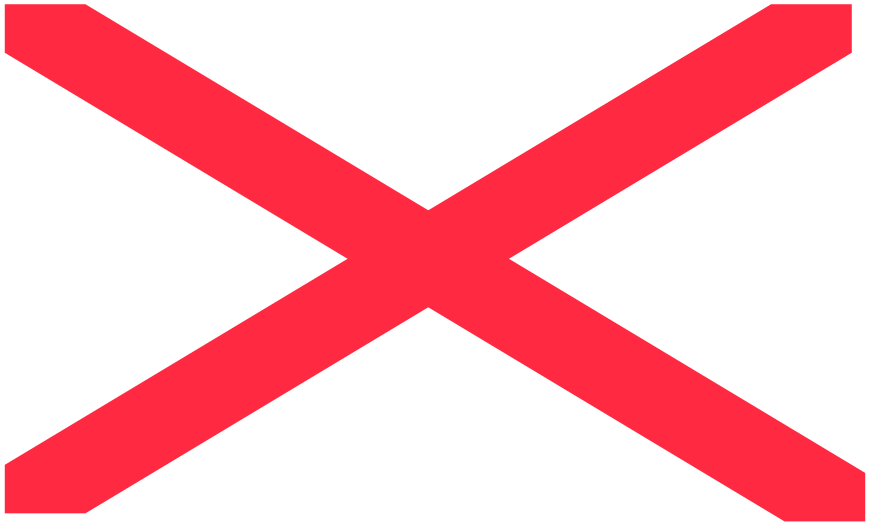
Low fat trials



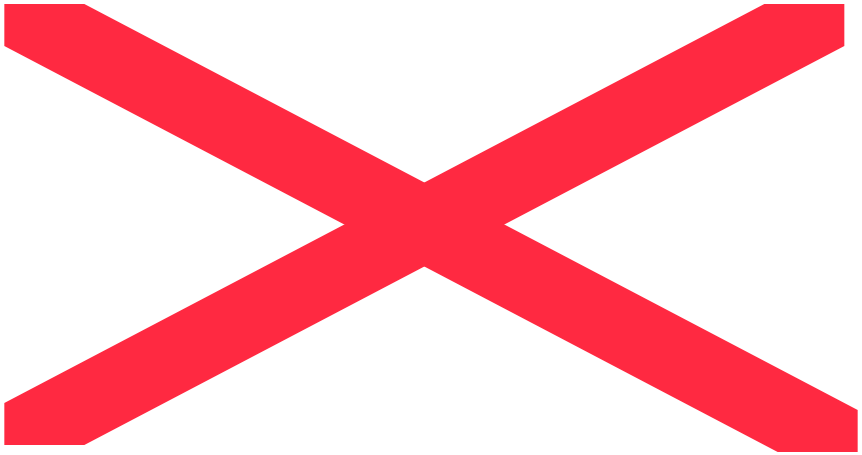
Obesity rates



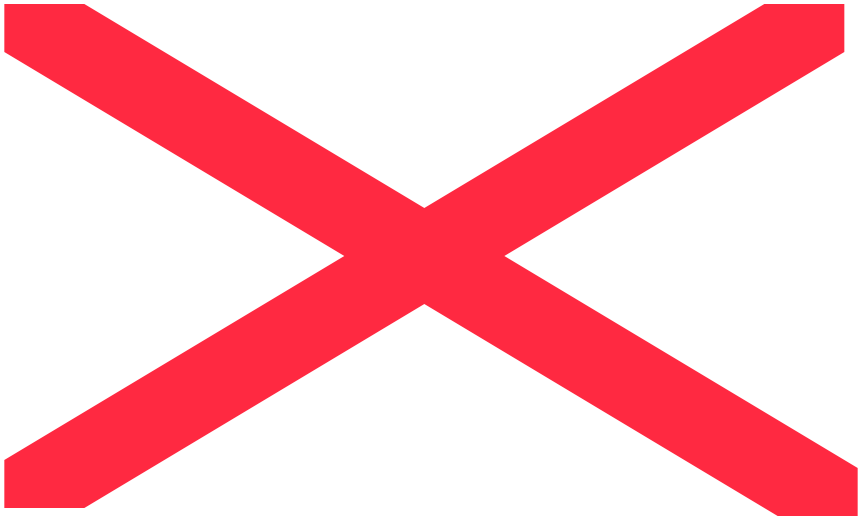
Sugar



Late at night



Insulin resistance



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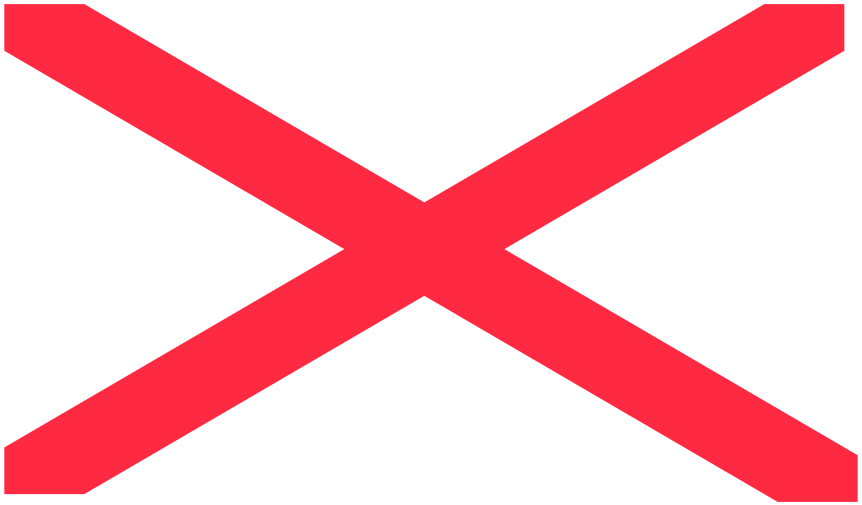
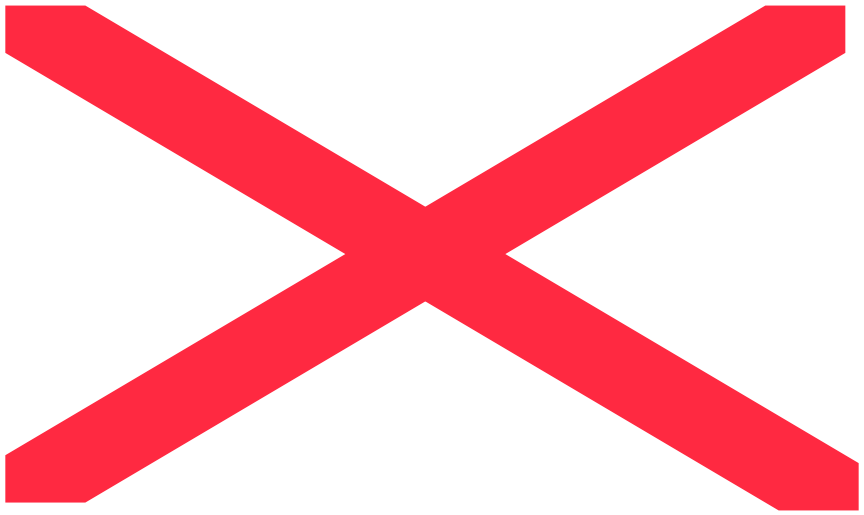
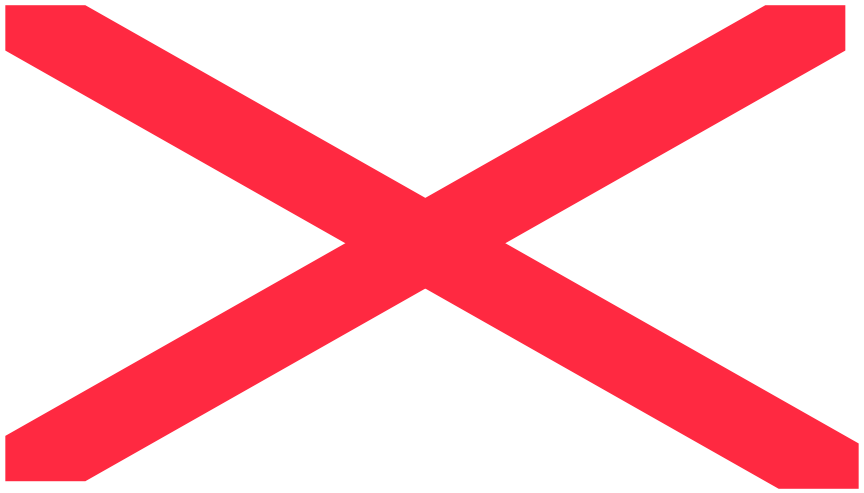


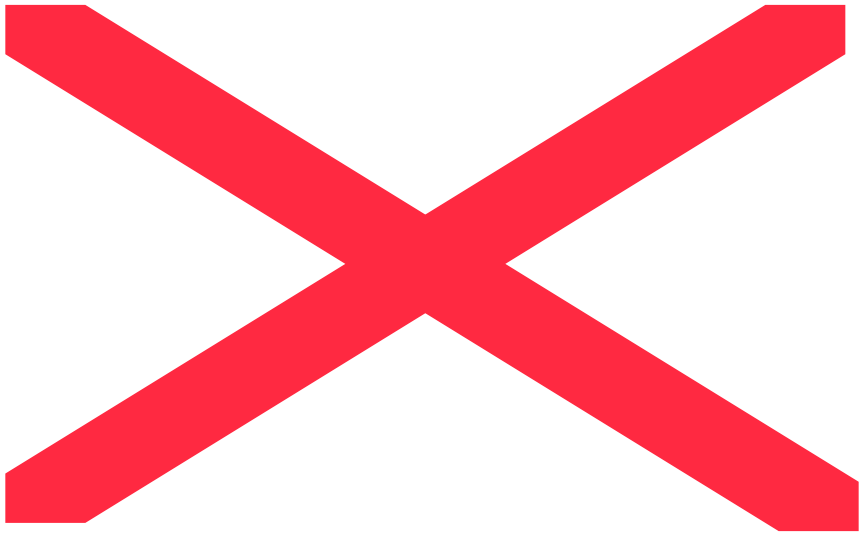
Insulin resistance



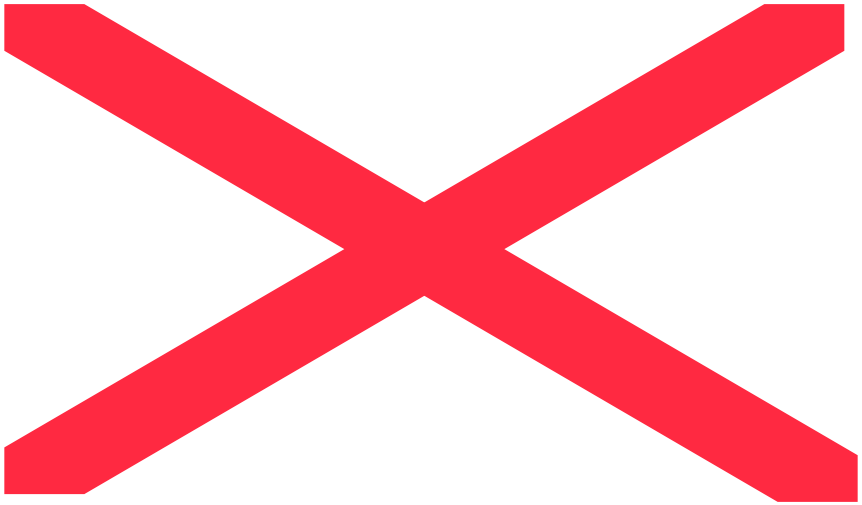
Metabolic factors



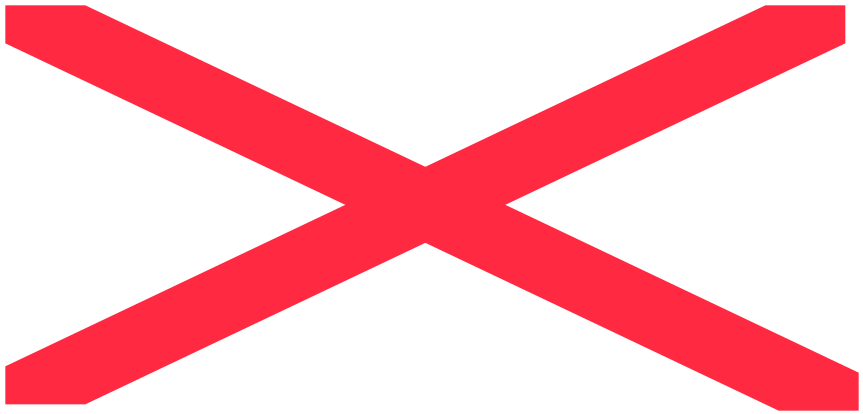
Population perspective



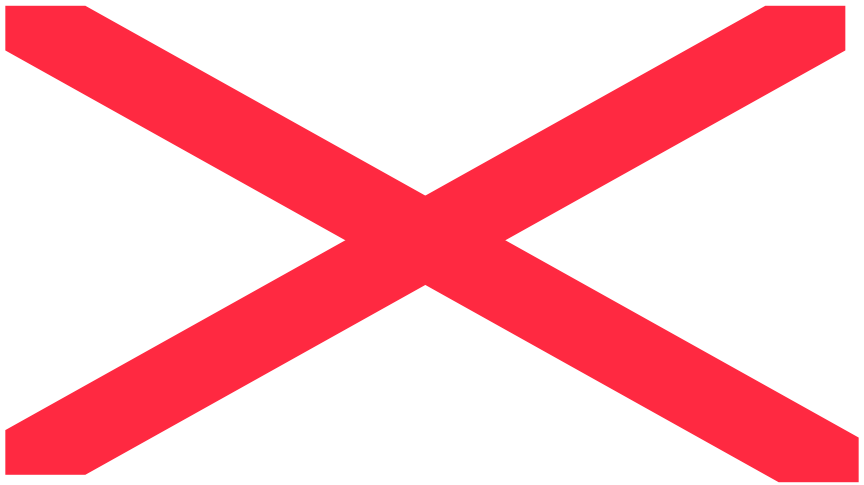
Population perspective



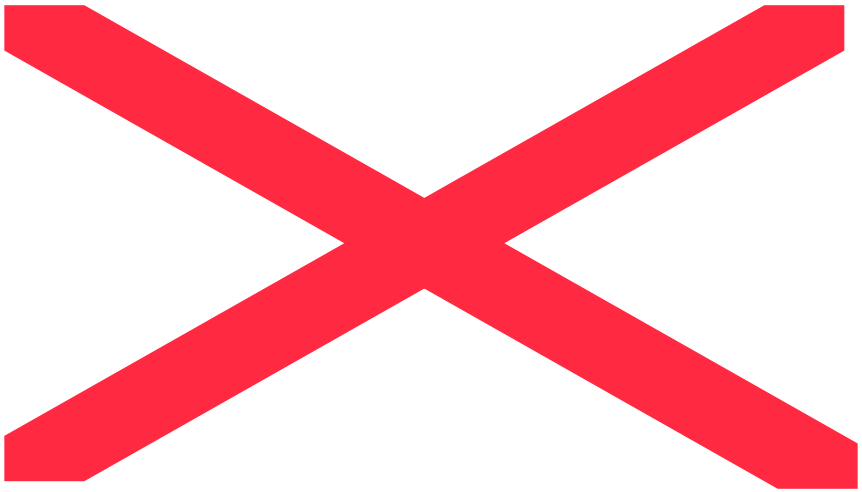
Technology features



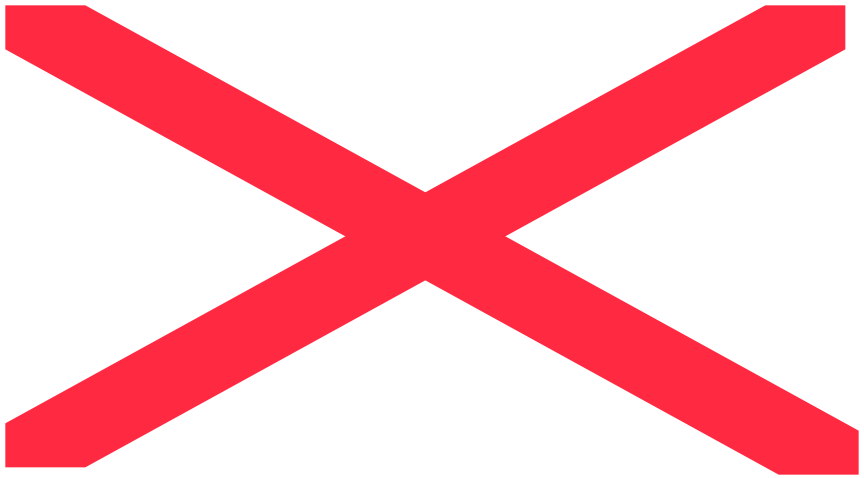
Lung cancer risk factors



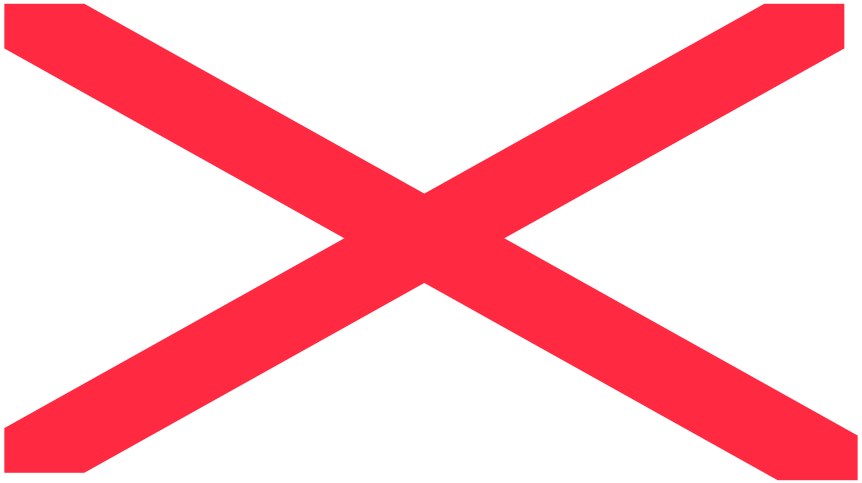
Sleep



Sleep and obesity/smoking



Physical Activity



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

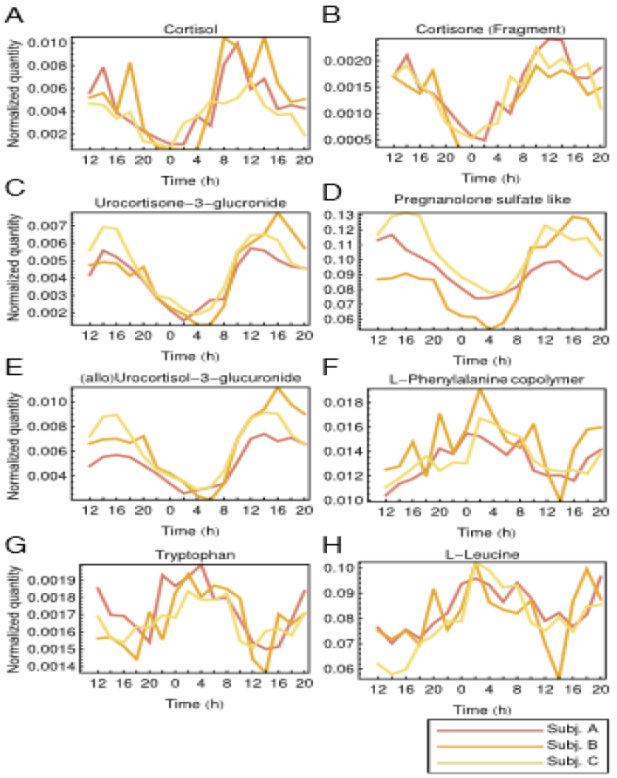
Circadian variation

Circadian variation

Internal body time is related to:
disease susceptibility
chronotherapy

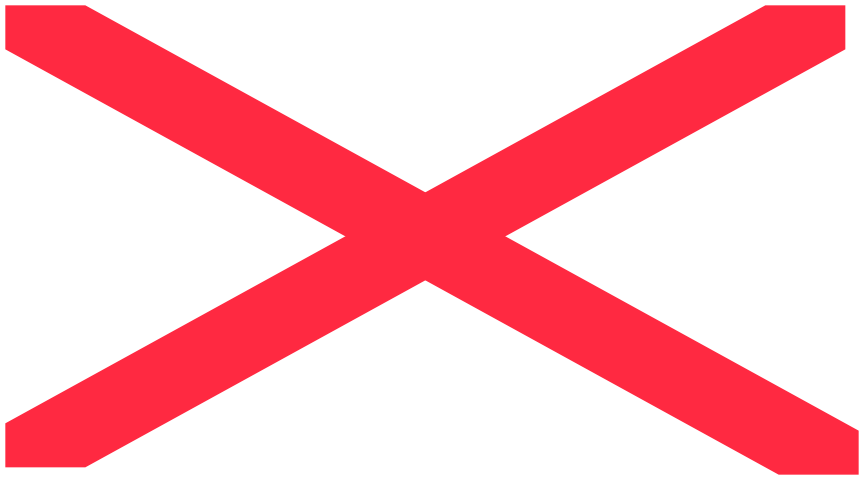
Internal body time determined by 2 blood samples

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



Human body metabolite timetable indicates internal body time.
PNAS 11sept2012 Kasukawa T et al.

Oxygen saturation

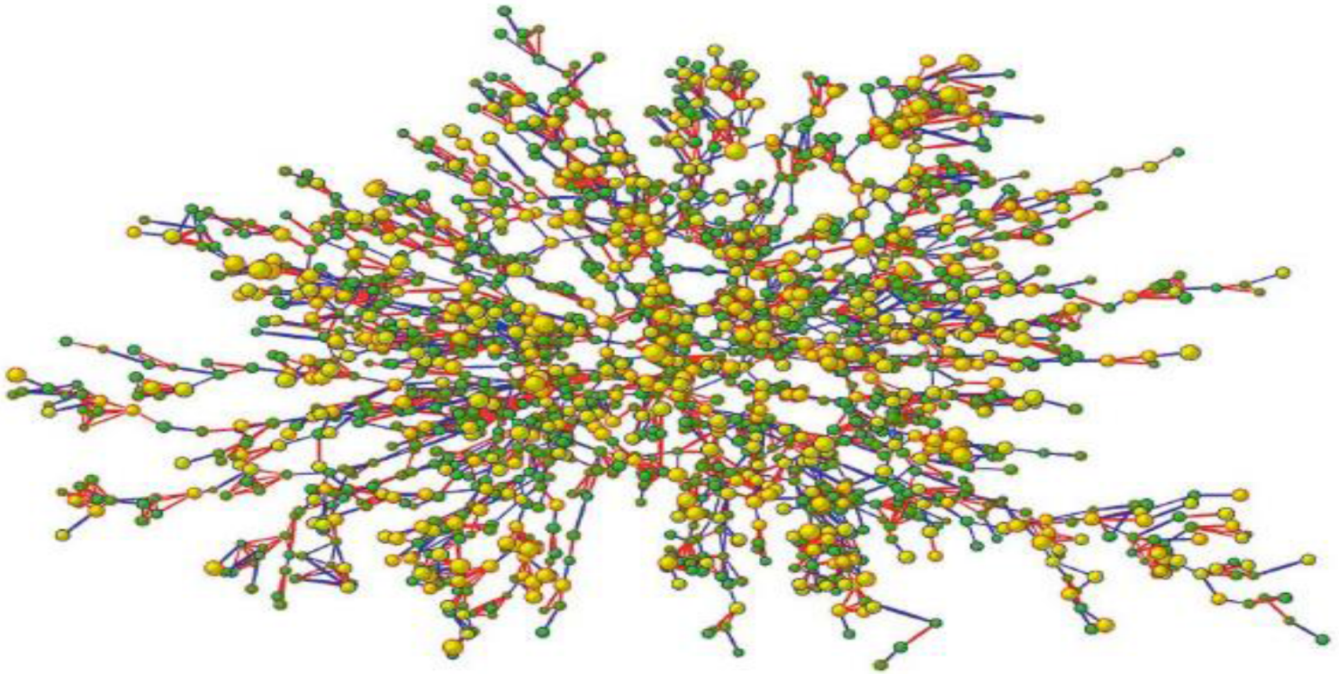


Social data

Social data

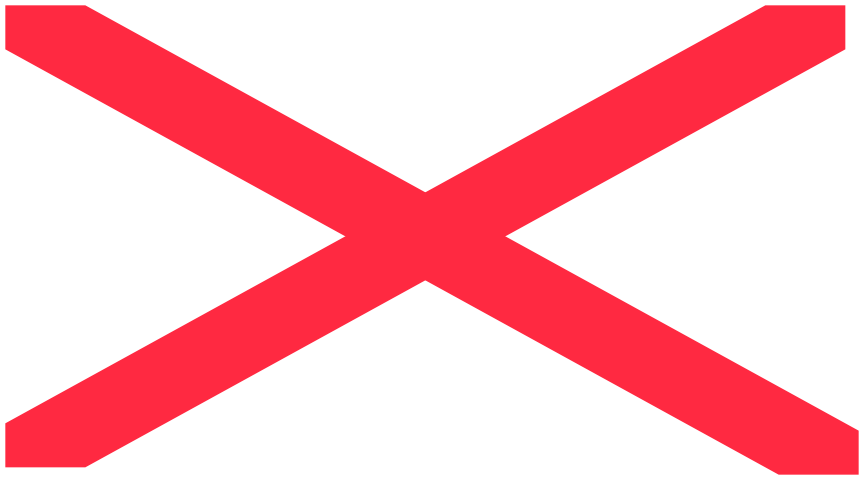
Data on social factors often absent from epidemiologic study designs
Can quantitate:
contacts,
'friends',
indices of interaction,
relationships,
frequency of contact

Social networks



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

Future applications



Virtual cohort