Epidemiology

Epidemiology

Translational Research in Clinical Oncology

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Neil Caporaso, MD
Chief, Genetic Epidemiology Branch,
Division of Cancer Epidemiology and Genetics,
National Cancer Institute
caporaso@nih.gov

A Population Perspective on Cancer

- *foundations (introductory concepts)*
- *tools epidemiologists use*
- *accomplishments*
- *challenges*
- *futures*

Population Perspective

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NIH epidemiology

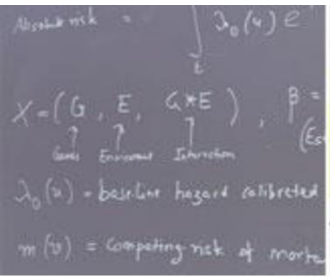
National Cancer Institute → We are **INTRAMURAL**
~ 85% $$ are extramural

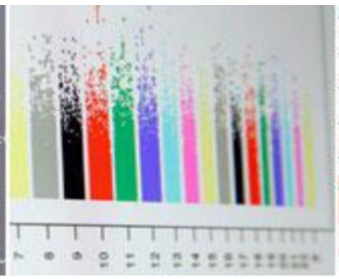
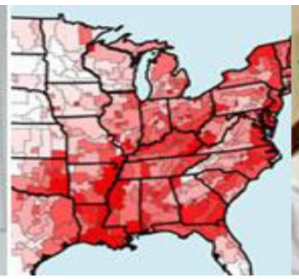
Division of Cancer Epidemiology and Genetics → Cancer **ETIOLOGY**

Genetic Epidemiology Branch

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

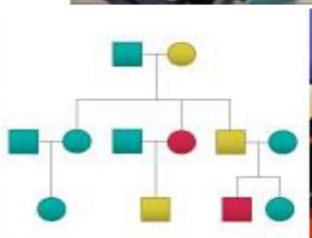
NCI DCEG





NCI's Division of Cancer Epidemiology and Genetics








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

National Cancer Institute

at the National Institutes of Health | www.cancer.gov

Division of Cancer Epidemiology & Genetics

Discovering the causes of cancer and the means of prevention

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DCEG Home | About DCEG | Our Research | Fellowships & Training | Tools & Resources | News & Events | Publications

Newly Tenured: Hormuzd Katki

Dr. Hormuzd Katki is now a senior investigator in the Biostatistics Branch. His research on risk stratification has led to the development of guidelines and risk-benefit models for cancer screening. He is particularly interested in the principle of "equal management of people at equal risk of cancer."

- Learn more about Dr. Katki

Complexity of NHL Subtypes

Newly Tenured: Hormuzd Katki

Physical Activity, Sedentary Behavior, and Cancer

The Division of Cancer Epidemiology and Genetics (DCEG) is a research program of the National Cancer Institute (NCI), one of the National Institutes of Health (NIH). The Division is the world's most comprehensive cancer epidemiology research group. Its renowned epidemiologists, geneticists, and biostatisticians conduct population and multidisciplinary research to discover the genetic and environmental determinants of cancer and new approaches to cancer prevention. The Division's research impacts public health policy in the United States and around the world.

Fellowships

DCEG offers a range of fellowships and research training opportunities in our research Branches and with specific investigators.

Learn about our training programs

Scientific Position Openings

Deputy Director

DCEG is recruiting an accomplished, senior scientist to serve as Deputy Director in the Office of the Director, DCEG. Learn more about this opportunity.

Postdoctoral Fellowship

The Radiation Epidemiology Branch is recruiting a postdoctoral fellow to conduct research on health effects

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

Epidemiology

- **Epidemiology = health and disease in human populations**

- **= *epi* (upon) + *demos* (the people) + *logia* (talk about)**
- **An 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…possible BIAS**
  - **Contrast with Clinical Research**

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 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

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

[6] ***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

Population Perspective

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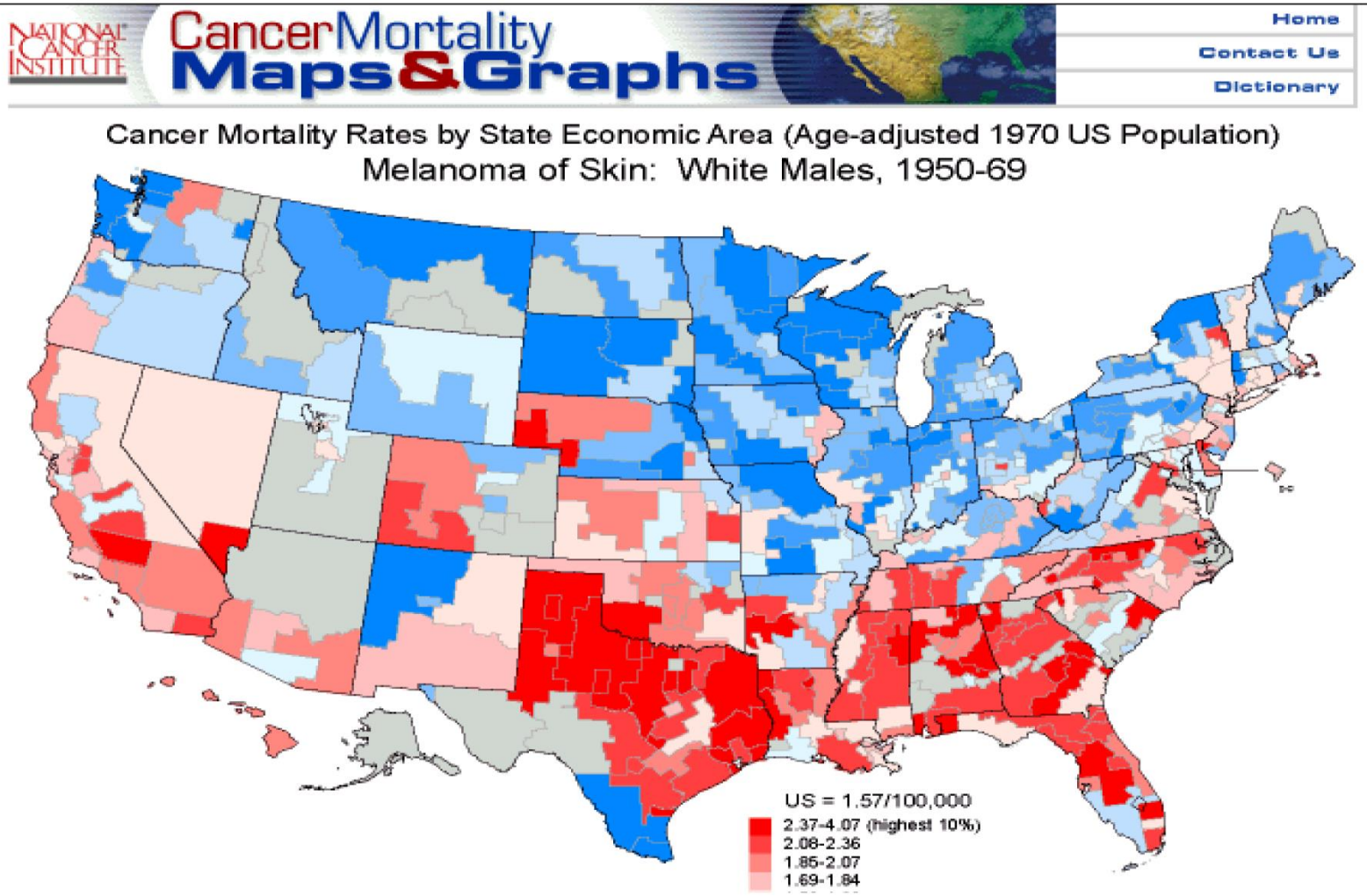
Cancer Maps

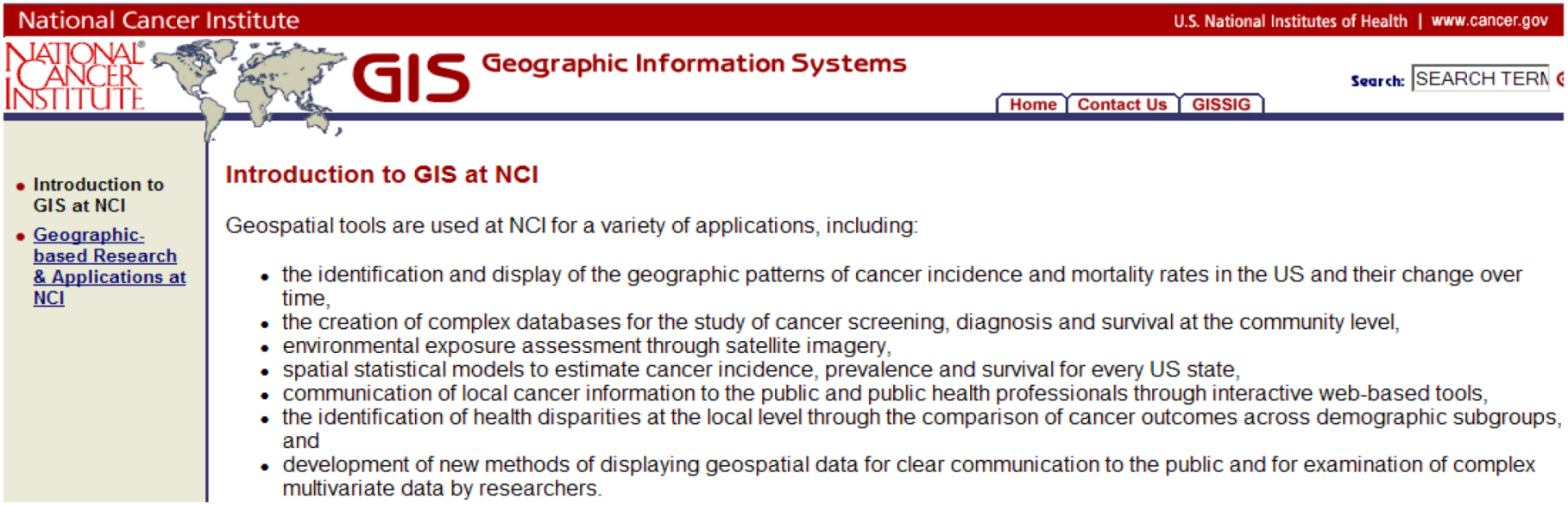
MAPS 1



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

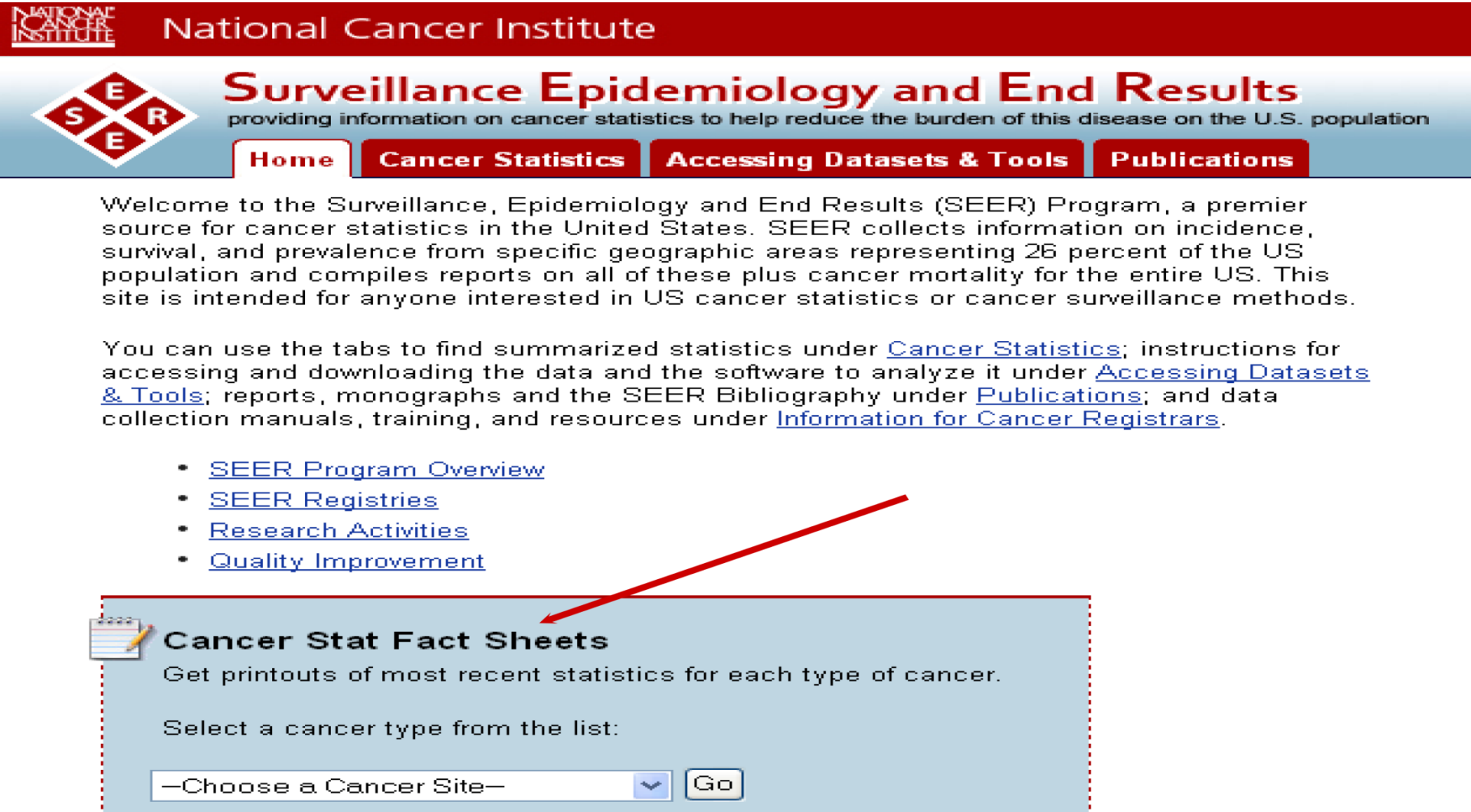
Surveillance, Epidemiology, and End Results (SEER) Program

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

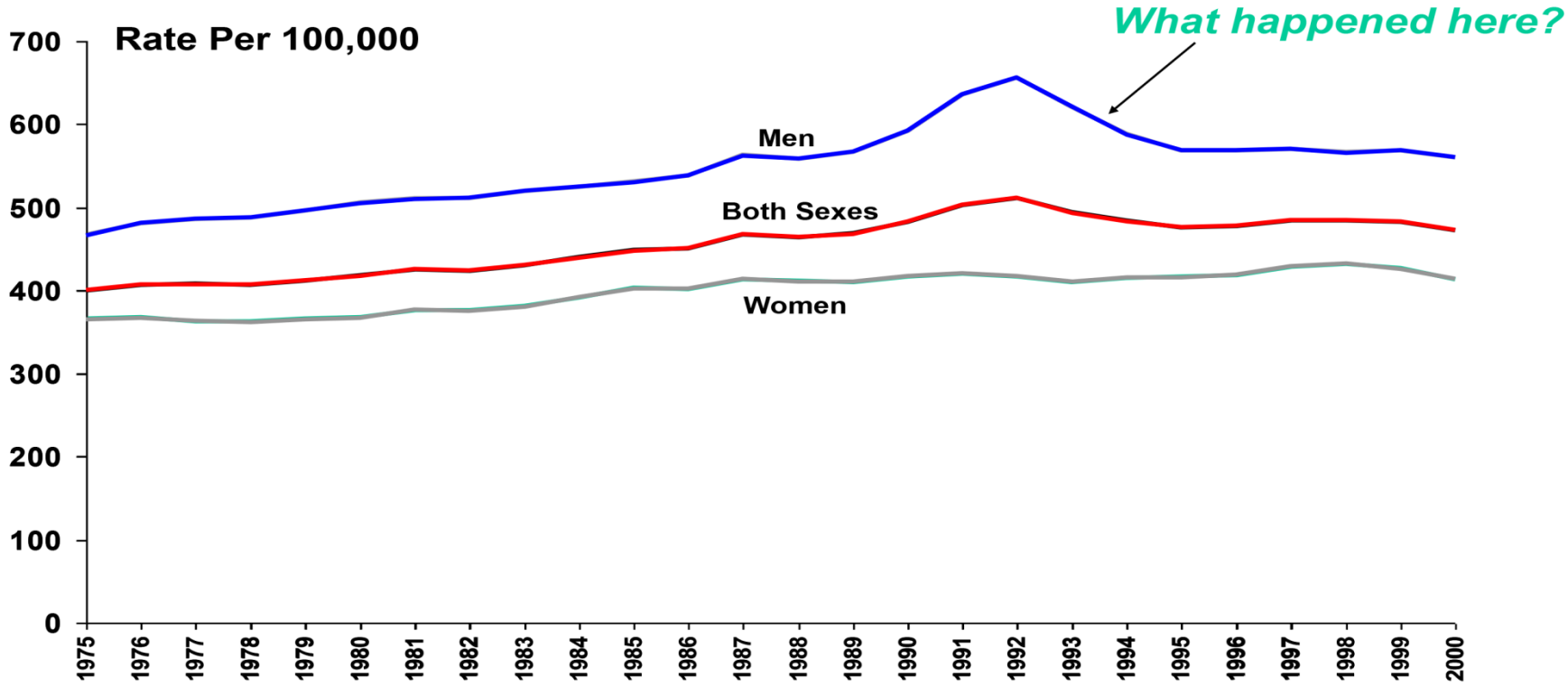
comprehensive source of population-based information

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

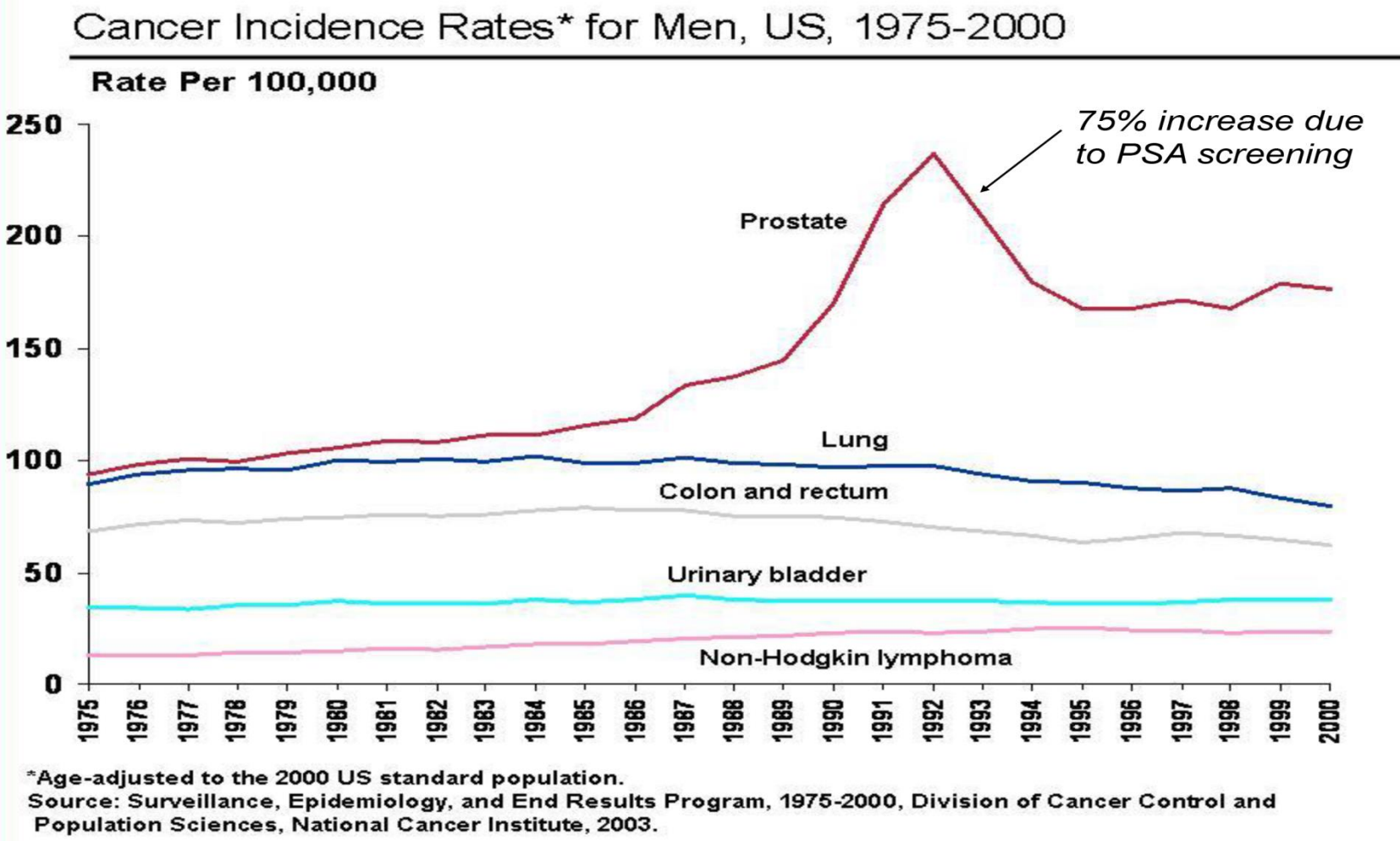
Cancer Incidence Rates

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

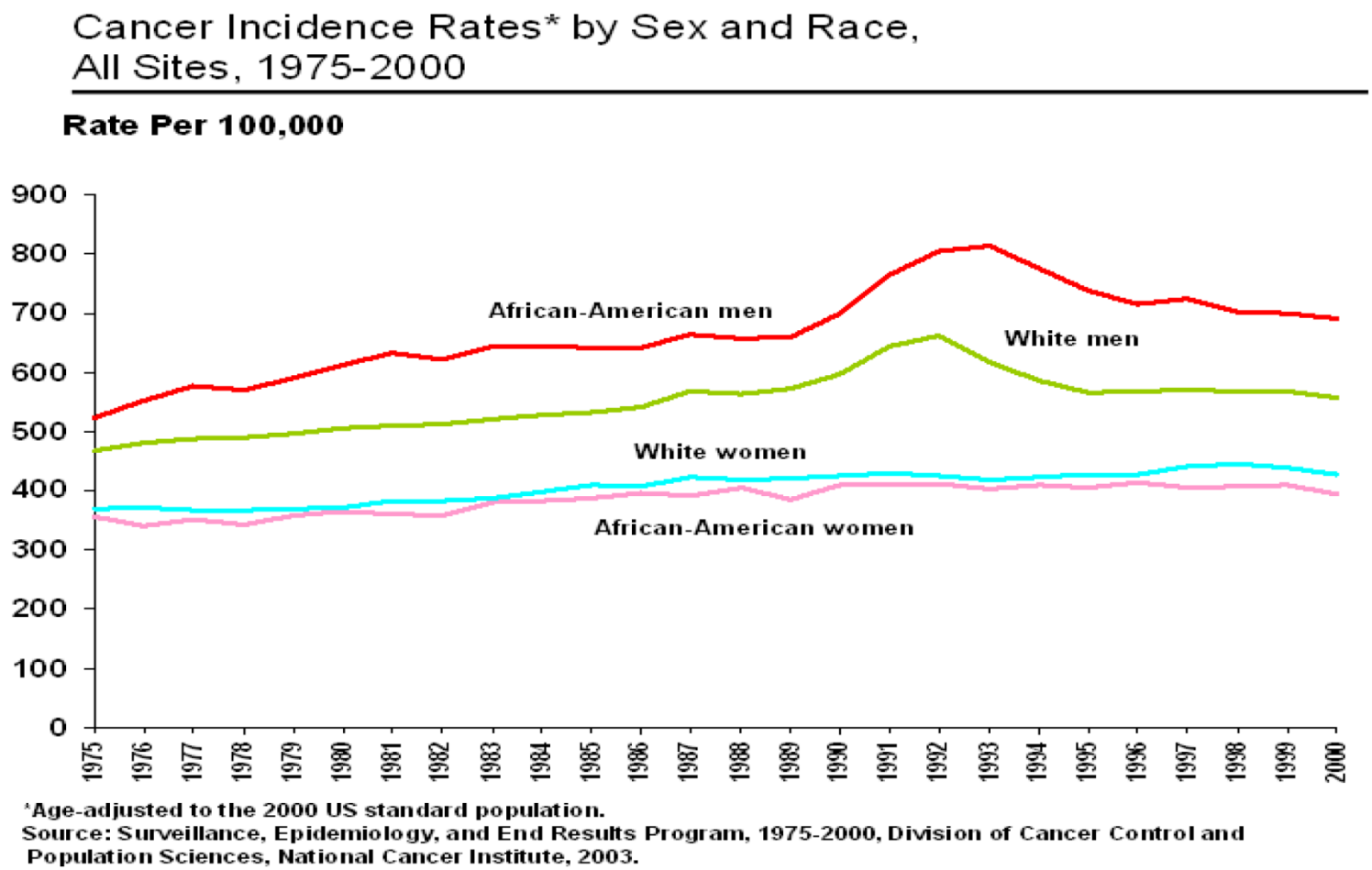


*Age-adjusted to the 2000 US standard population.
Source: Surveillance, Epidemiology, and End Results Program, 1973-1999, Division of Cancer Control and Population Sciences, National Cancer Institute, 2003.

Cancer Rates for Men

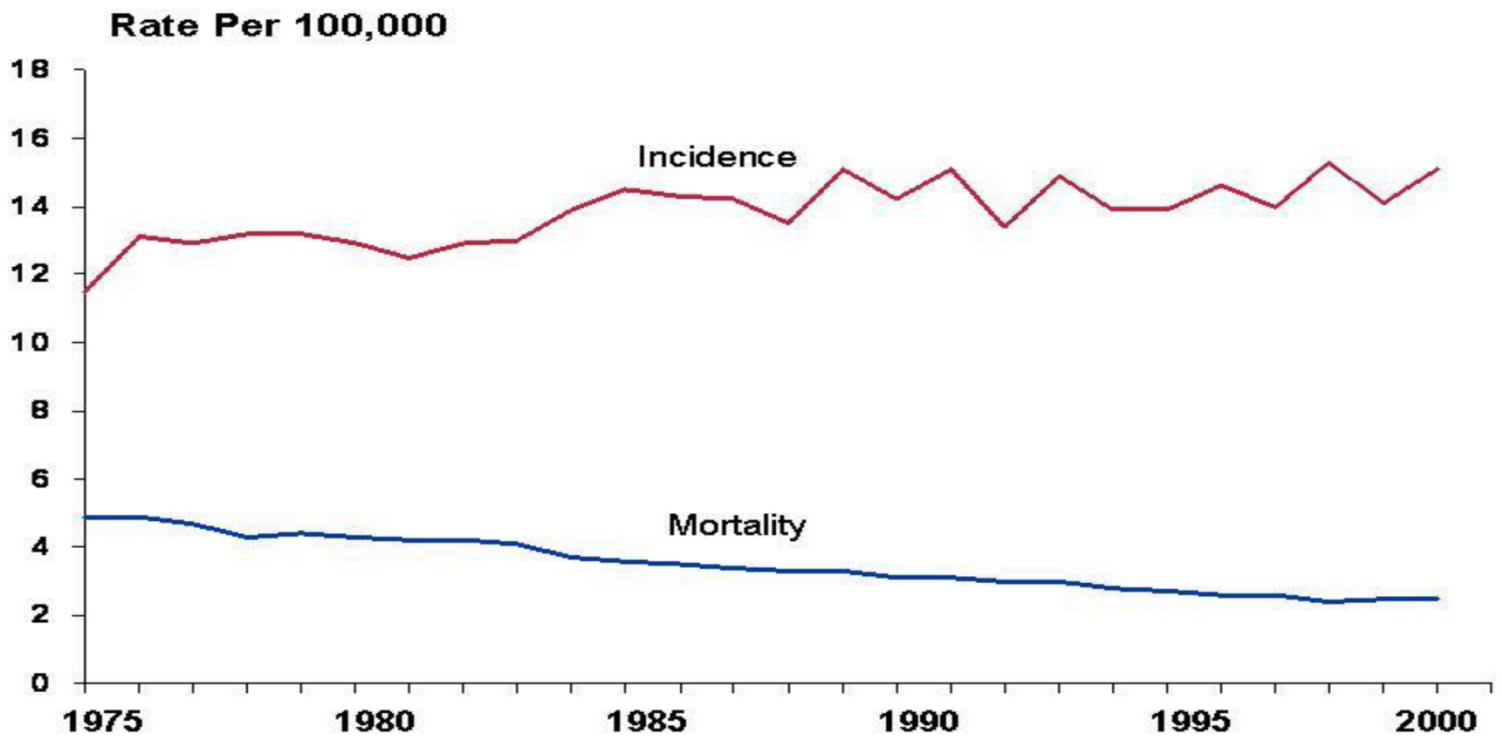


Cancer by sex and race



Cancer and Children

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

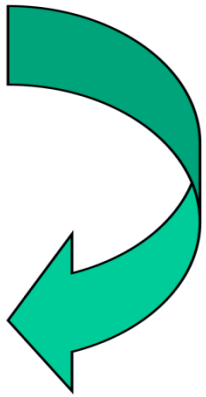


*Age-adjusted to the 2000 Standard population.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2000, Division of Cancer Control and Population Sciences, National Cancer Institute, 2003.

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**
- **Etiology -- poorly understood**



Treatment Effective !

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?

How do you prove a cause?

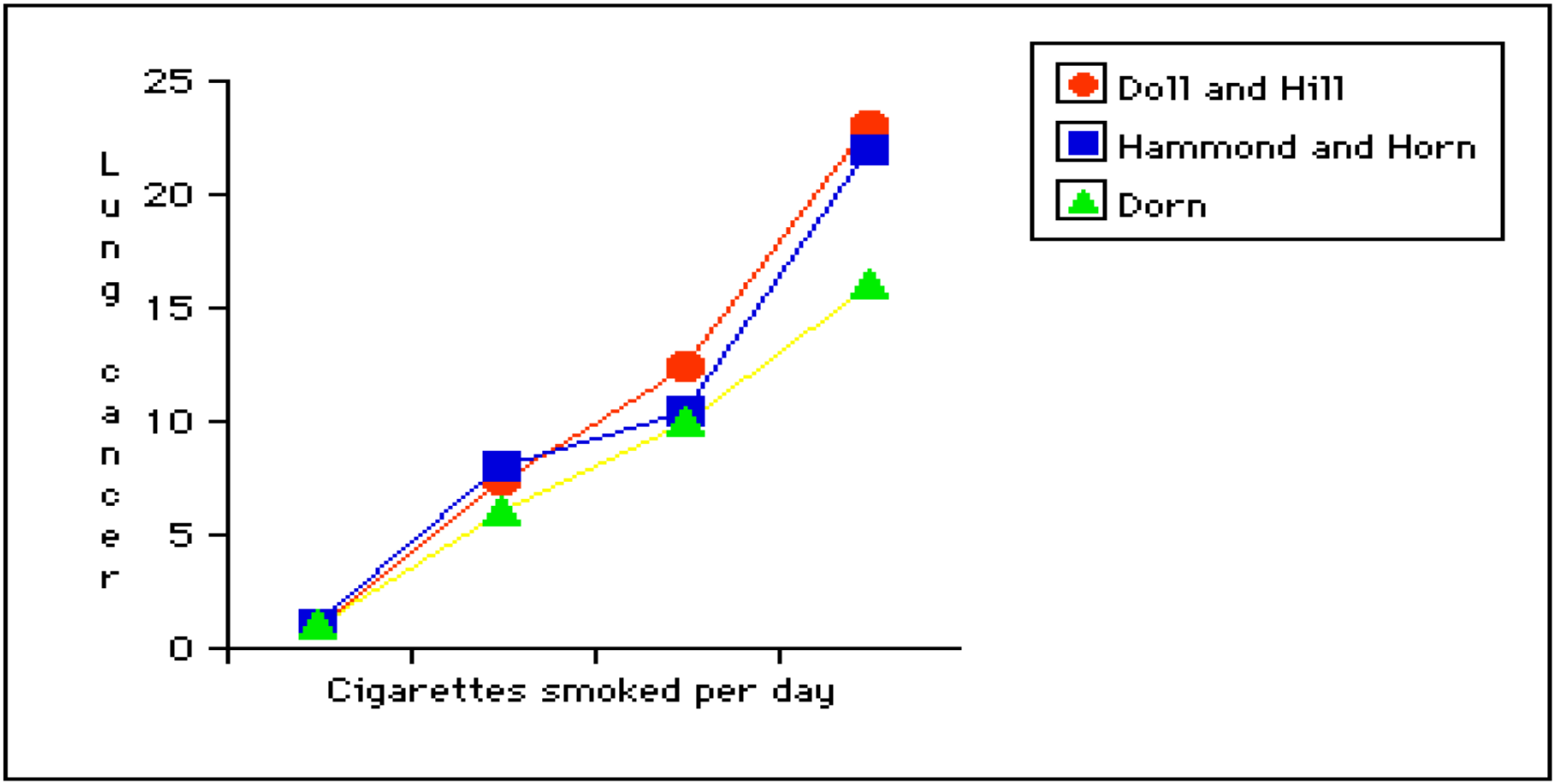
(TODAY)

1. Mendelian Randomization

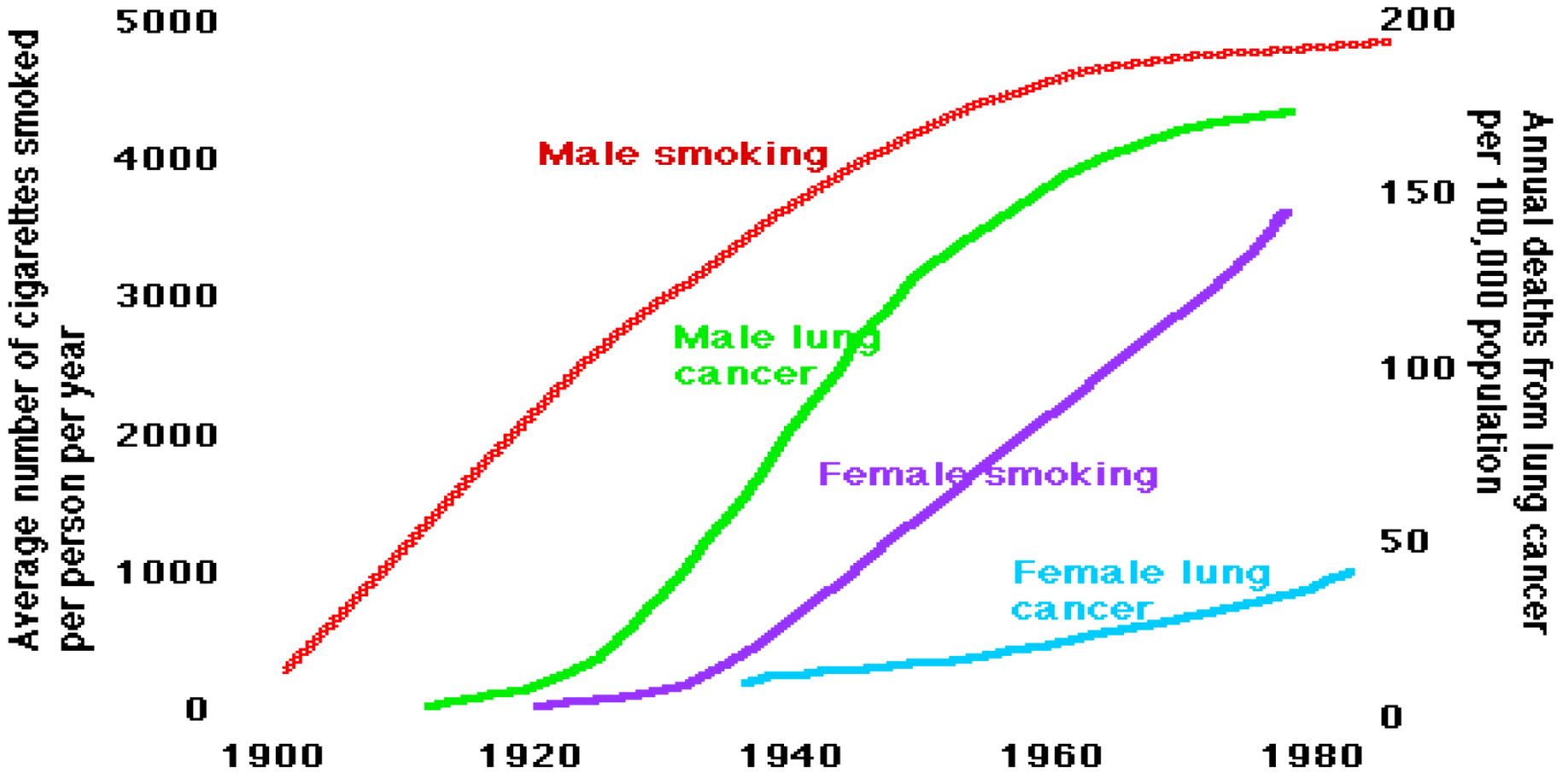
2. Molecular Epidemiology

3. Mediation analysis

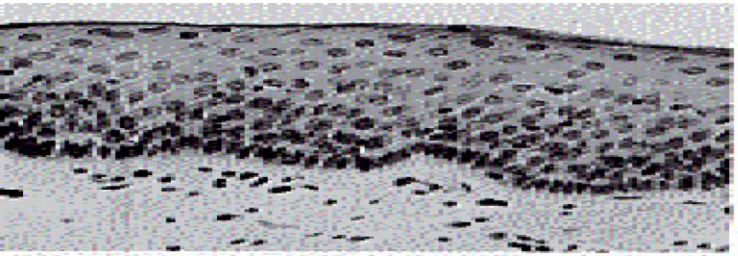
Lung Cancer and smoking

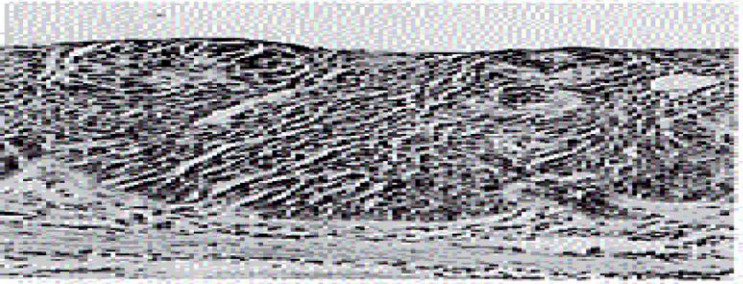


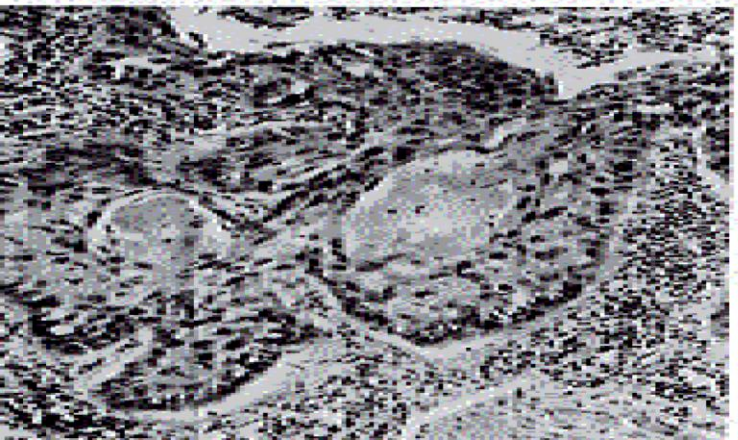
Lung cancer

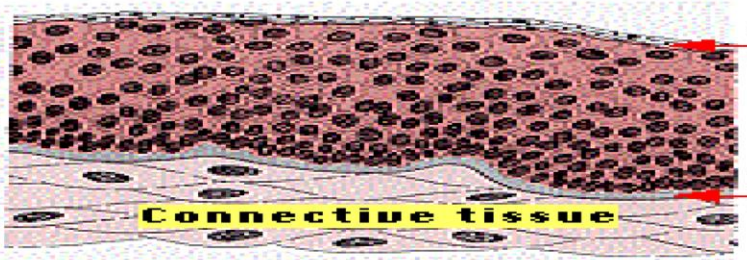

Average number of cigarettes smoked per person per year
5000
4000
3000
2000
1000
0
Annual deaths from lung cancer per 100,000 population
200
150
100
50
0
1900
1920
1940
1960
1980
Male smoking
Male lung cancer
Female smoking
Female lung cancer

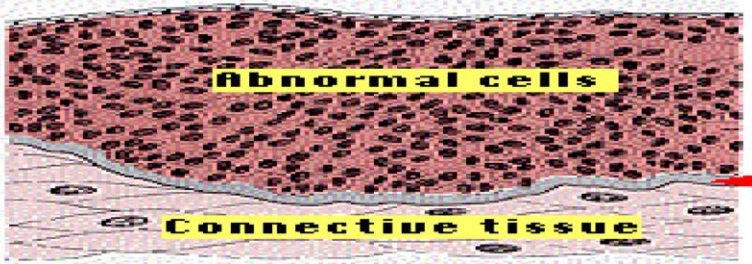
Lung cancer

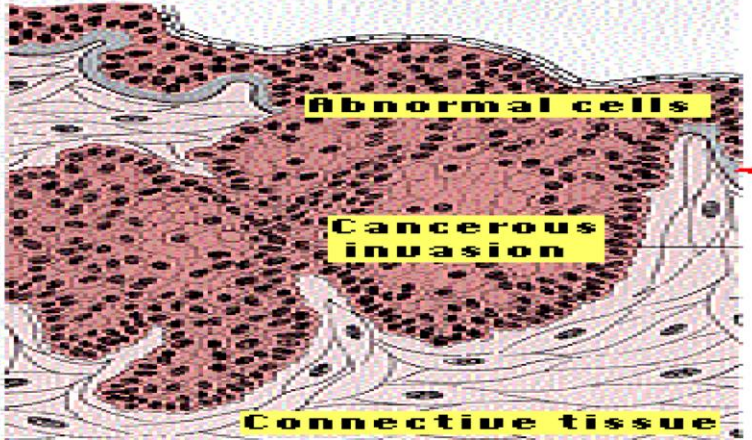




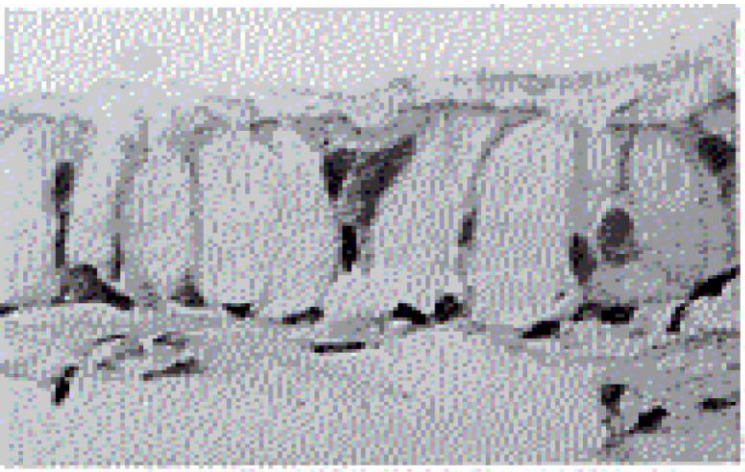


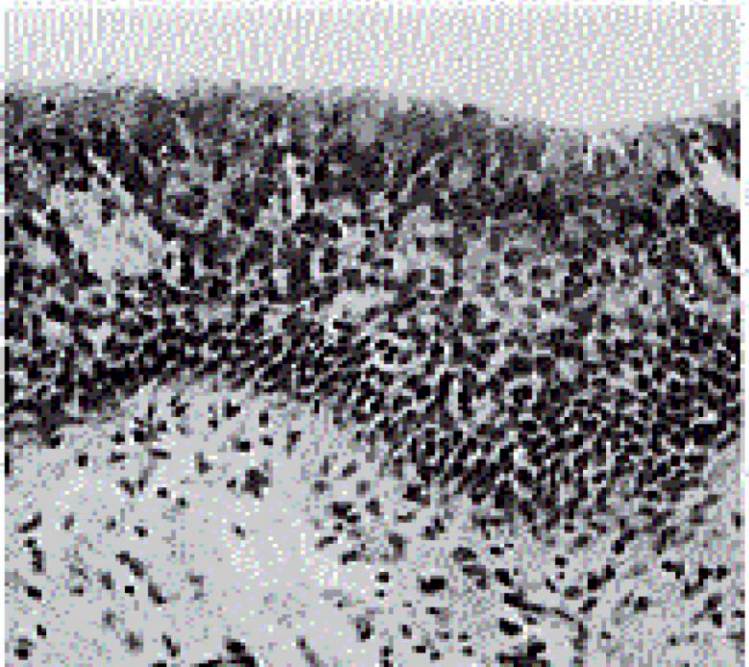

Squamous epithelium
Basement membrane
Connective tissue

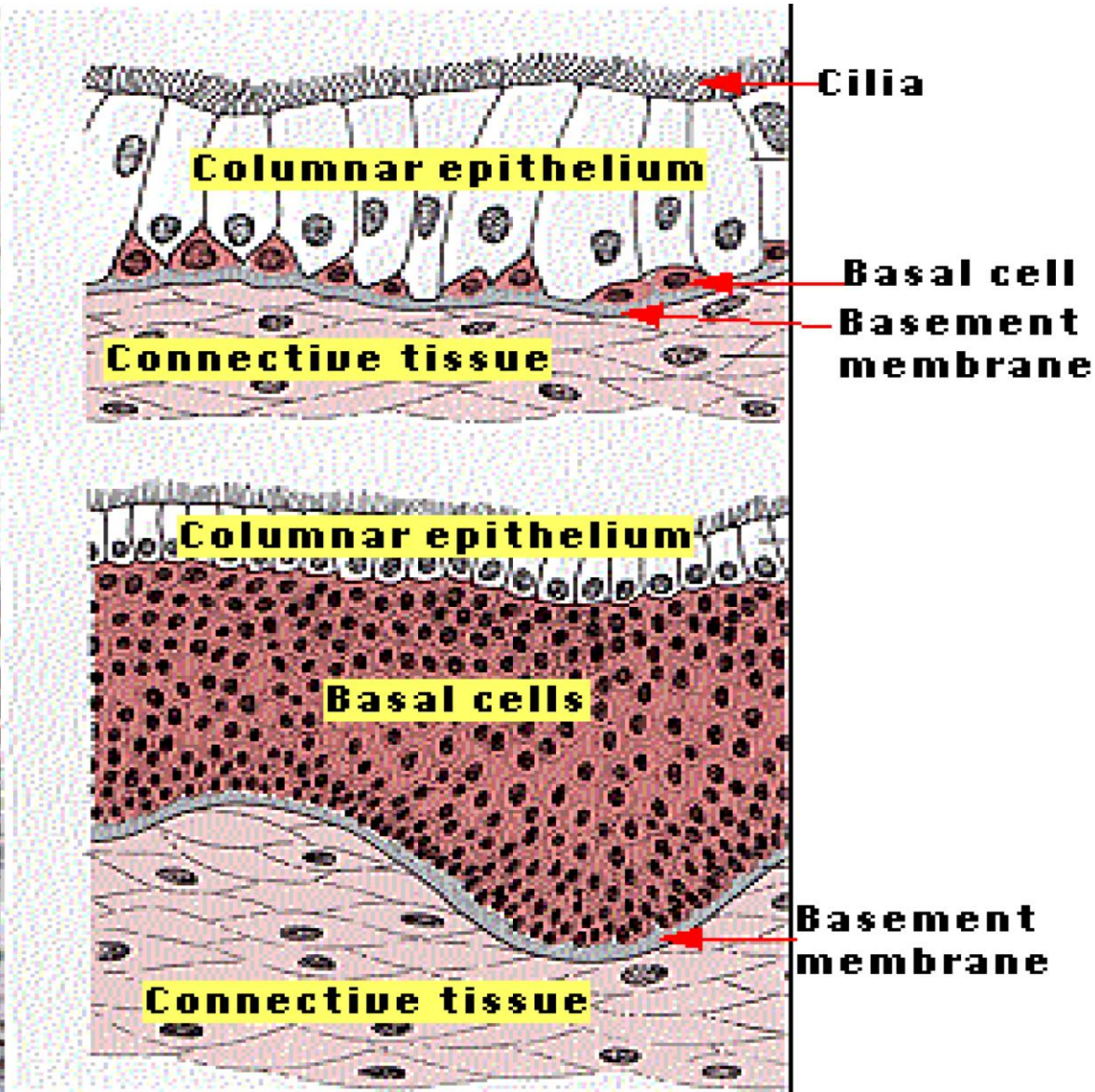

Abnormal cells
Basement membrane
Connective tissue


Abnormal cells
Basement membrane
Cancerous inuasion
Connective tissue

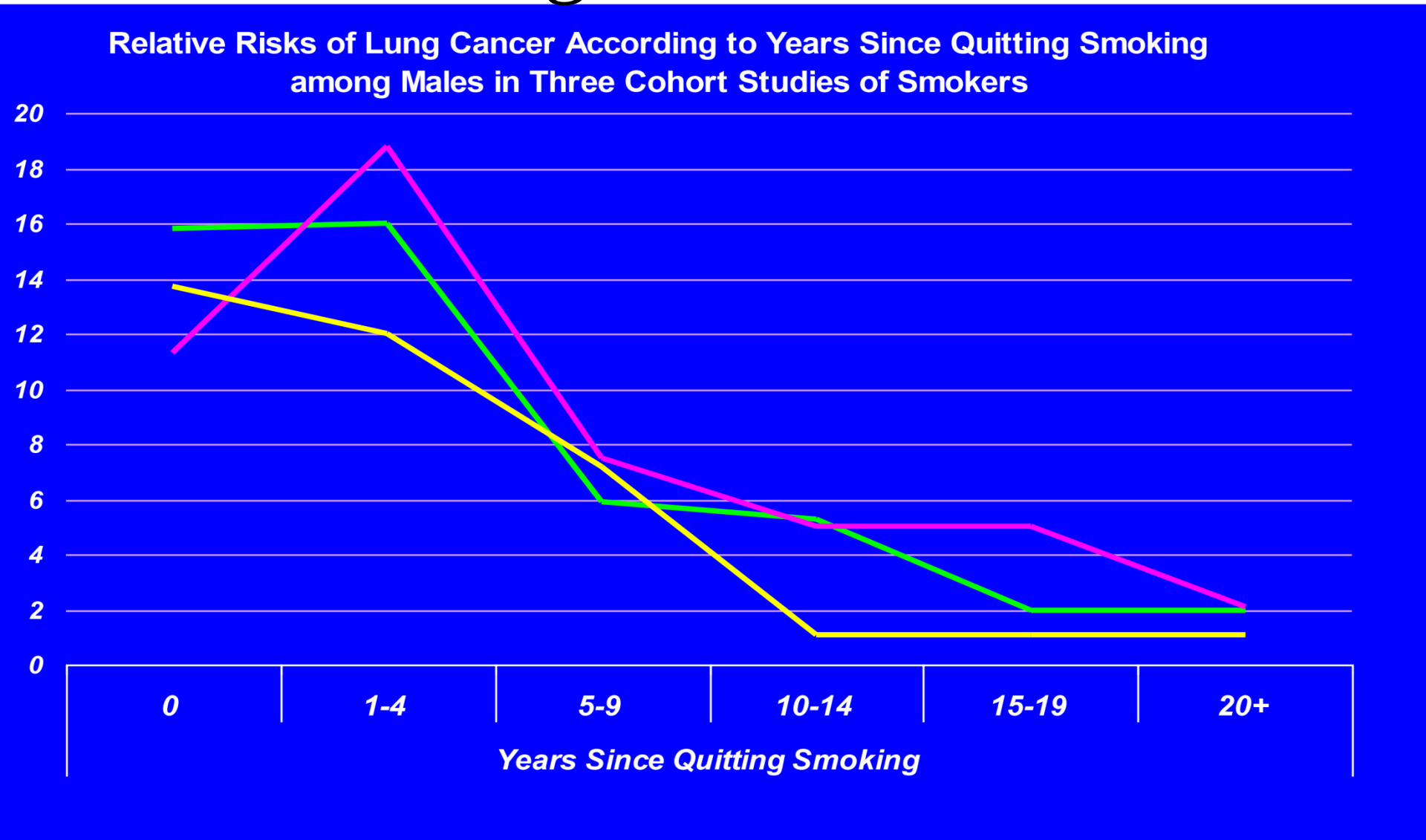
Lung cancer






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

Lung cancer risks



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Coffee and mortality

72 media calls

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
nd the risk of death remains unclear.

ociation of coffee drinking with subsequent total and cause-
ng 229,119 men and 173,141 women in the National Institutes
and Health Study who were 50 to 71 years of age at baseline.
r, heart disease, and stroke were excluded. Coffee consumption
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.

Smoking and bladder cancer

ORIGINAL CONTRIBUTION

Association Between Smoking and Risk of Bladder Cancer Among Men and Women

Neal D. Freedman, PhD, MPH
Debra T. Silverman, ScD, ScM
Albert R. Hollenbeck, PhD
Arthur Schatzkin, MD, DrPH†
Christian C. Abnet, PhD, MPH

Context Previous studies indicate that the population attributable risk (PAR) of bladder cancer for tobacco smoking is 50% to 65% in men and 20% to 30% in women and that current cigarette smoking triples bladder cancer risk relative to never smoking. During the last 30 years, incidence rates have remained stable in the United States in men (123.8 per 100 000 person-years to 142.2 per 100 000 person-years) and women (32.5 per 100 000 person-years to 33.2 per 100 000 person-years); however, changing smoking prevalence and cigarette composition warrant revisiting risk estimates for smoking and bladder cancer.

Objective To evaluate the association between tobacco smoking and bladder cancer.

Design, Setting, and Participants Men (n=281 394) and women (n=186 134) of the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study cohort completed a lifestyle questionnaire and were followed up between October 25, 1995, and December 31, 2006. Previous prospective cohort studies of smoking and incident bladder cancer were identified by systematic review and relative risks were estimated from fixed-effects models with heterogeneity assessed by the I^2 statistic.

Main Outcome Measures Hazard ratios (HRs), PARs, and number needed to harm (NNH).

Results During 4 518 941 person-years of follow-up, incident bladder cancer oc-

MORE THAN 350 000 INDIviduals are diagnosed with incident bladder cancer per year worldwide,[1] including more than 70 000 per year in the United States.[2] In data from Surveillance, Epidemiology, and End Results Program, incidence rates in white individuals aged 50 years or more have remained stable during the past 30 years (1976-2006), from 123.8 per

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

Accomplishments (highly selected)

- *Identification of the general and specific **causes** of cancer*
- *Role as advocates of **public health**/ prevention*
- *Identification of **tobacco** as causal factor for lung cancer*
- *Role of **secondary tobacco smoke***
- ***Molecular Epidemiology***

What are the general risk factors for cancer?

Increasing age

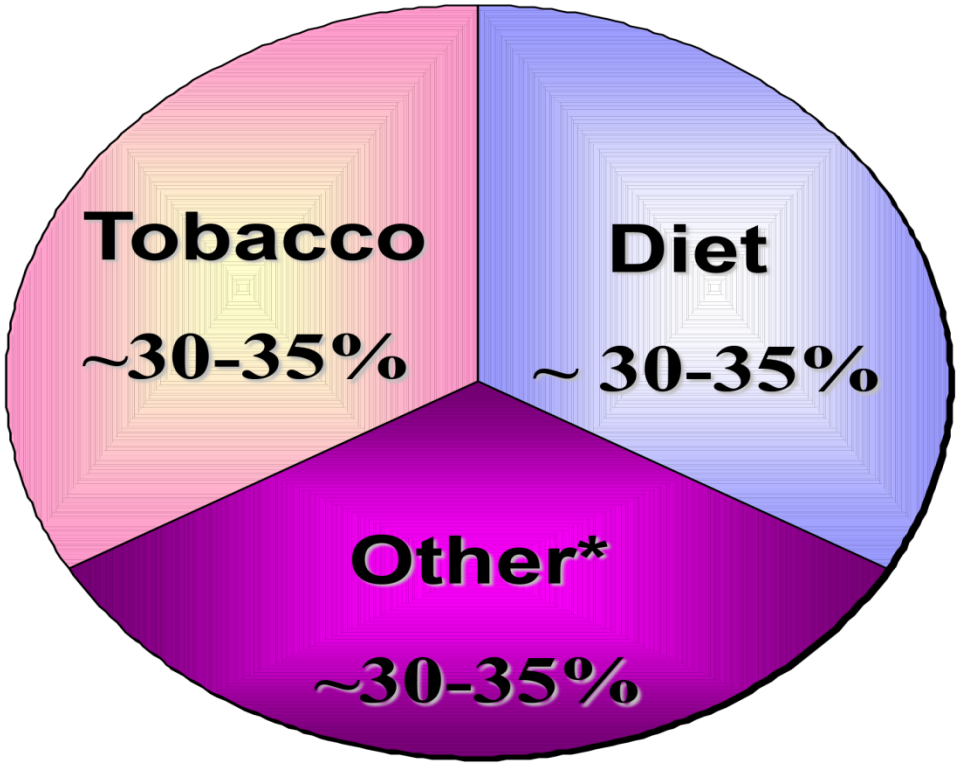
Environmental factors

Genetic factors

Combinations of the above!

Causes of death

Causes of Cancer Deaths



* Environmental pollution, Infectious agents, Lifestyle, Alcohol use, Occupational factors, Medicine, Radiation, Genetic susceptibility, other & unknown causes

Most Cancer is due to the Environment

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

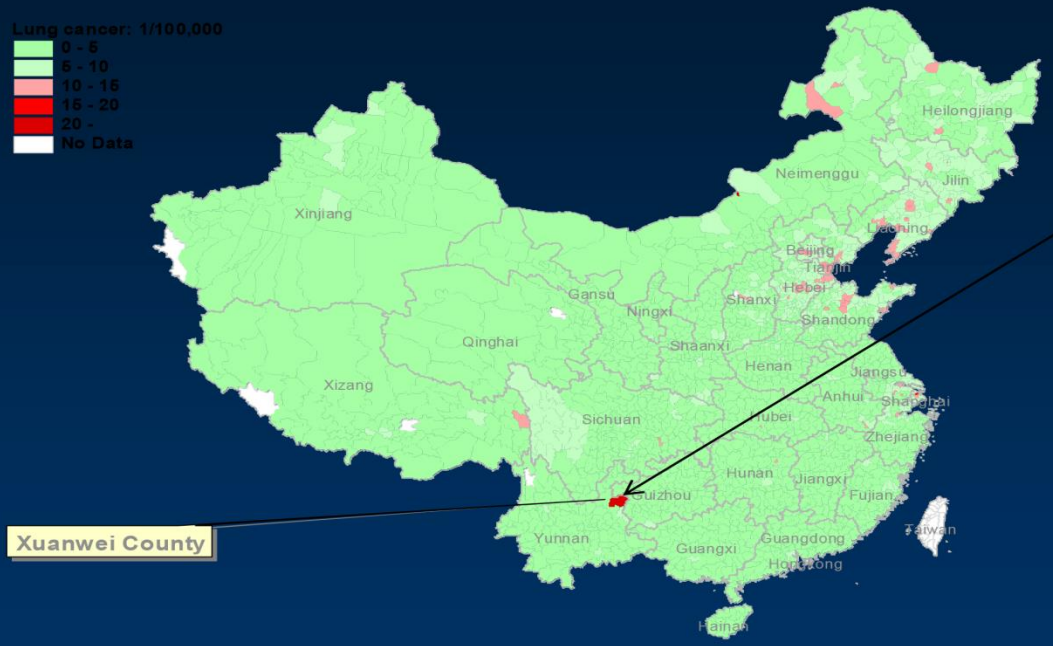
Established by a vast body of descriptive, ecological, and analytical epidemiology

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

Lung cancer mortality

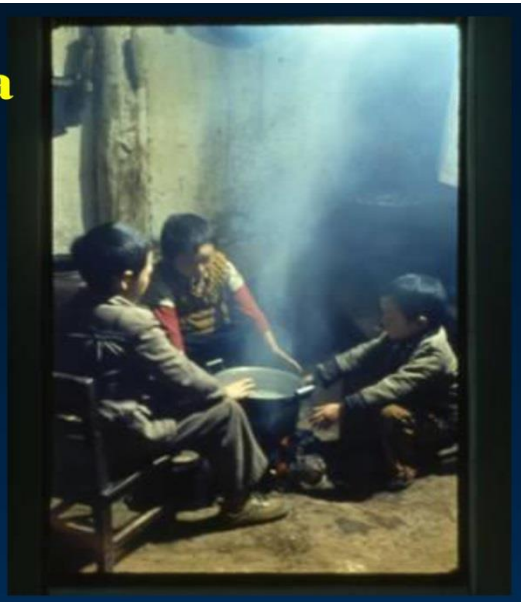
Lung cancer mortality rate in Xuan Wei is among the highest in China



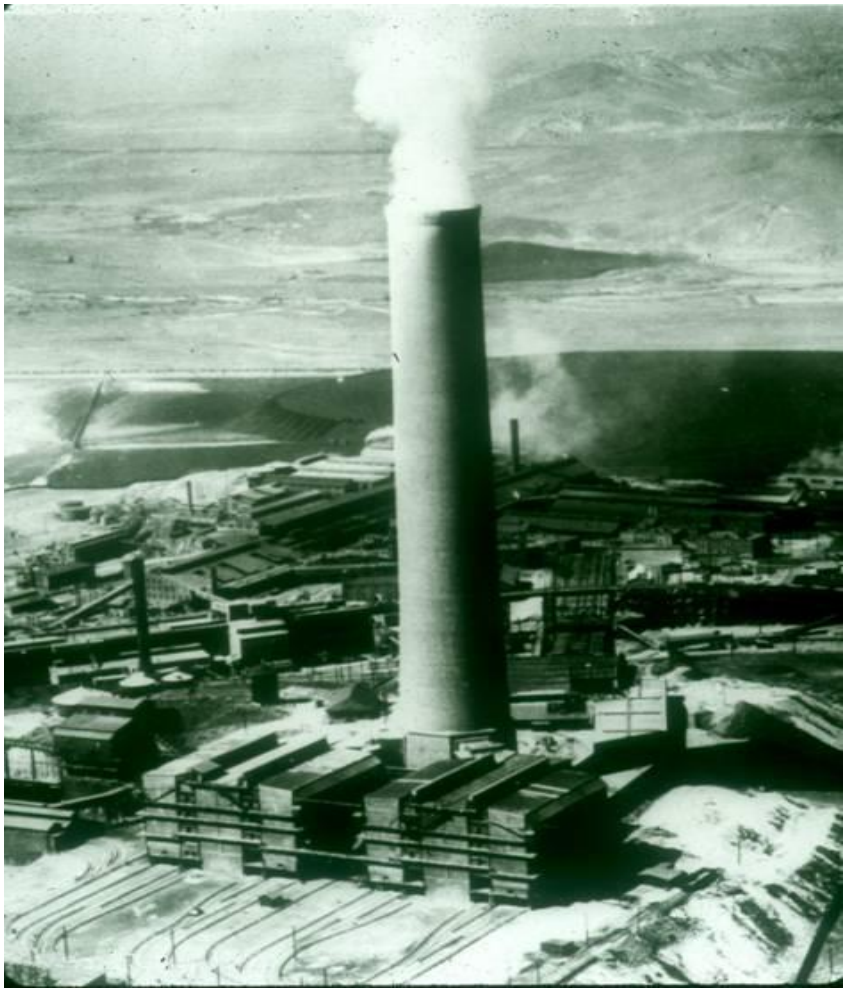
County-specific female lung cancer mortality rates (per 100,000, 1973-75)

Air pollution

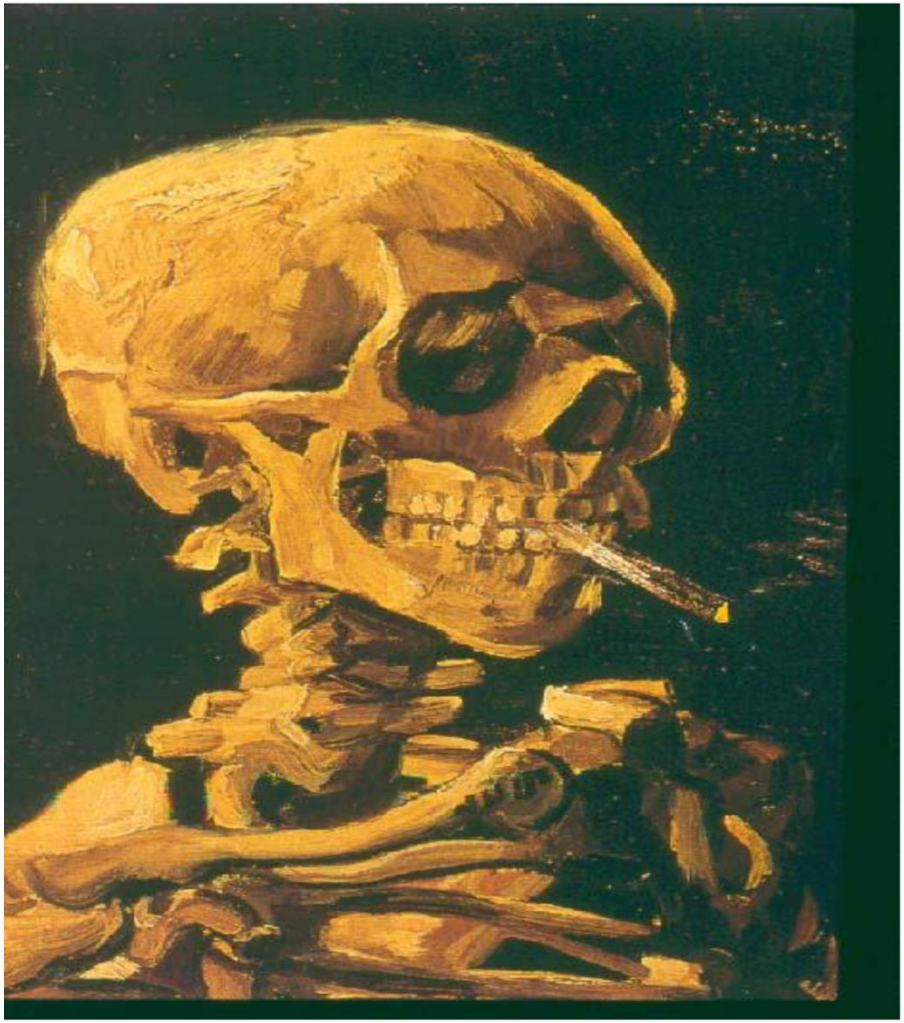
Indoor Air Pollution in China



Air pollution



Skull



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

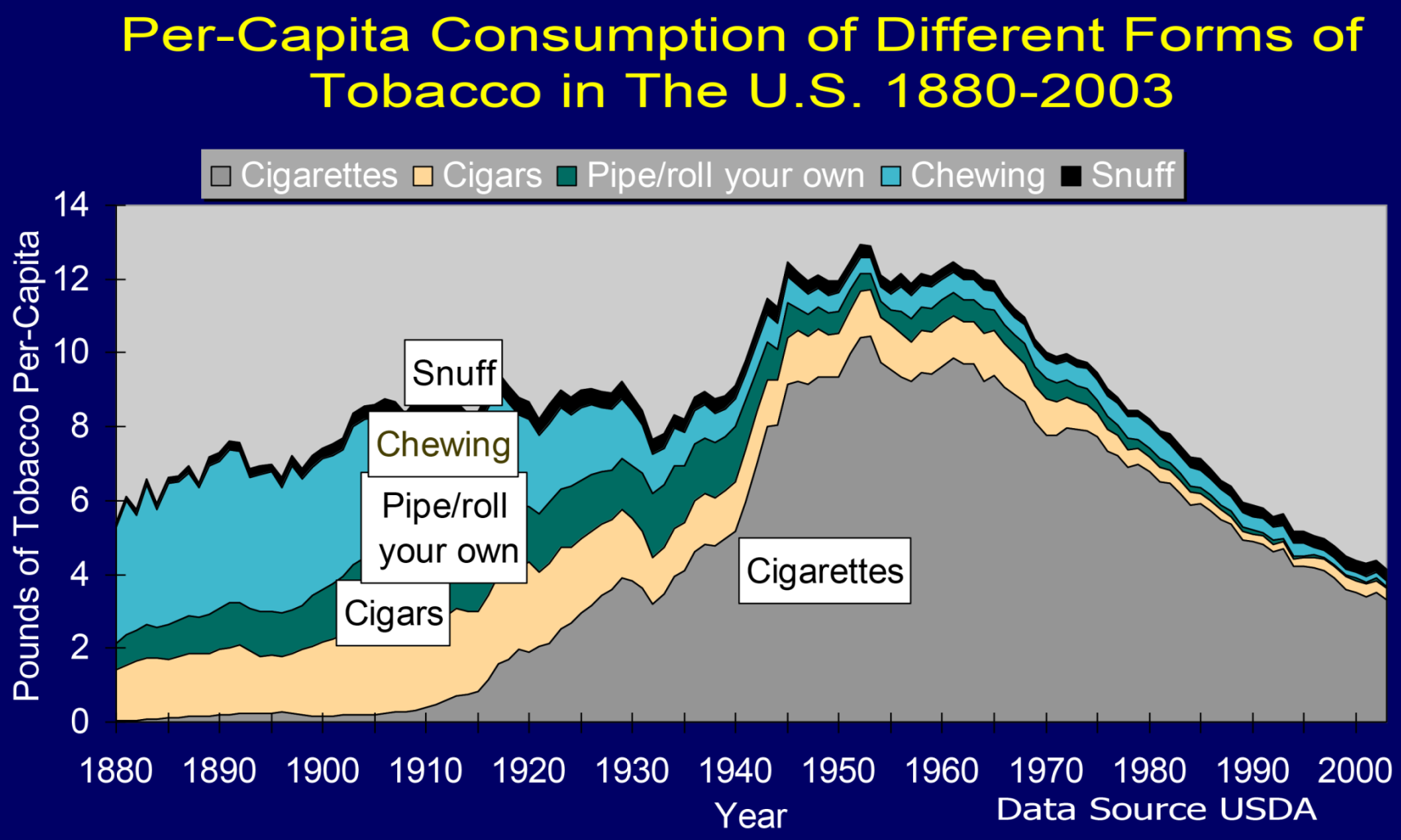
Medicare/ Medicaid > $10B/yr each

In spite of widespread knowledge of the health consequences of smoking

- rates in US adults, 15% (2014)

- individual smoking cessation very difficult

Tobacco consumption



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

What are alcohol-associated cancers?

Oral

Pharynx

Esophagus

Larynx

Liver

Ionizing Radiation

Leukemia (AML, but not CLL*)

Breast

Lung

Thyroid

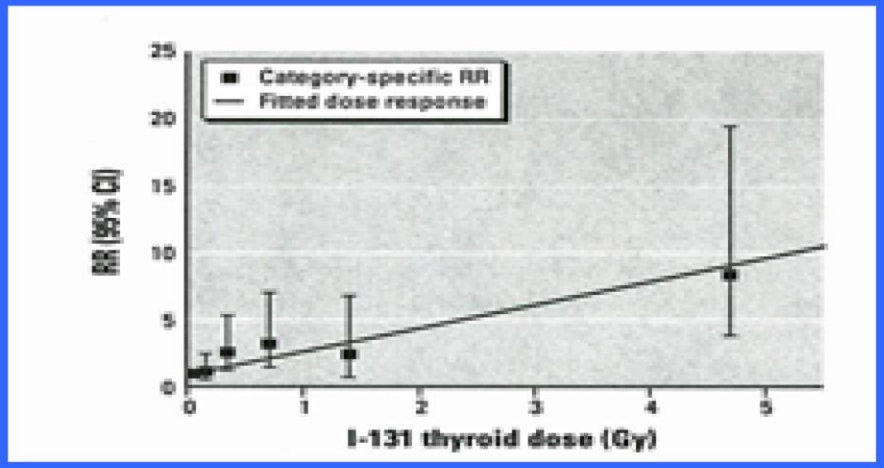
Head and neck cancer

Ionizing Radiation and Cancer

Type of XRT	Study Implicated	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	Thorotrast (Th-232)	Leukemia, Liver
Radionuclides	Spondylytis	Bones (Ra-224)
Occupation	Radium Dial painters	Bone
Occupation	Rad Technicians	Leukemia
Occupation	Chernobyl Cleanup	?
Environmental	Indoor radon	Lung

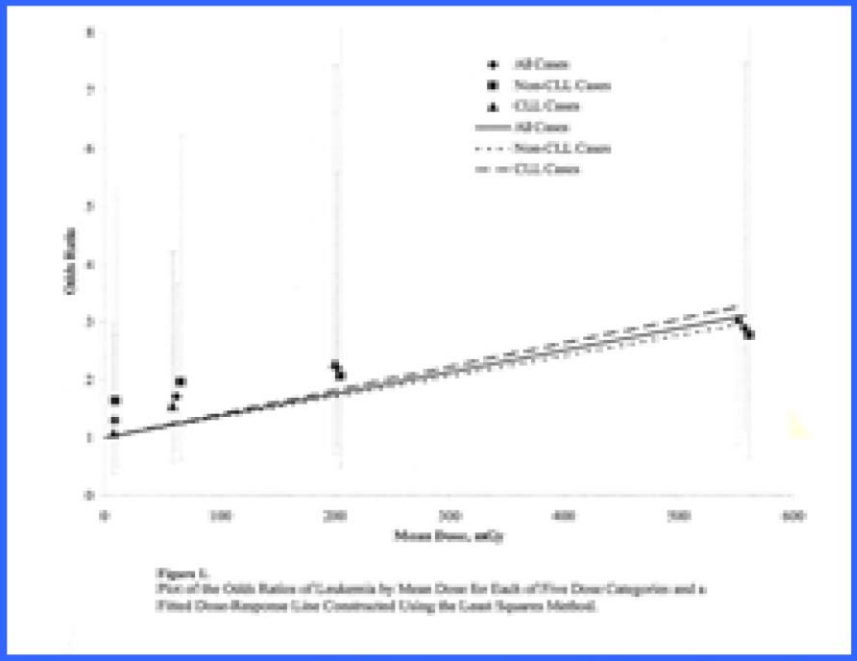
Cancer risk

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

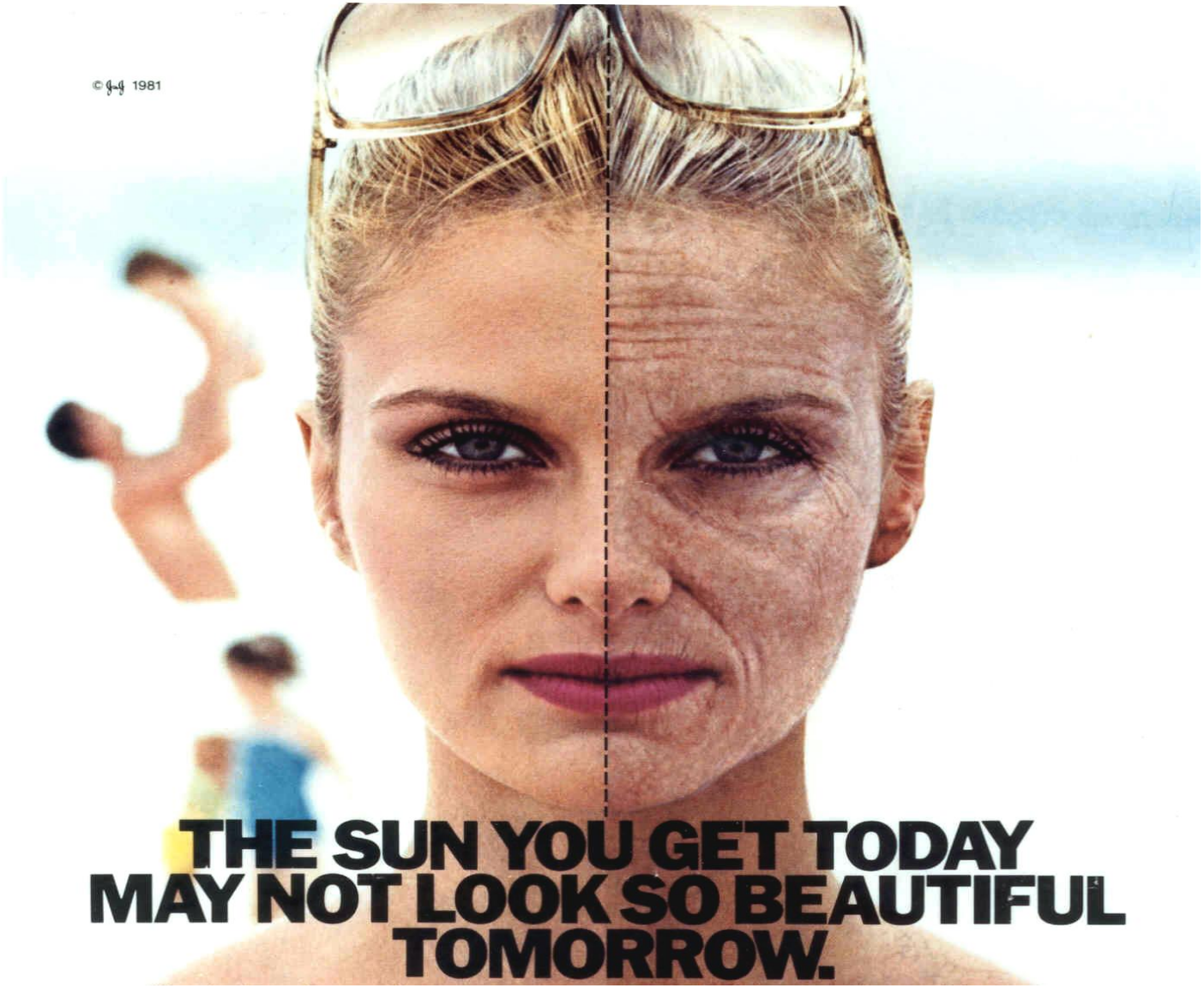
Skin cancer

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

Oropharynx cancer

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

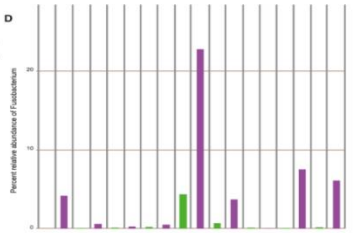
HPV type and antibody	Cases N=135 N (%)	Controls N=1599 N (%)	OR (95%CI)
		Specific	Strong
HPV16 E6	47 (34.8%)	9 (0.6%)	274 (110 to 681)
HPV16 E7	27 (20.0%)	178 (11.3%)	2.4 (1.5 to 3.9)
HPV16 E1	22 (16.3%)	63 (3.9%)	5.7 (3.2 to 10)
HPV16 E2	33 (24.4%)	72 (4.5%)	9.5 (5.7 to 16)
HPV16 L1	56 (41.5%)	329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

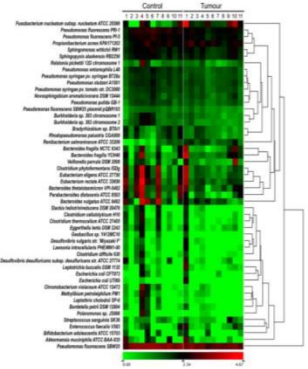
Kreimer et al, Manuscript under review

Colon cancer

Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma

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





Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma

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

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

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

- *foundations (introductory concepts)*
- *tools epidemiologists use*
- *accomplishments*
- ***challenges***
- *futures*

gaps on the ENVIRONMENT side

- *For many cancers, risk factors are unknown?*
- *For cancers where general 'cause', is understood, individual susceptibility is poorly understood*
- *How G and E work in concert is poorly understood.*
- *Some potential causes are poorly studied……*

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

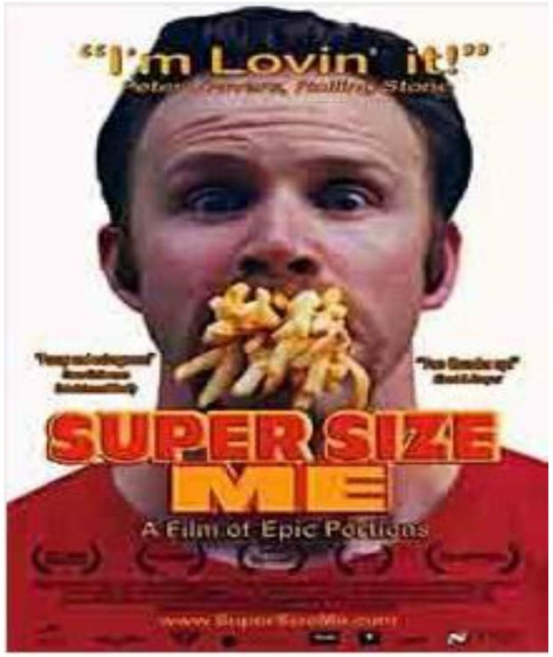
DIETARY RISK FACTORS

What are some dietary risk factors?

High calories
Low fiber
Micronutrients
Diet contaminants

Uterine
Colon
Lung (?)
Liver

Diet and lung cancer



Diet and lung cancer

Many questions…..

1.Failure of 'nutrient' based interventions (ATBC and beta carotene)

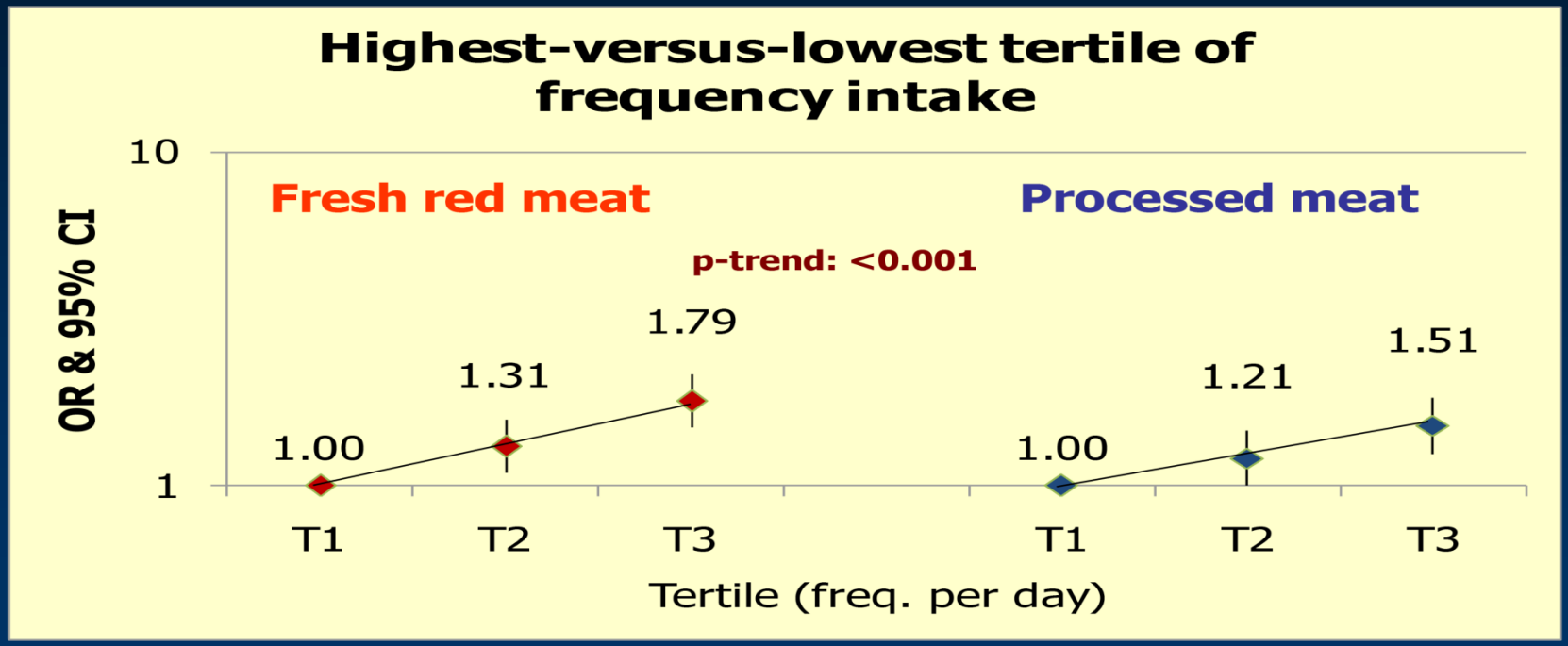
2. Role of 'processed' vs. 'traditional' food

3. Food?/nutrients?
How to best aggregate consumed items to identify risk or protection?

4. Meat and vegetable consumption

Diet and lung cancer

Higher frequency of fresh red and processed meat intake **increased** lung cancer risks



Lam et al, 2009, Cancer Res.

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)

Family history

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
Any family member	1430 213	1142 294	1.57 (1.25-1.98)

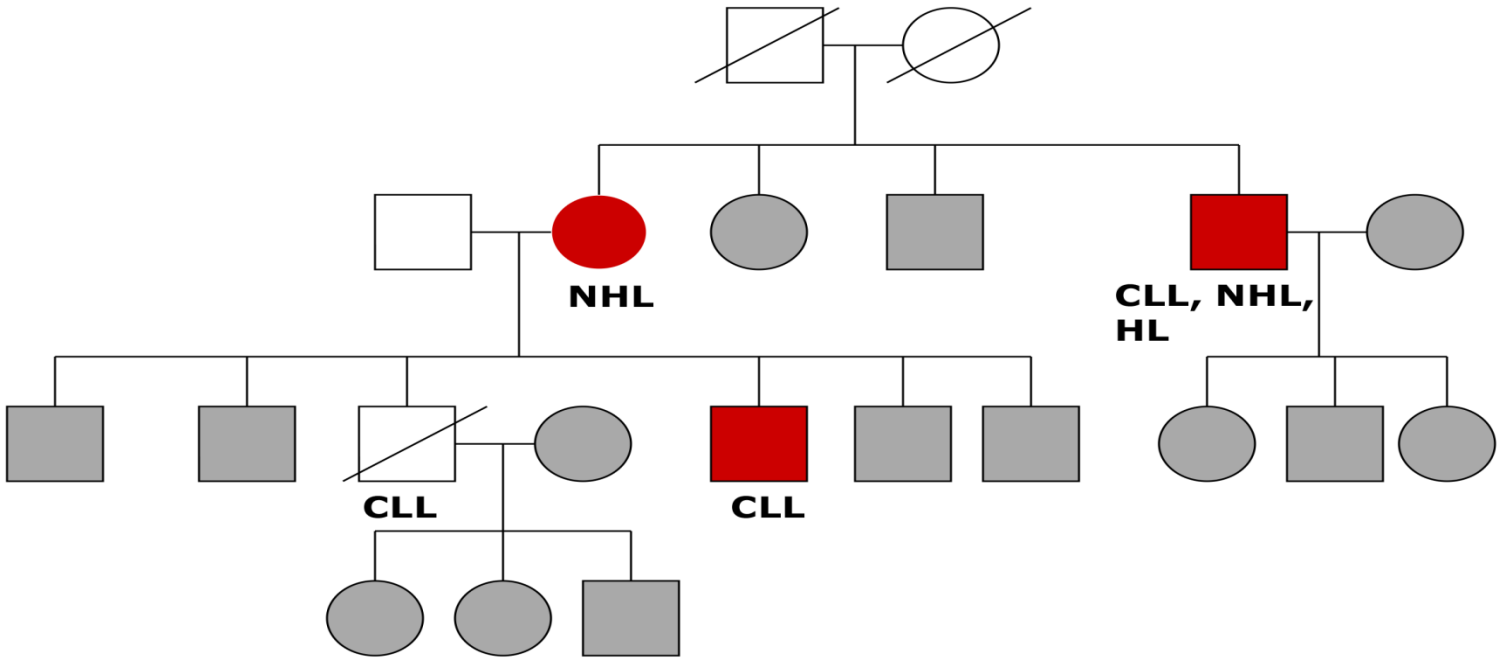
- Adjusted for 5 year age-interval, sex, residence (5 areas), education (5 categories), personal smoking status (packs/day, duration in years, and years since the last cigarette)
- Data on family history available on 2116 controls and 1946 cases

Squamous (32%), Adenocarcinoma (51%), 195 (12%), large (4.5%)

Gao et al 2009

Rare Genes

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



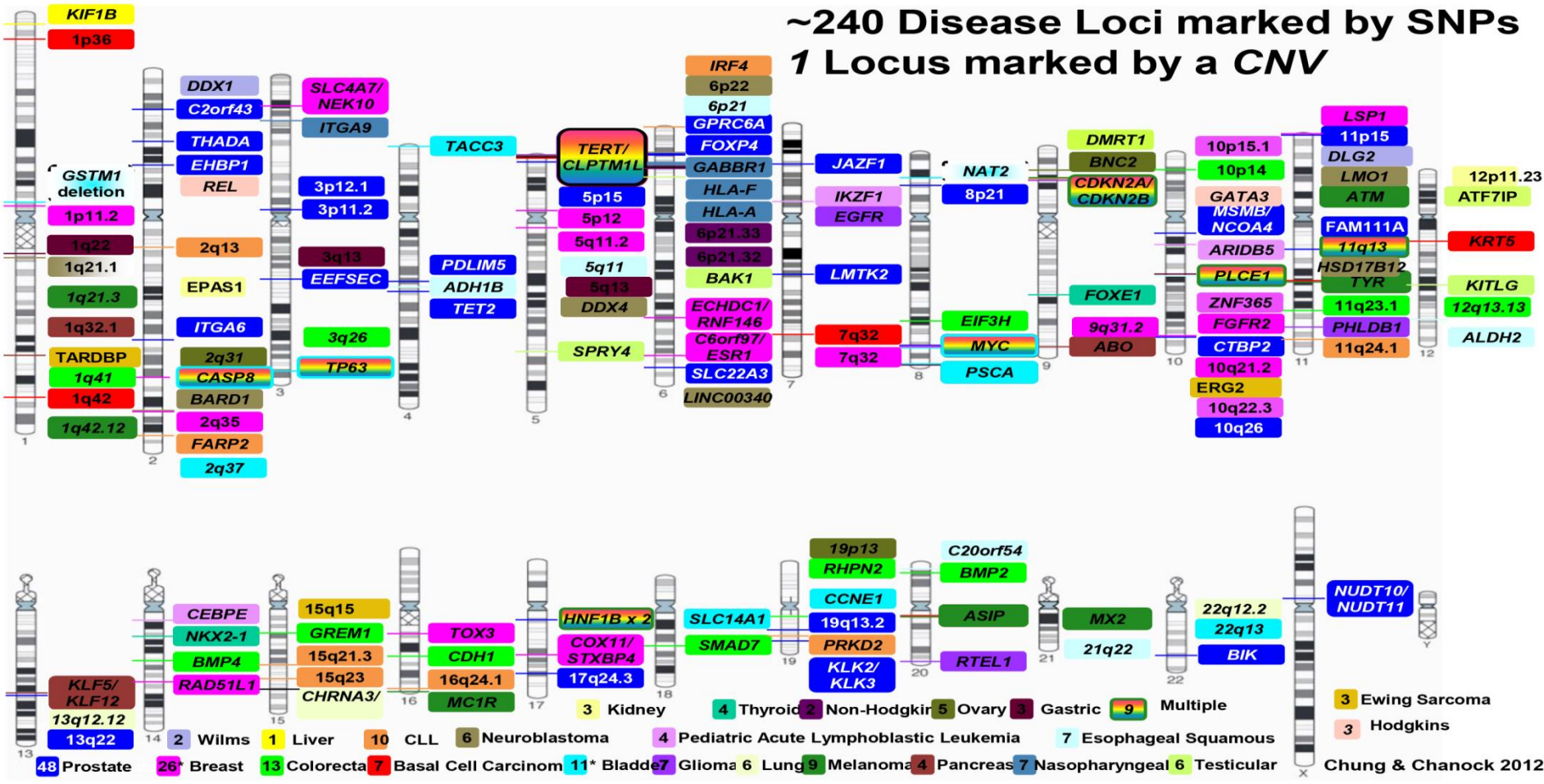
High risk kindreds like this likely harbor rare genes that confer high risk- if we knew what were they would be clinically important….

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



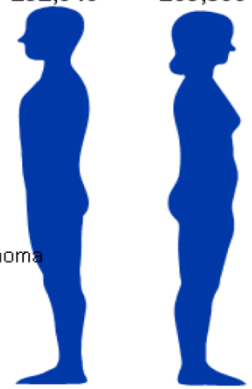
Lung cancer challenge

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



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

Traditional epidemiology

Traditional epidemiology

E → D

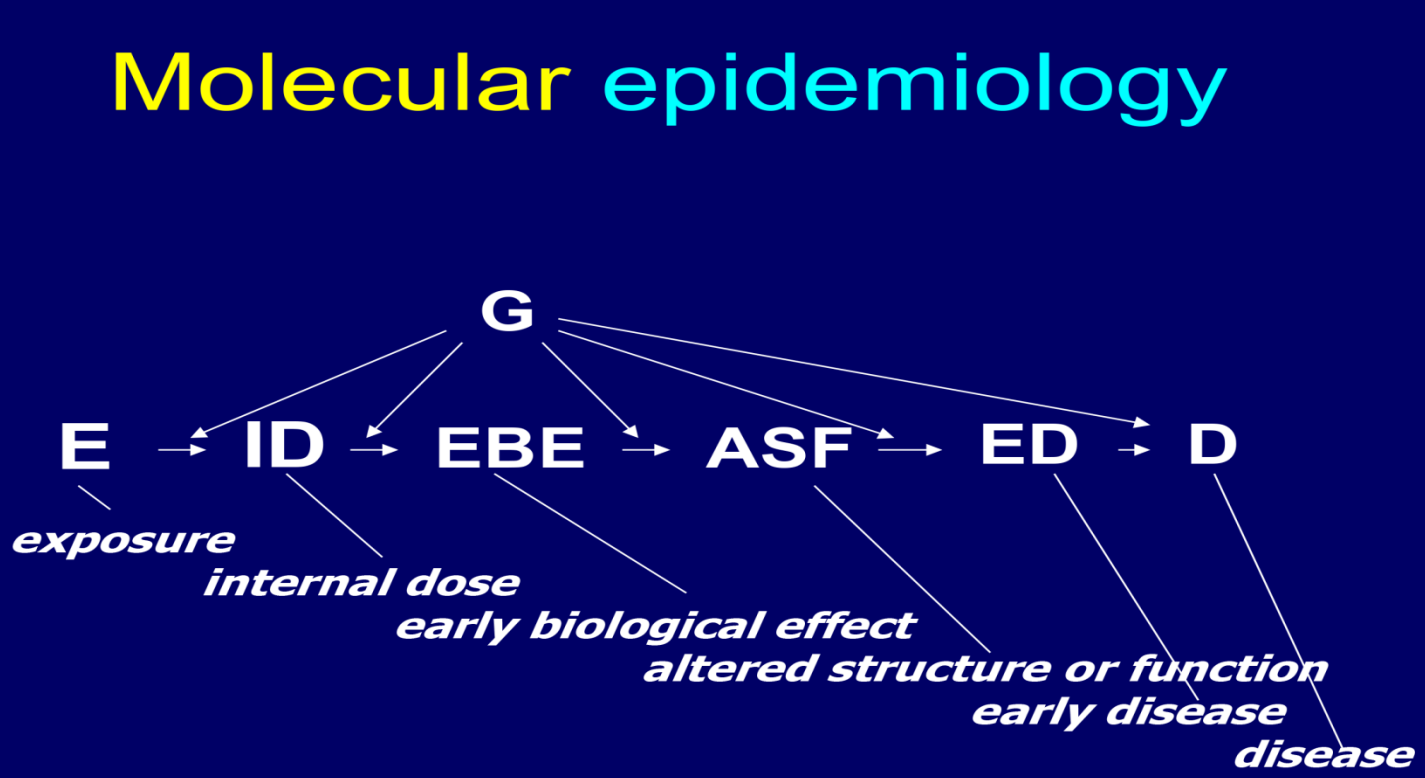
Exposure

Disease

Tobacco

Lung Cancer

Molecular epidemiology

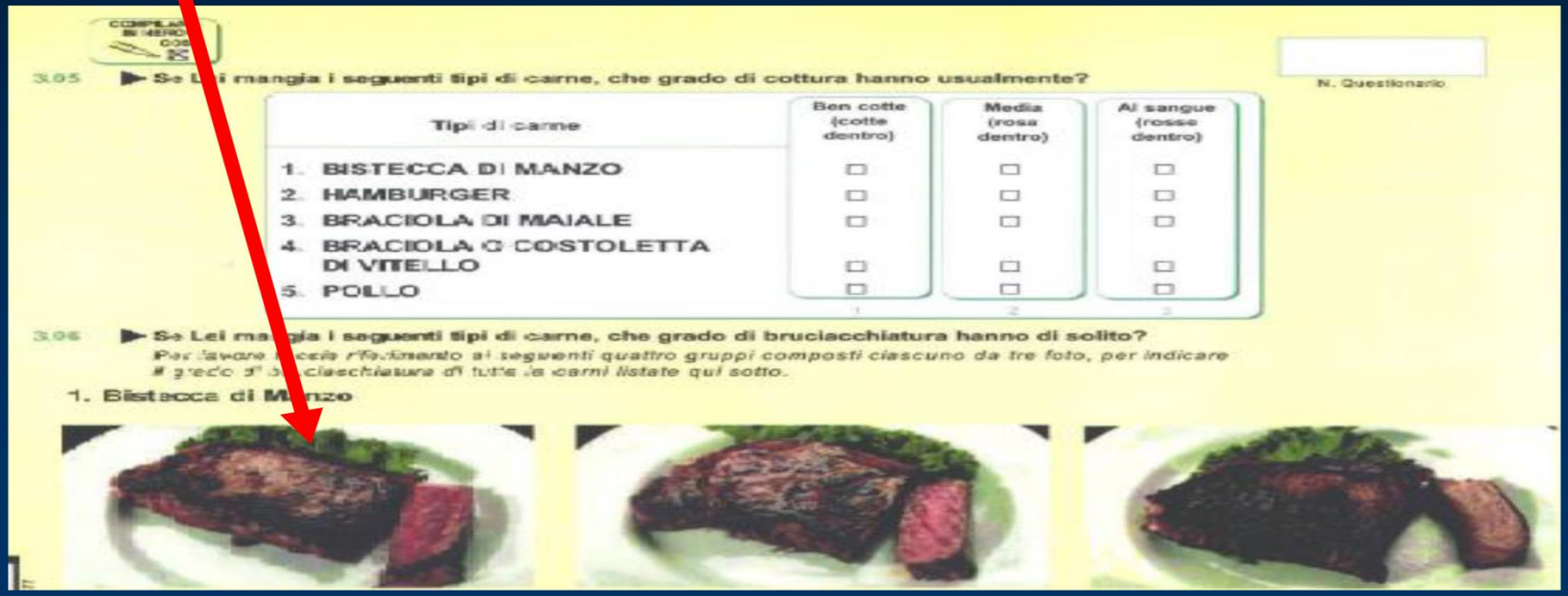


Lung cancer case control

EAGLE example

EAGLE example: molecular epidemiology approach

Epidemiology
'doneness module'



What has molecular epidemiology contributed?

3 examples……

1 HPV is the cause of 100% of cervical cancer

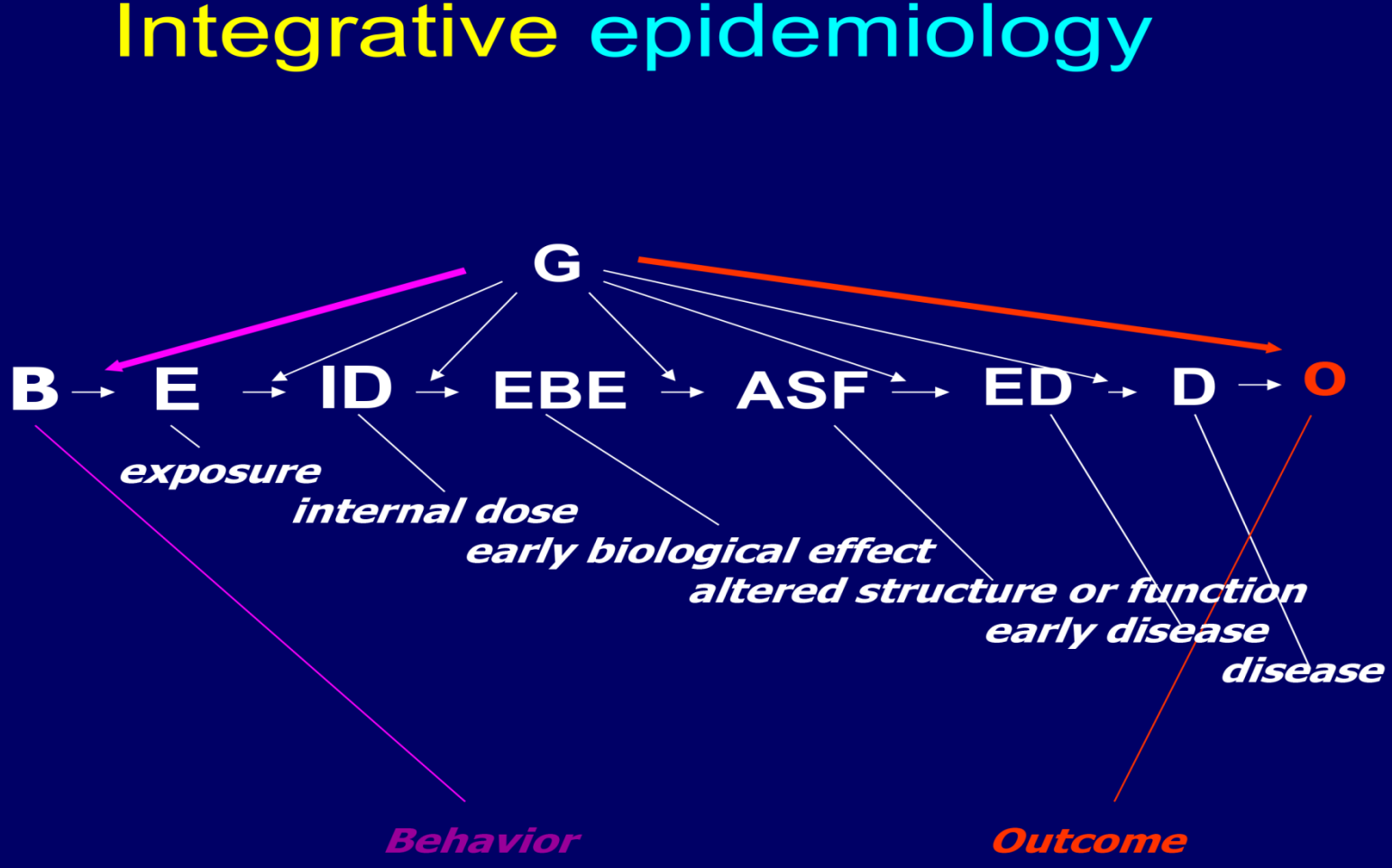
- prevention is possible (vaccine)

2 ‘Cutting down’ on smoking is ineffective

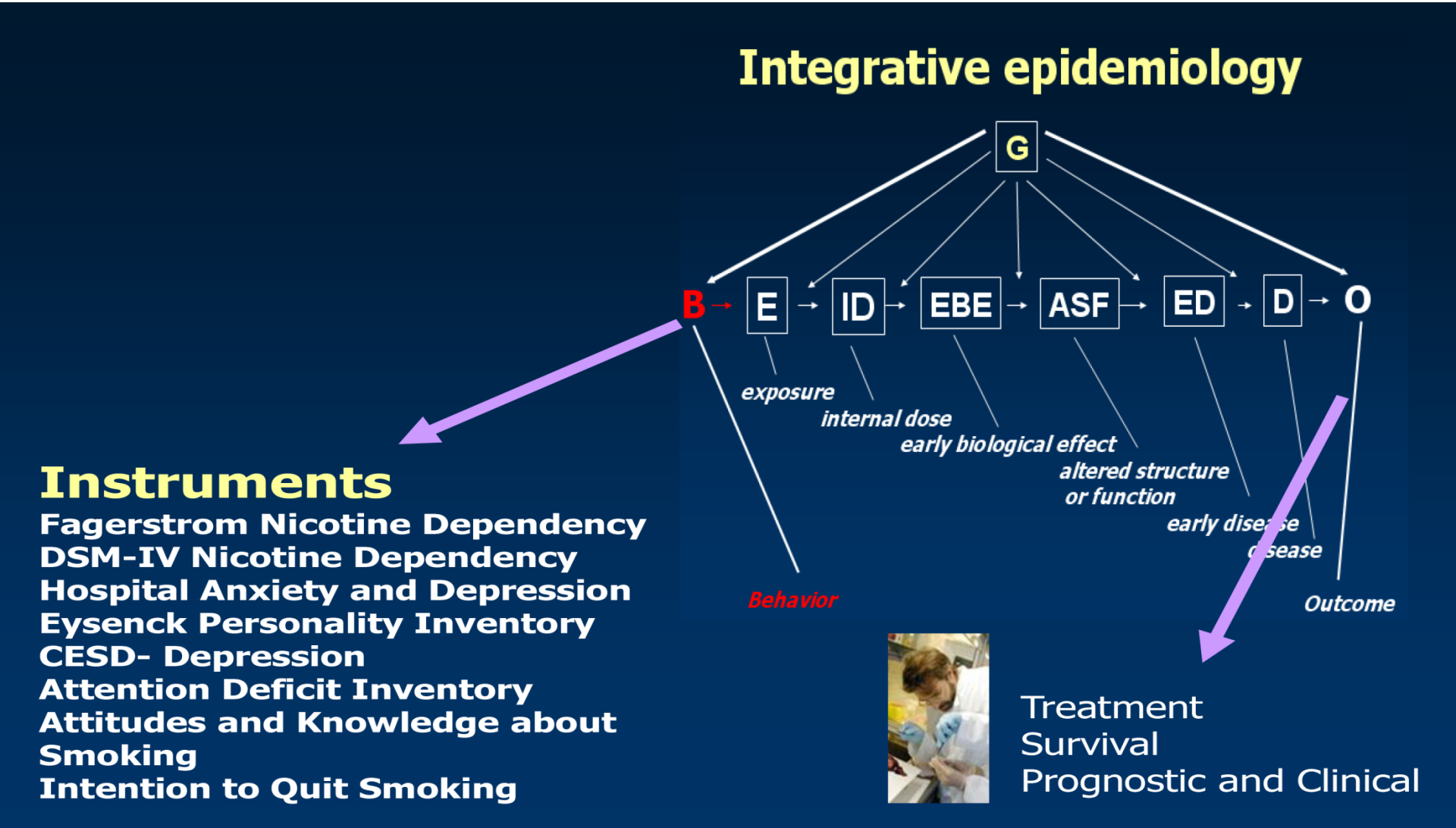
- biomarker studies show levels of carcinogens don’t decline

3. GWAS studies (100 + conditions) based on biospecimen collections…

Integrative epidemiology



Integrative epidemiology



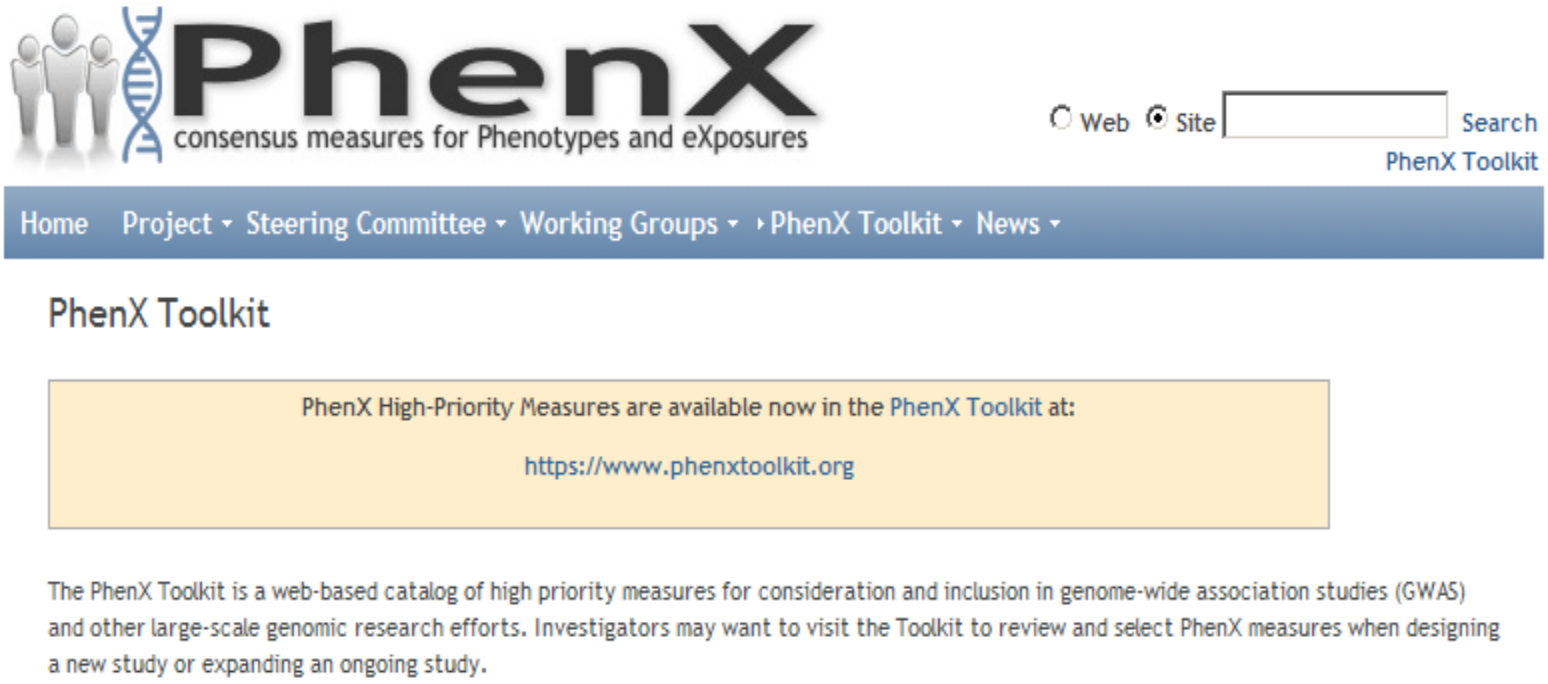
Consortia

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)

4.2+ million subjects followed in cohorts

PhenX…approach to expand data collection and reduce misclassification



Exposure: gaps in understanding

- Contribution of **environment** to cancer
  - Universally estimated to be substantial
  - Clear success for selected risk factors/cancers
  - **limited understanding** of extrinsic environmental risks for many cancers: prostate, leukemia's, brain, sarcomas, pediatric, lung in nonsmokers, etc.
  - International variation poorly understood
  - Many exposures that are thought to be important- are difficult or impossible to access

EXPOSURE AREAS

Exposure areas with candidate emerging technologies:

Sleep

Physical activity/inactivity

Vital signs- heart rate

Social factors

Location

Smoking

Weather/climate

Circadian variation

examples:

Sleep

Physical activity/inactivity

Vital signs- heart rate

Social factors

Location

Smoking

Weather

Circadian variation

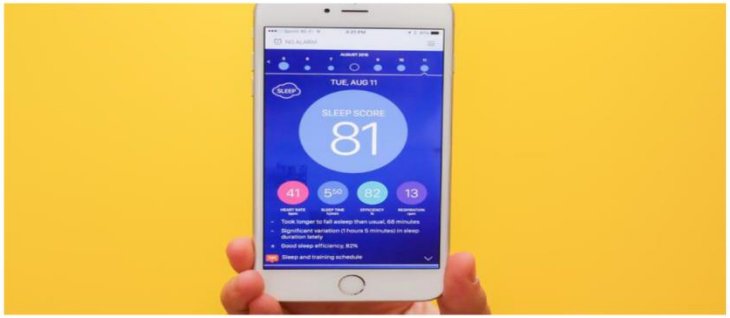
SLEEP

Sleep

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

Technologies

misfit



Technologies very rapidly evolving

EXAMPLES:

Sleep

Physical activity/inactivity

Vital signs- heart rate

Social factors

Location

Smoking

Weather

Circadian variation

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

examples:

Sleep

Physical activity/inactivity

Vital signs- heart rate

Social factors

Location

Smoking

Weather

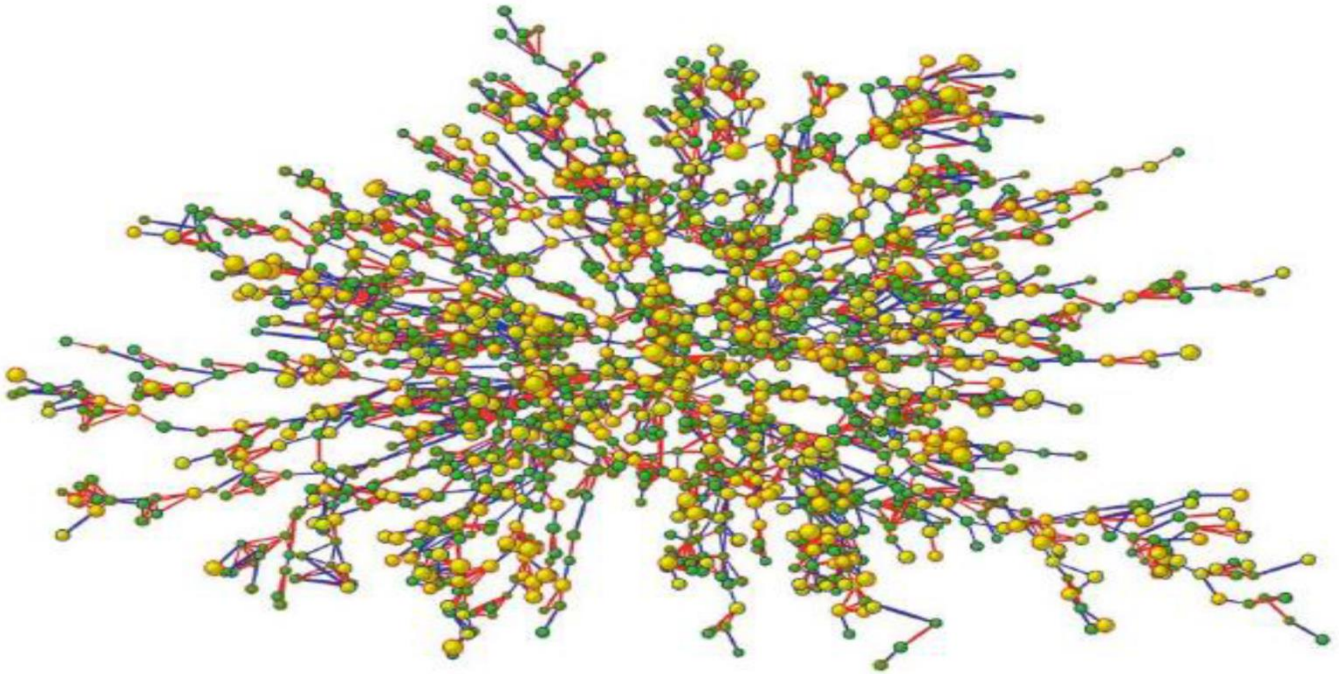
Circadian variation

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.

examples:

Sleep

Physical activity/inactivity

Vital signs- heart rate

Social factors

Location

Smoking

Weather

Circadian variation

Location

Local economic factors, SES
Employment types/occupational exposures
Zipcode
Health care access
Amount and sources of pollution
Degree and type of urbanization
Weather and climate (sun exposure/ozone)
Local travel/time travelling/type of travel
Characterize time and features of auto travel

examples:

Sleep

Physical activity/inactivity

Vital signs- heart rate

Social factors

Location

Smoking

Weather

Circadian variation

Help for Smokers

Help for smokers!!

Cancer help

Smoking help

Apps!

Teens

Tobacco info

examples:

Sleep

Physical activity/inactivity

Vital signs- heart rate

Social factors

Location

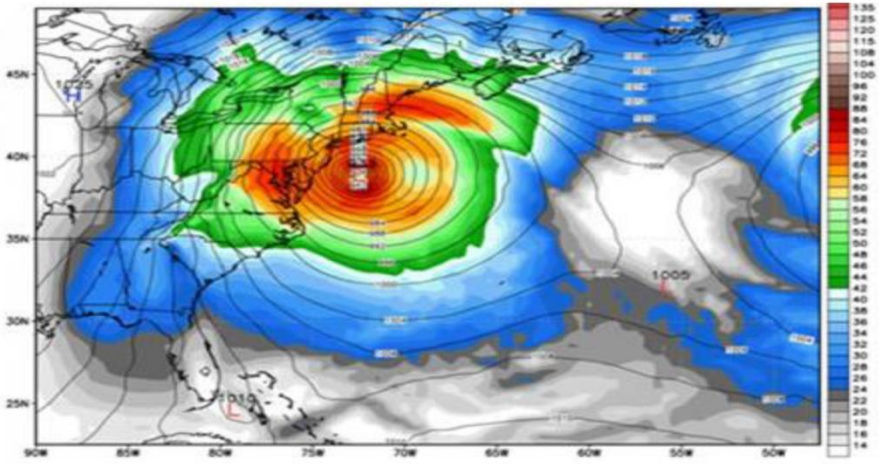
Smoking

Weather/Climate

Circadian variation

Climate and Cancer

Climate and Cancer



- Specific extreme weather events
- Pollution (air, water, land)
- Impact on food/nutrition
- Hydrology (water supply)
- Dominant air masses
  - mP, cP, cA, mT
- Sea level
- Salinity of water
- Biosphere
- Sun exposure (albedo, cloud cover)
- Insect vectors
- Degree and type of vegetation
- Climate zones (progression)

examples:
Sleep
Physical activity/inactivity
Vital signs- heart rate
Social factors
Location
Smoking
Weather
Circadian variation

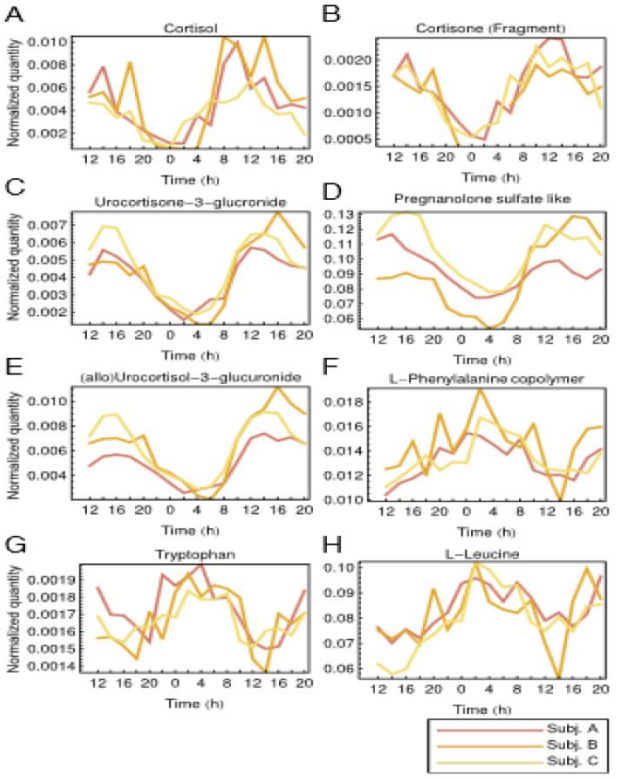
Circadian variation

Circadian variation

Internal body time is related to:
disease susceptibility
chronotherapy

Internal body time determined by 2 blood samples

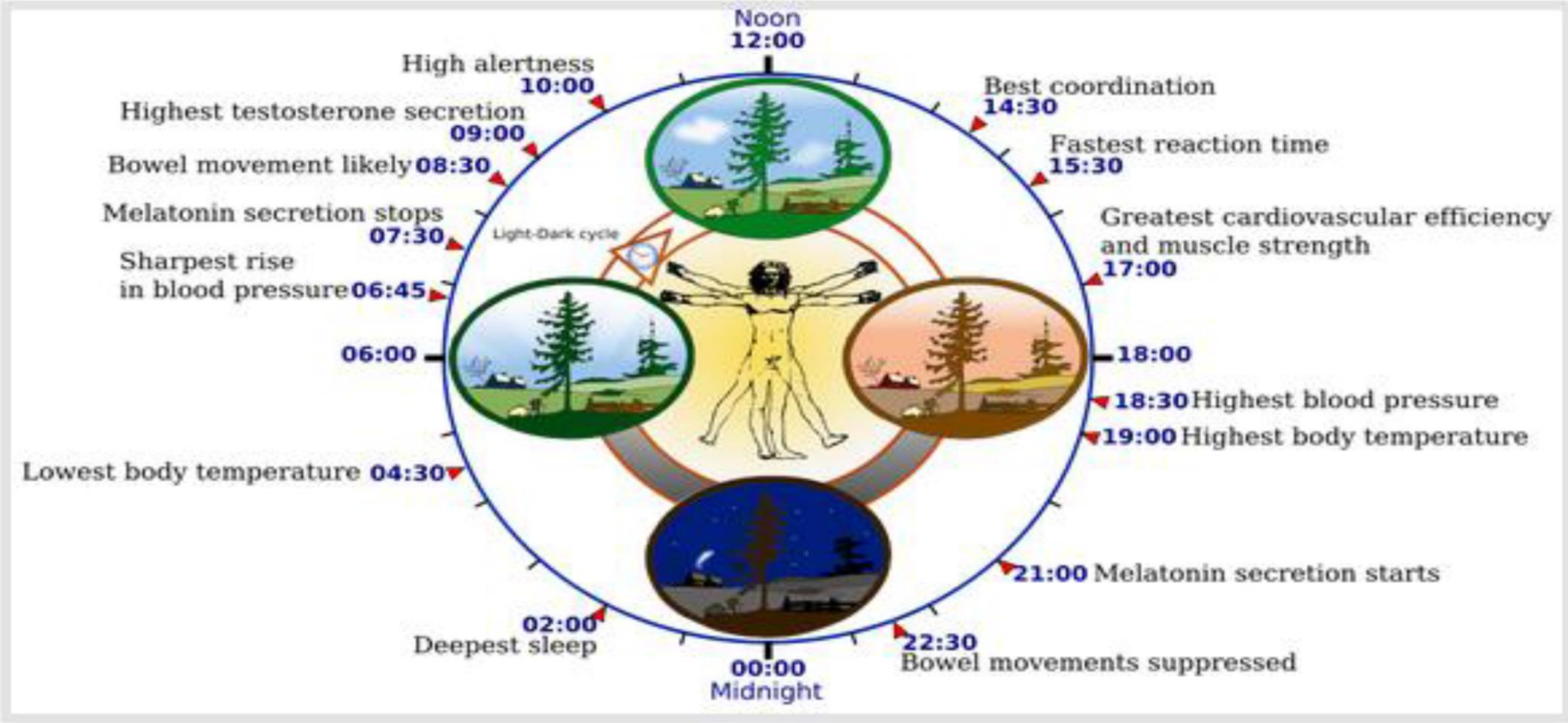
Also can be determined by **activity/sleep/food** cycles



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

Tracking daily activity

Tracking daily activity



Next step: **‘virtual’ cohort**

Sign up in diverse locations: hospital/healthy

Regional biorepository with tissue access

Link to pathology/medical records

Database

Consent, security, privacy protection

Disease ascertainment

Lifestyle, habits, hobbies, home, workplace

Regular electronic follow-up