Epidemiology

Epidemiology

Translational Research in Clinical Oncology

October 19, 2020

Neil Caporaso, MD
Occupation and Environmental Studies Branch,
Division of Cancer Epidemiology and Genetics,
National Cancer Institute
caporaso@nih.gov

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

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

Cigarettes and culture

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

Decades of change

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

Epidemiology

Epidemiology is concerned with human populations

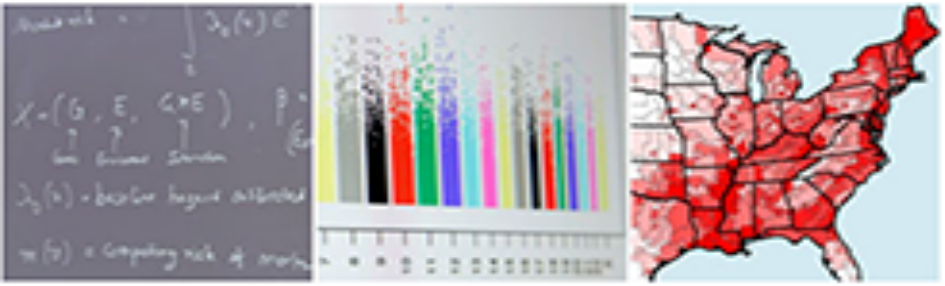
= *epi* (upon) + *demos* (the people) + *logia* (talk about)

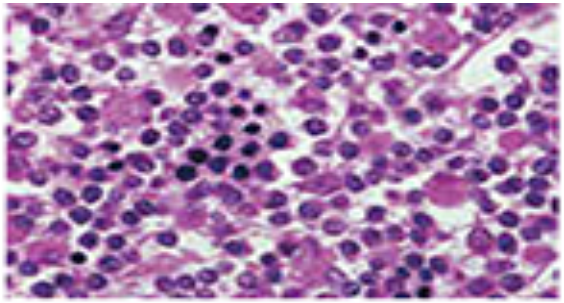
OBSERVATIONAL science (like astronomy, evolutionary biology)

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

Potter, 2001 Nature Genetics

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 → Cancer **ETIOLOGY**

Genetic Epidemiology Branch

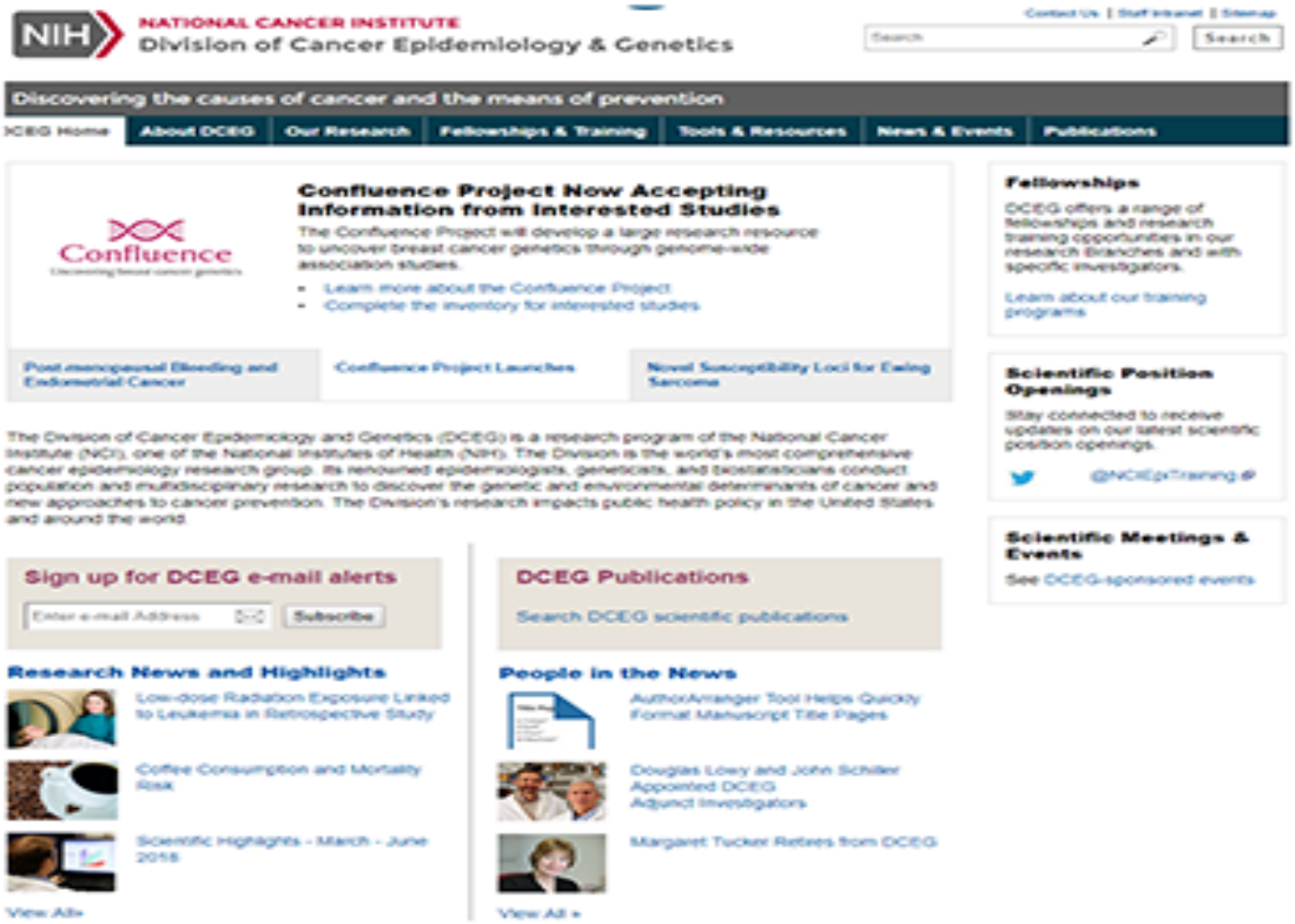
Other Branches focus on
Nutrition, Hormones, Infection,
Occupation, Statistics, Radiation

DCEG

NIH

NCI

DCEG



Collaborations

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

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

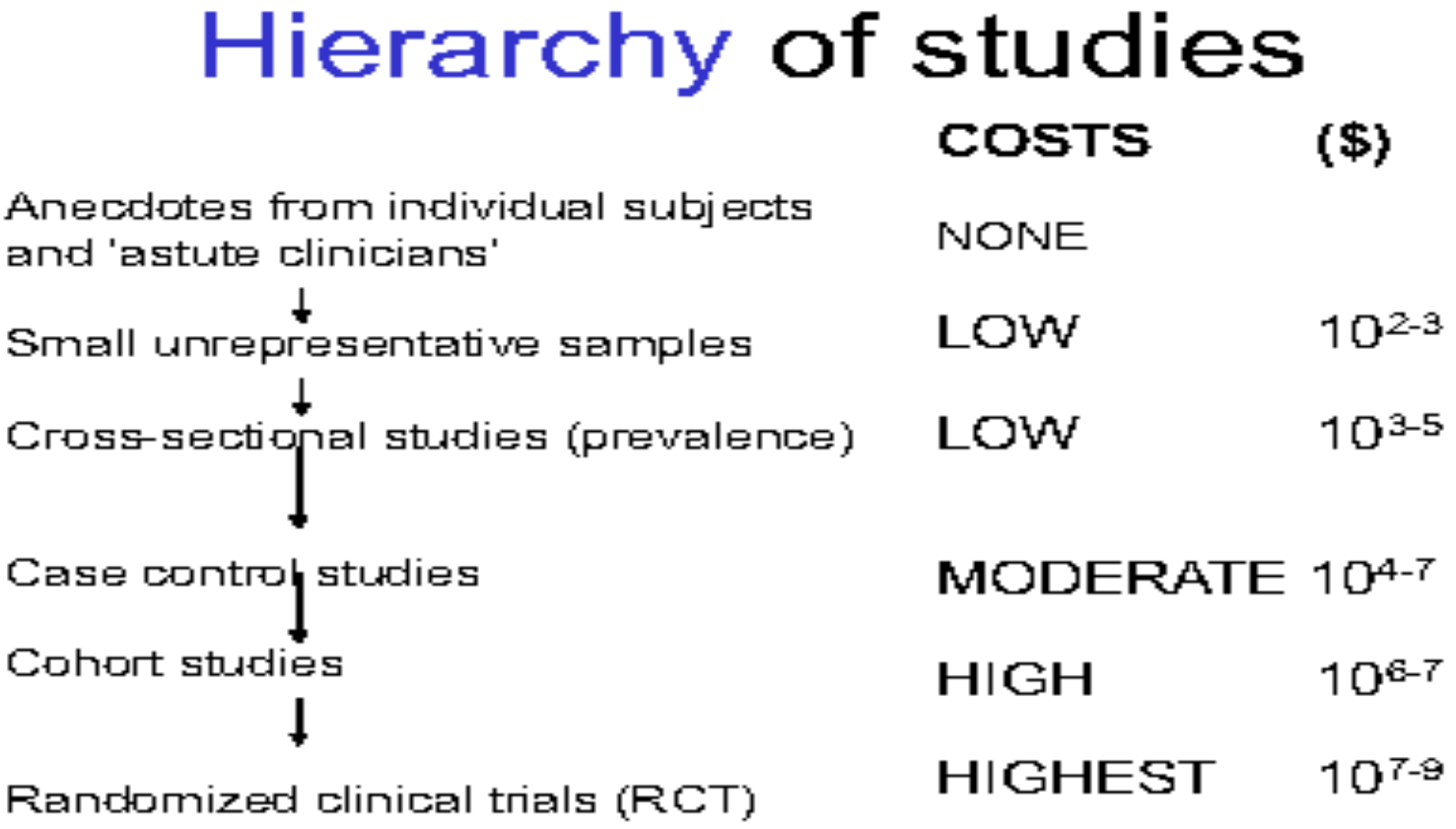
Goals of epidemiology

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

Potter. 2001 *Nature Genetics*

Hierarchy of studies



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

[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.)

Participation rate. Can you explain

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%

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 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)

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

A Population Perspective on Cancer

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

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

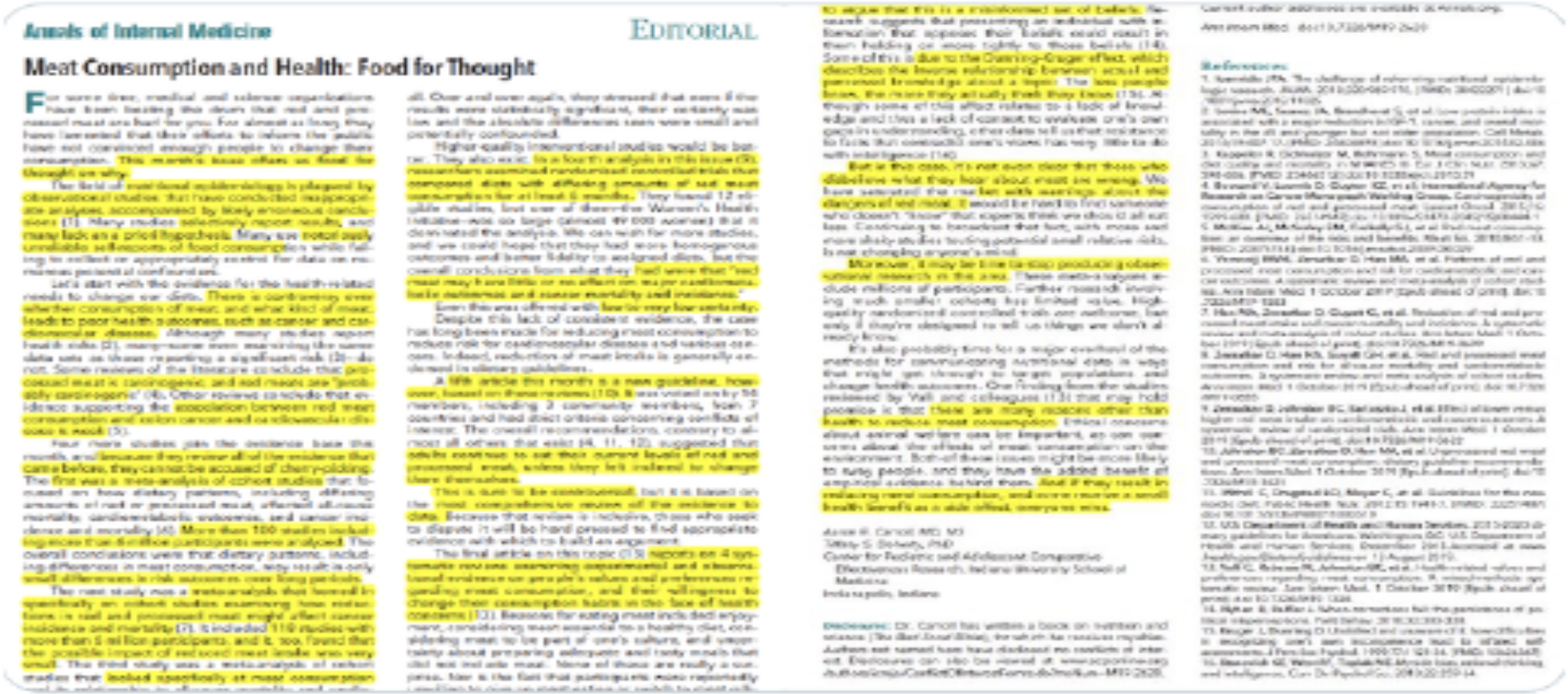
Considerations that call into question **low risks**:

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…."

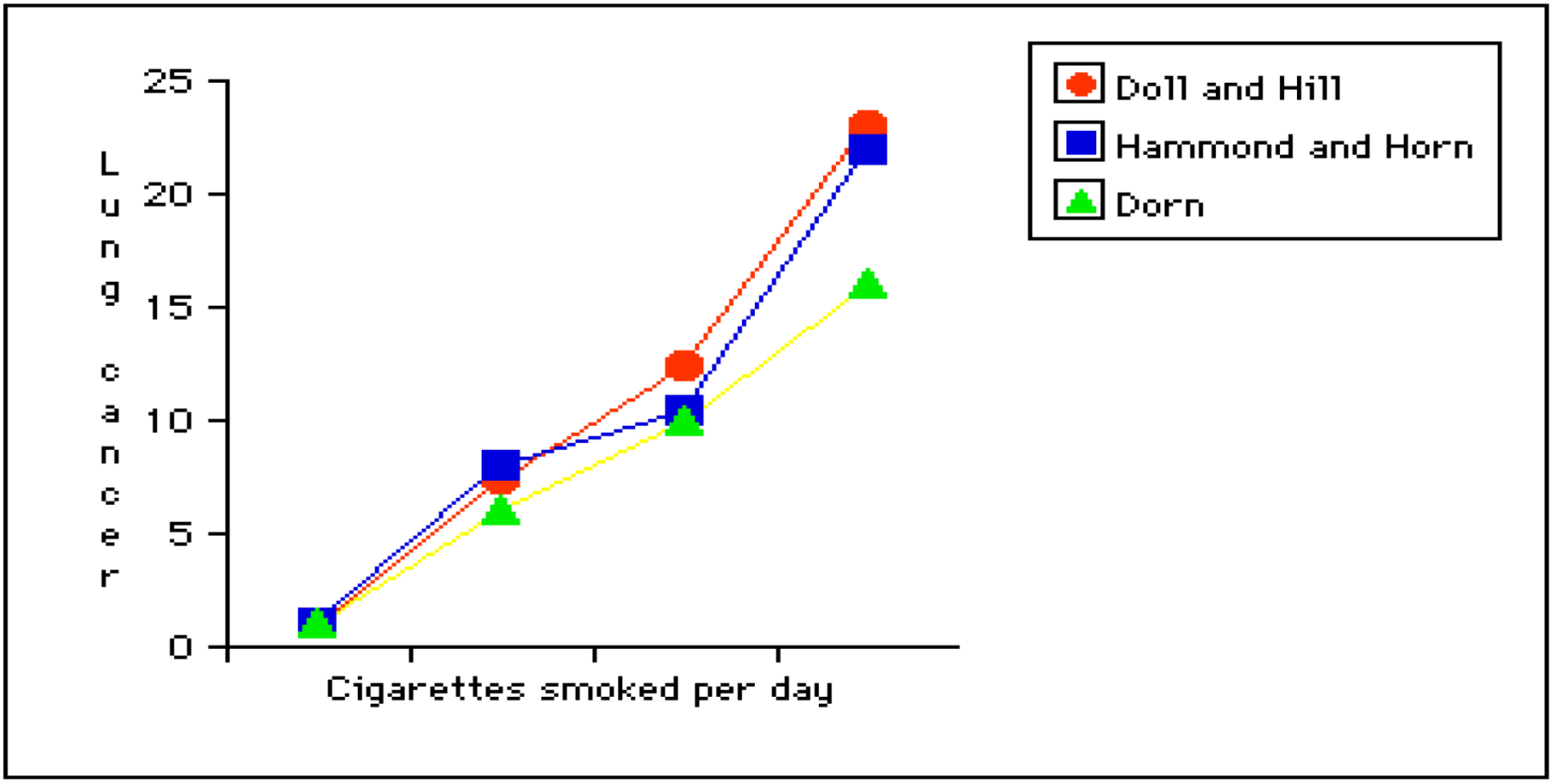


Annals of Internal Medicine

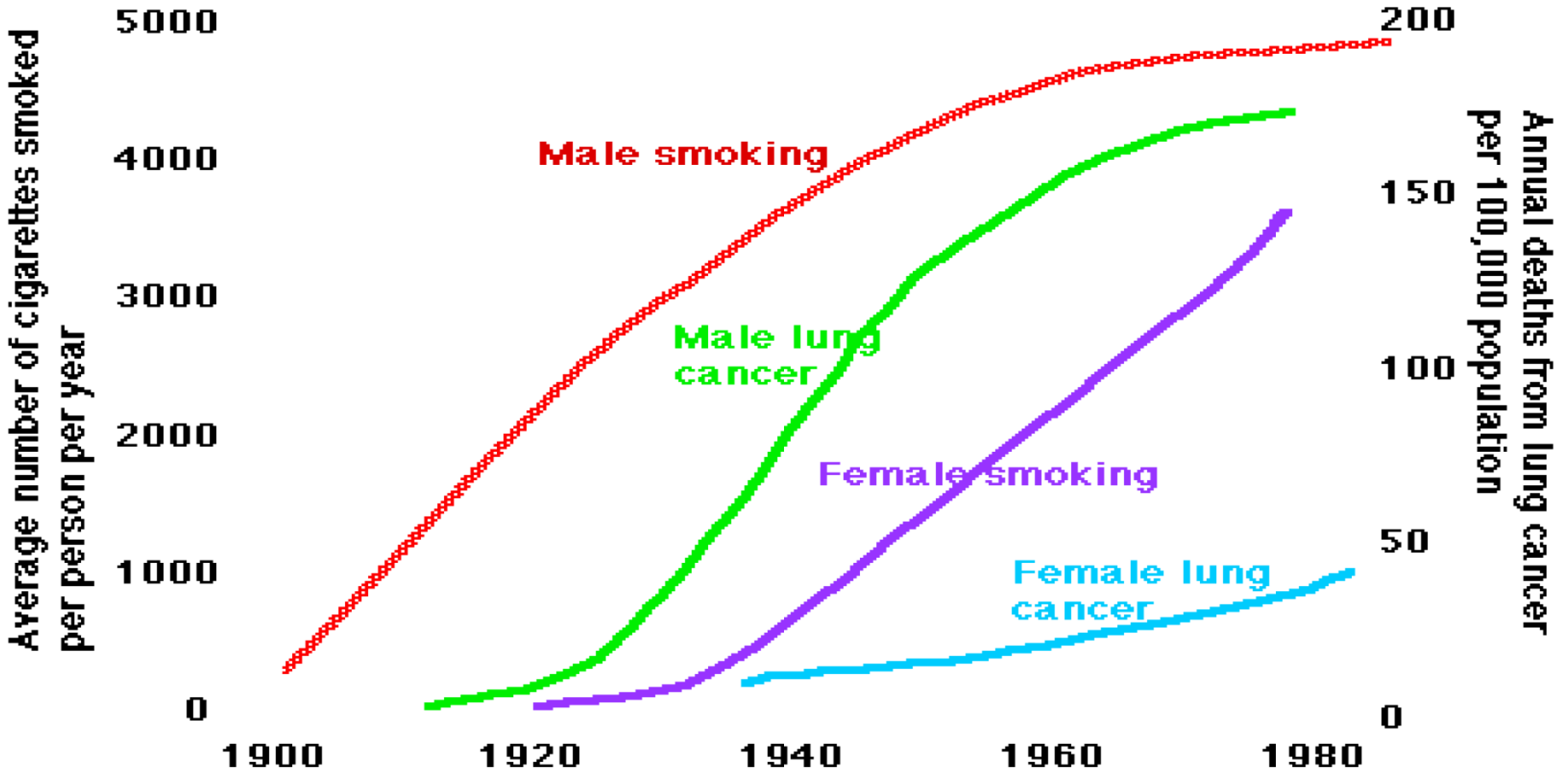
EDITORIAL

Meat Consumption and Health: Food for Thought

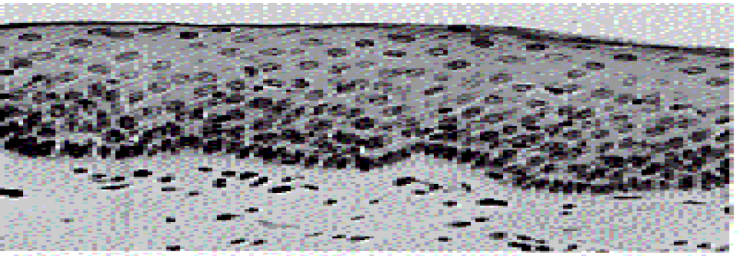
Lung Cancer and smoking

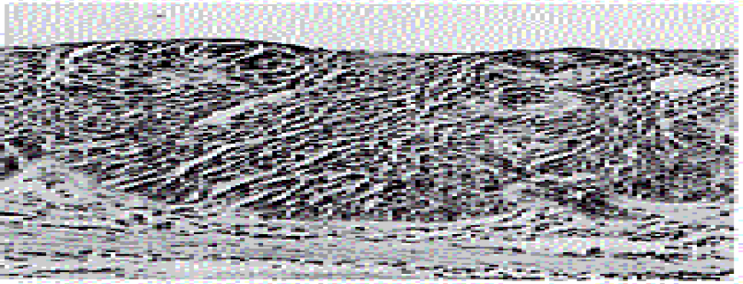


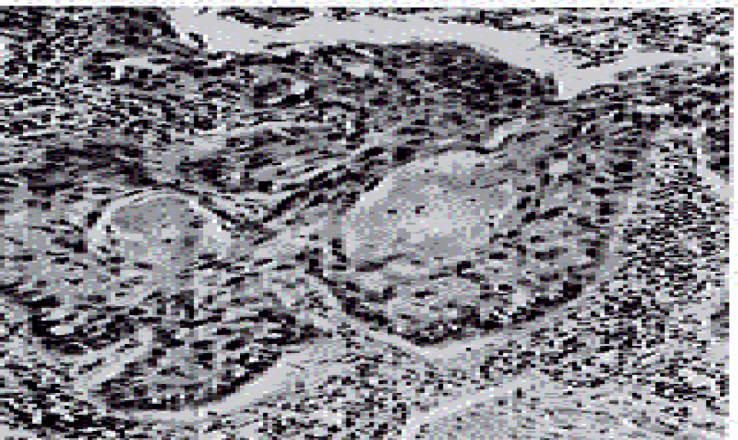
Lung cancer

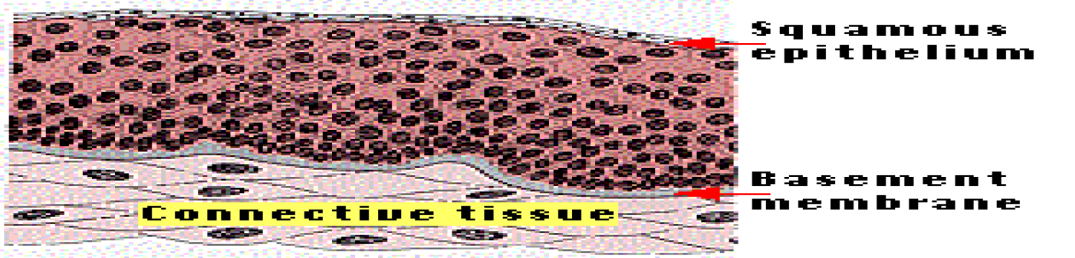

Average number of cigarettes smoked per person per year
5000
4000
3000
2000
1000
0
1900
1920
1940
1960
1980
200
150
100
50
0
Annual deaths from lung cancer per 100,000 population
Male smoking
Male lung cancer
Female smoking
Female lung cancer

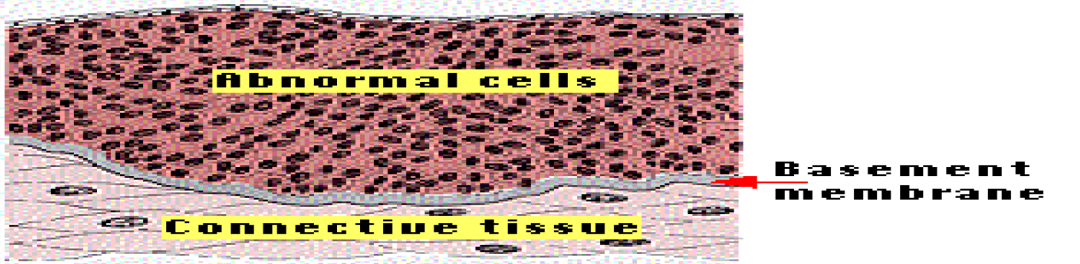
Lung cancer

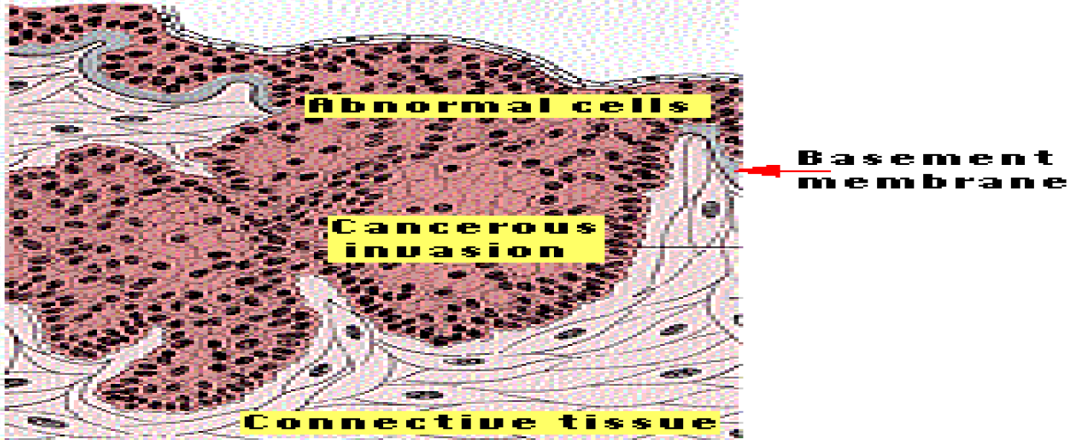




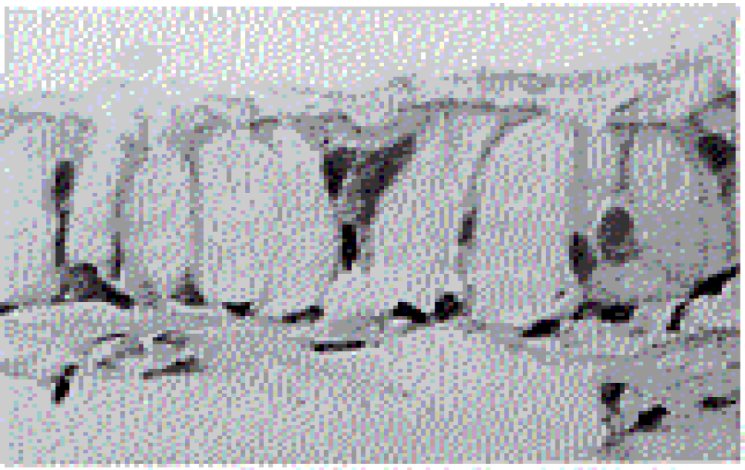


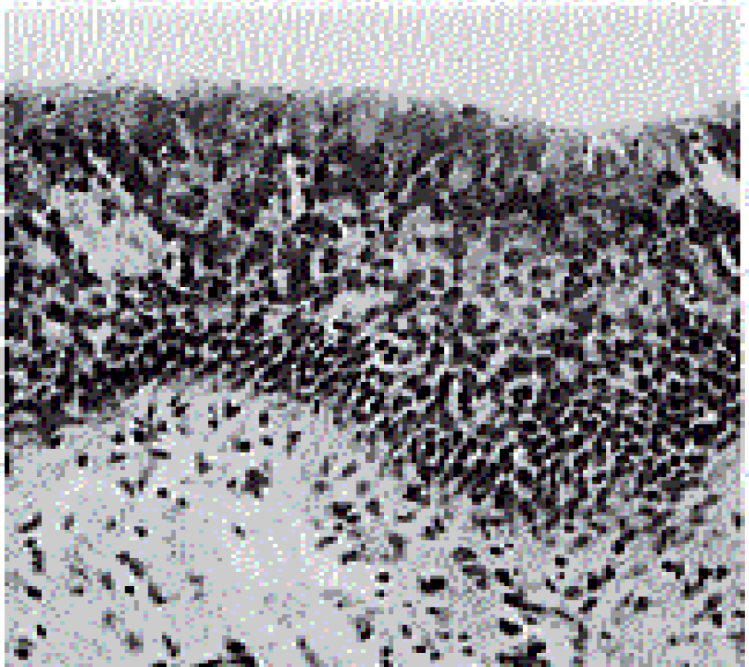

Squamous epithelium
Basement membrane
Connective tissue

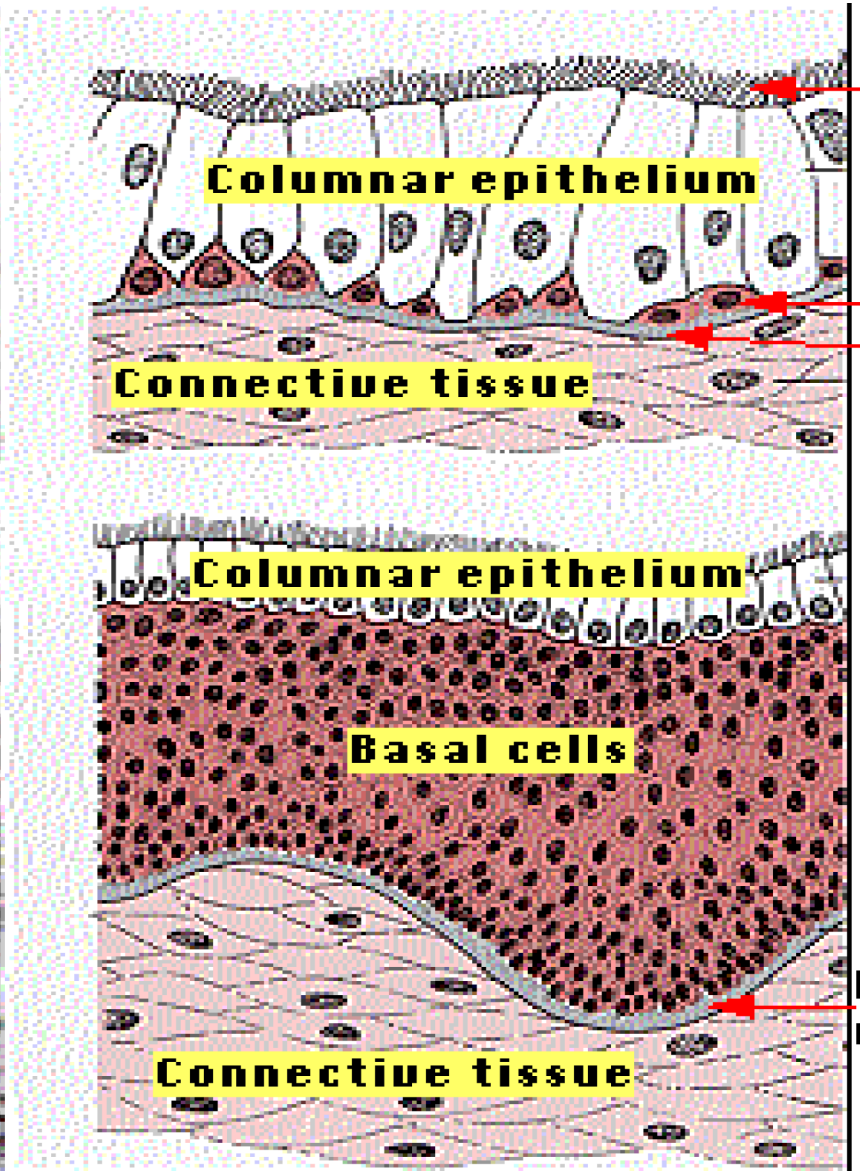

Abnormal cells
Basement membrane
Connective tissue


Abnormal cells
Basement membrane
Cancerous invasion
Connective tissue

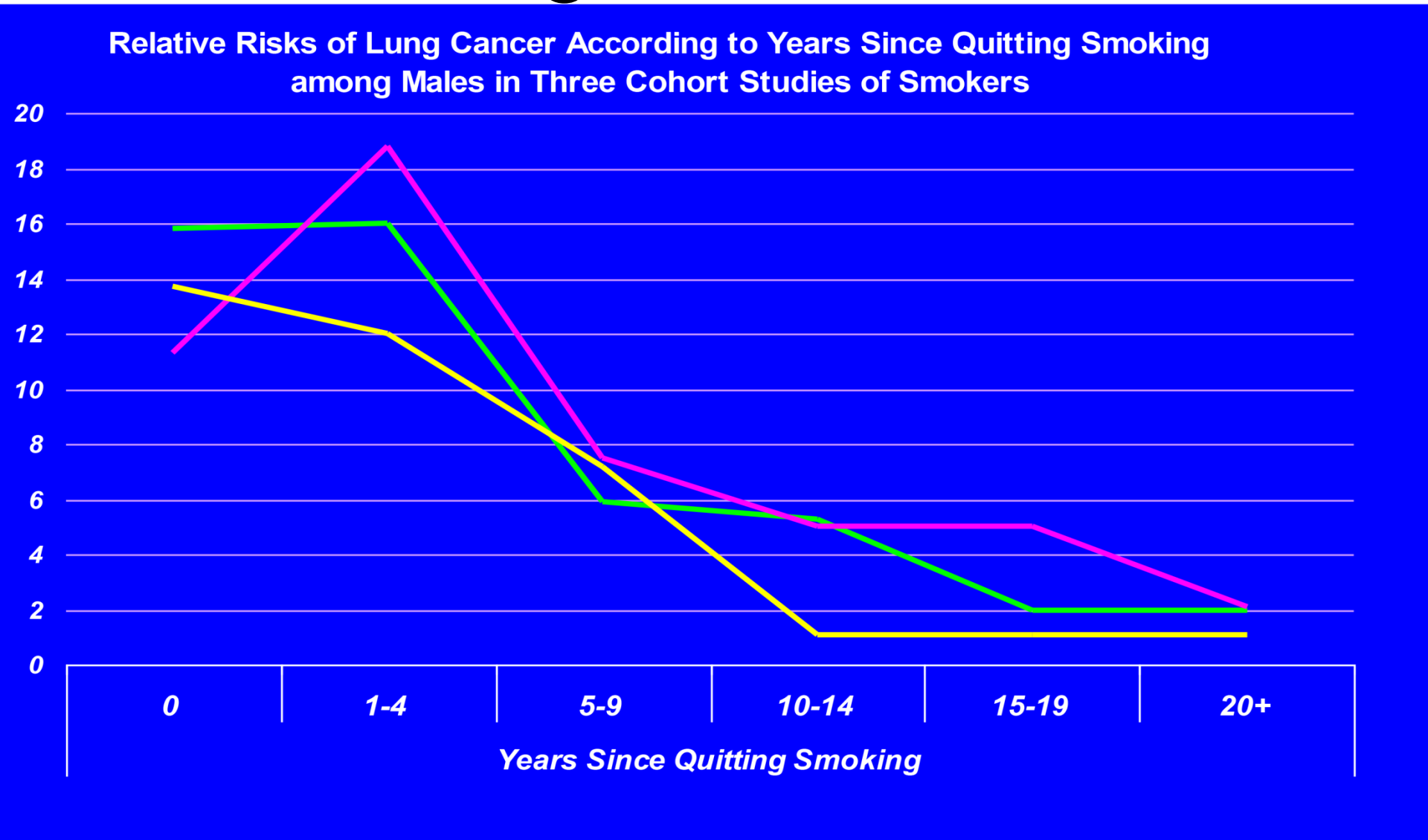
Lung cancer






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

Lung cancer risks



Population perspective

A Population Perspective on Cancer

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

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-13:978-0-19-514963-6, Oxford University Press, New YorkNew York (Telephone: 800-445-9714, FAX: 919-677-1303, E-mail: customs.us@oup.com), 2006, 1392 pp., $230.00 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?*
- *What has epidemiology accomplished?*
- *What are some classic controversies?*
- *What can go wrong?*
- *What next?*

Classic controversies

A Population Perspective on Cancer

- *What is epidemiology?*
- *What has epidemiology accomplished?*
- ***What are some classic controversies?***
- *What can go wrong?*
- *What next?*

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

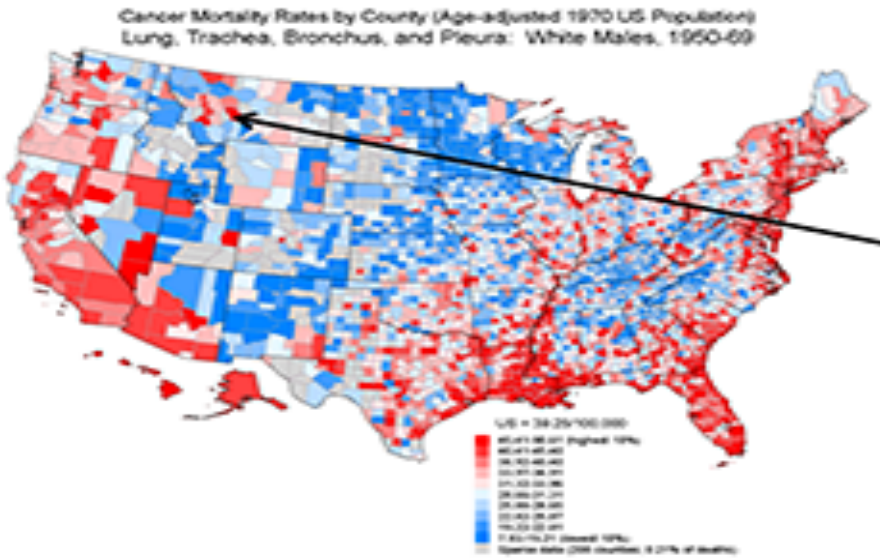
Cancer rates

International Variation in Cancer Rates

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

Cancer maps implicate exposures



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

Causes of cancer and potential reduction in burden through prevention

CAUSE	%Caused	DeathsUSA	%Reduction possible
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

Science Tanslational Medicine 28 Mar 2012. Graham Colditz et al.

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

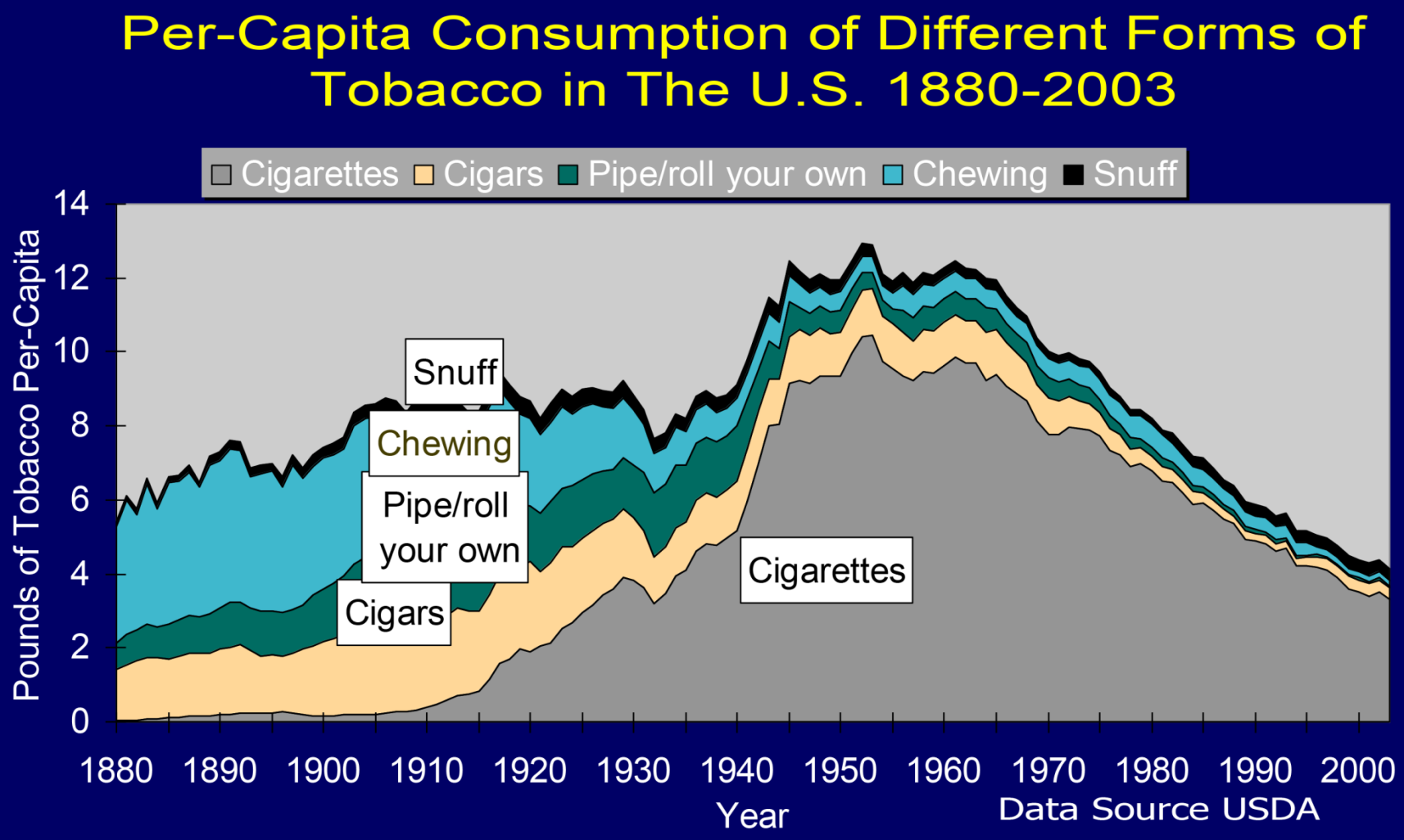
tobacco related disease costs

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



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:

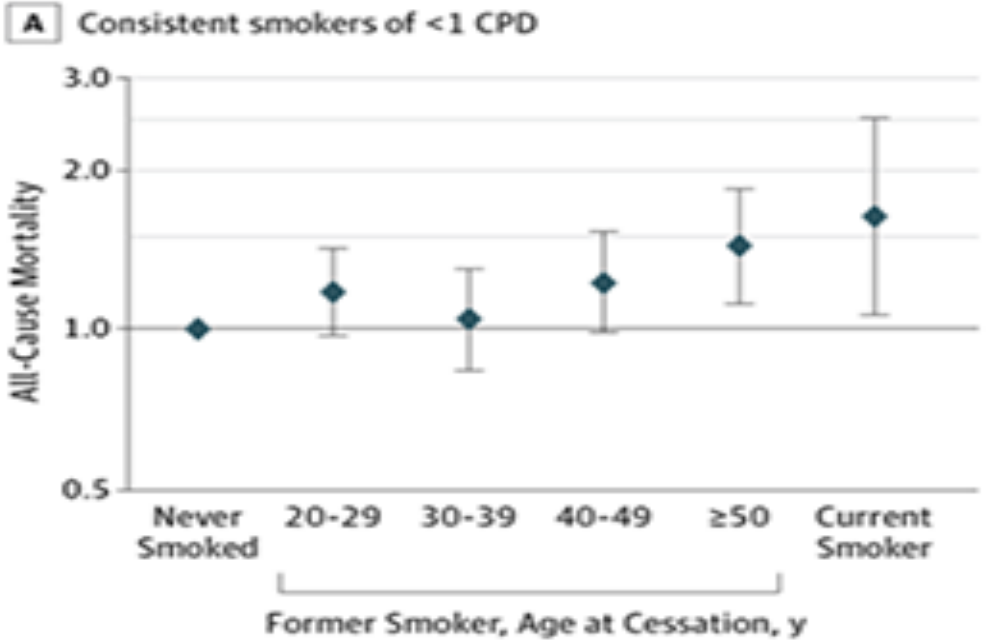
African Americans, Hispanics
Higher education
Young smokers
Started smoking later

Less dependent smokers

Reyes-Guzman....Caporaso. Cancer, Epidemiology, Biomarkers, Prev. 2016

Smoking increases mortality

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



JAMA Int Med, 2016

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.

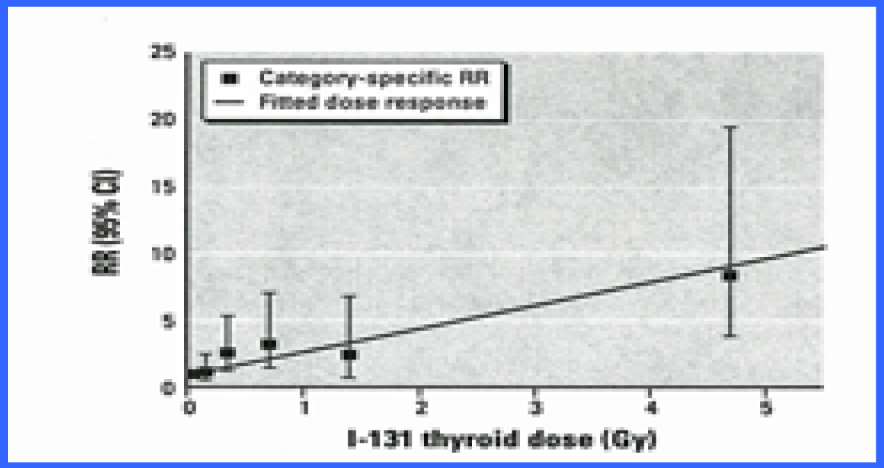
From the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD (N.D.F., Y.P., C.C.A., R.S.); and AARP, Washington, DC (A.R.H.). Address reprint requests to Dr. Freedman at the Nutritional Epidemiology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

Ionizing Radiation

Leukemia (AML, but not CLL*)
Breast
Lung
Thyroid
Head and neck cancer

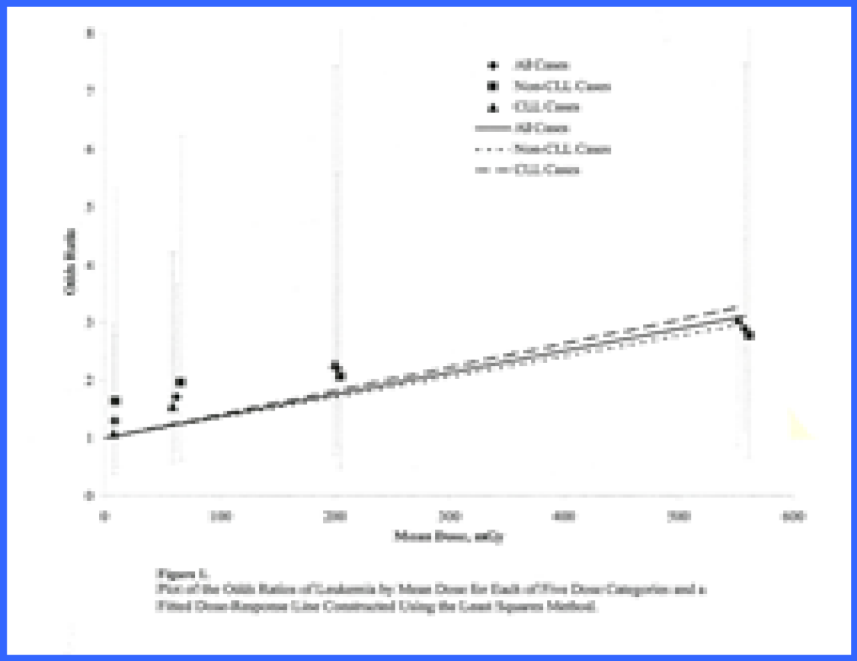
Cancer risk

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

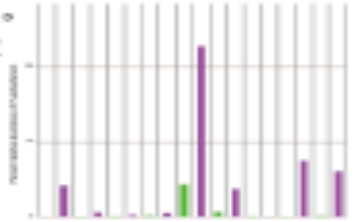
Newer infectious hypotheses

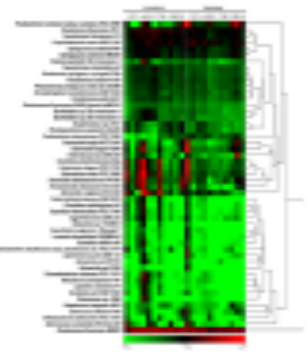
VIRUS	Human Cancer (hypothesized)
HCV	hepatocellular cancer
	NHL
EBV	NPC
	Hodgkin's lymphoma
	leiomyosarcoma
KSHV (HHV8)	Kaposi's sarcoma
HPV-16, -18, -33, -39	Vulvo-vaginal cancer
	Anal cancer
	Penile cancer
	Oropharyngeal cancer
Polyomavirus	Merkel cell virus/ **CLL?**
HIV	NHL

Fusobacterium and colorectal carcinoma

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,[1,5] Josep Tabernero,[5] José Baselga,[5] Chen Liu,[6] Ramesh A. Shivdasani,[3] Shuji Ogino,[2,7] 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*

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)

Kreimer et al, Manuscript under review

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

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

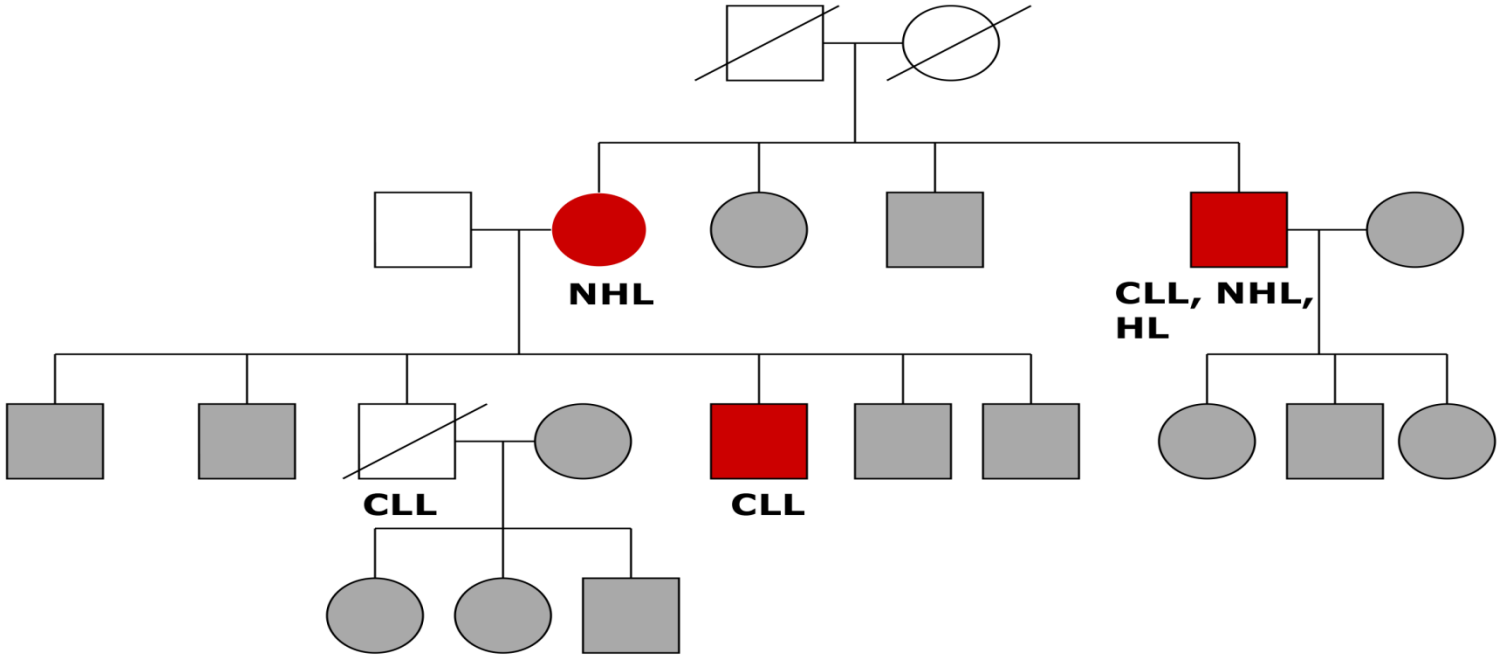
1. Germline or Somatic
   (inherited or in the tumor)

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……



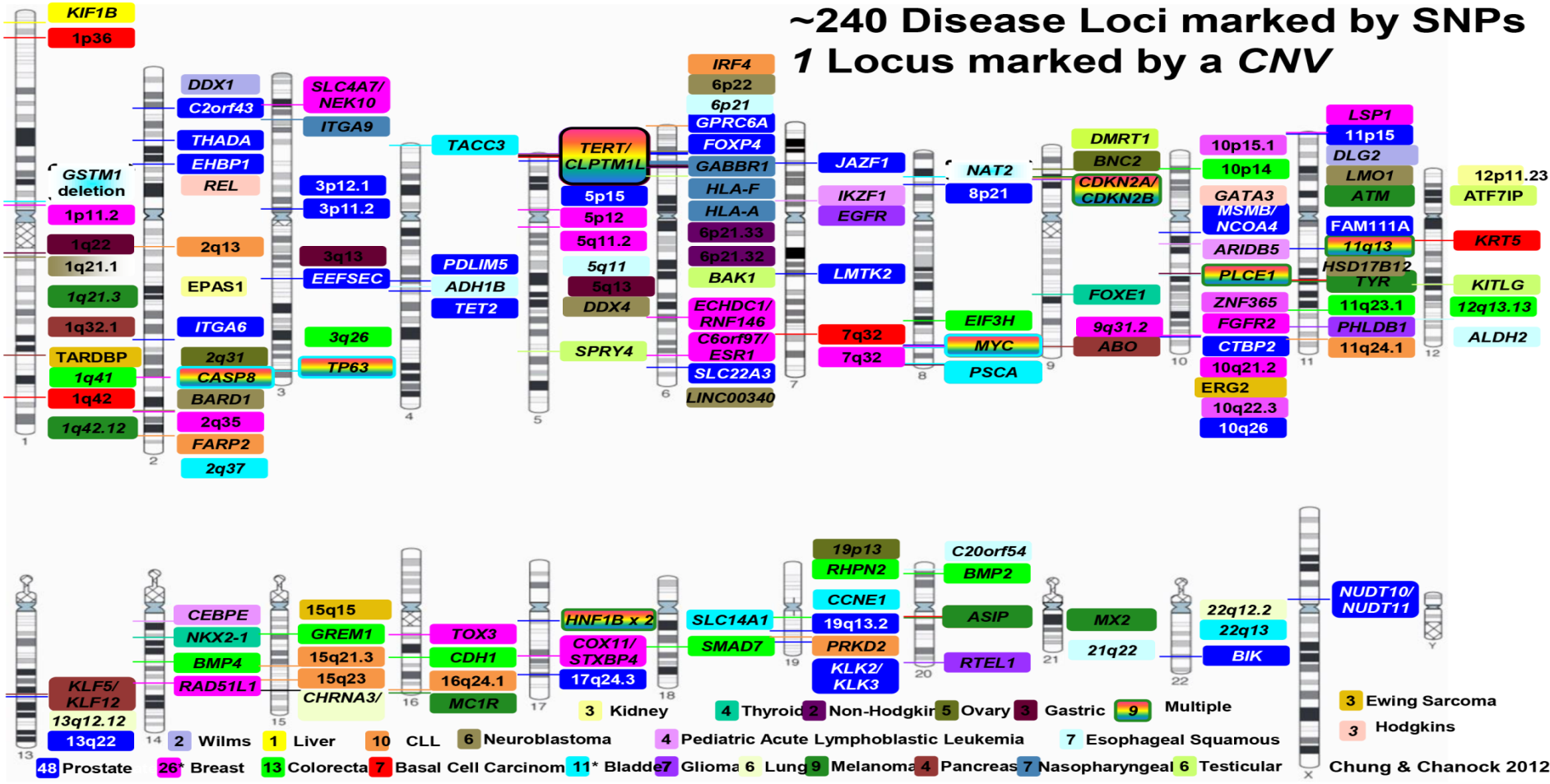
High risk kindreds like this likely harbor rare genes that confer high risk- if we knew what were they would be clinically important….

Cloned 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



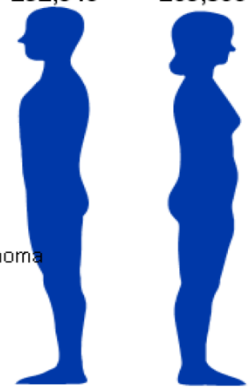
Lung cancer challenge

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

EAGLE

10 years ago we fielded **EAGLE**

Environment **a**nd
Genetics in **L**ung 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

Open Access

Environment And Genetics in Lung cancer Etiology (EAGLE) study: An integrative population-based case-control study of lung cancer

Maria Teresa Landi*[1], Dario Consonni[2], Melissa Rotunno[1], Andrew W Bergen[3], Alisa M Goldstein[4], Jay H Lubin[1], Lynn Goldin[1], Michael Alavanja[5], Glen Morgan[5], Amy F Subar[5], Ilona Linnoila[6], Fabrizio Previdi[7], Massimo Corno[7], Maurizia Rubagotti[7], Barbara Marinelli[7], Benedetta Alberti[2], Antonio Colombo[2], Margaret Tucker[1], Sholom Wacholder[1], Angela C Pesatori[2], Neil E Caporaso[3] and Pier Alberto Bertazzi[2]

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
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

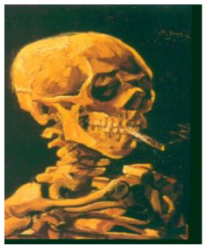
Traditional epidemiology

Traditional epidemiology

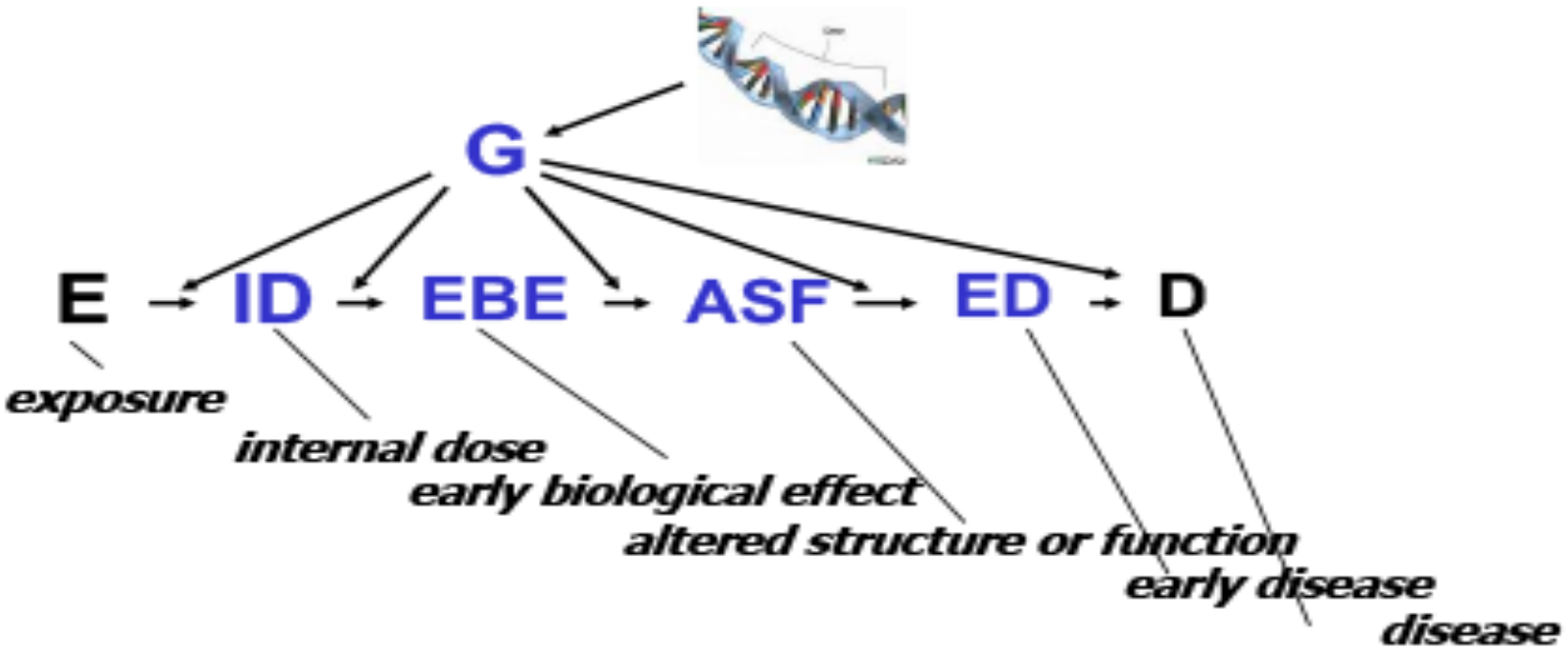
E → D

Exposure — Disease

Tobacco — Lung Cancer

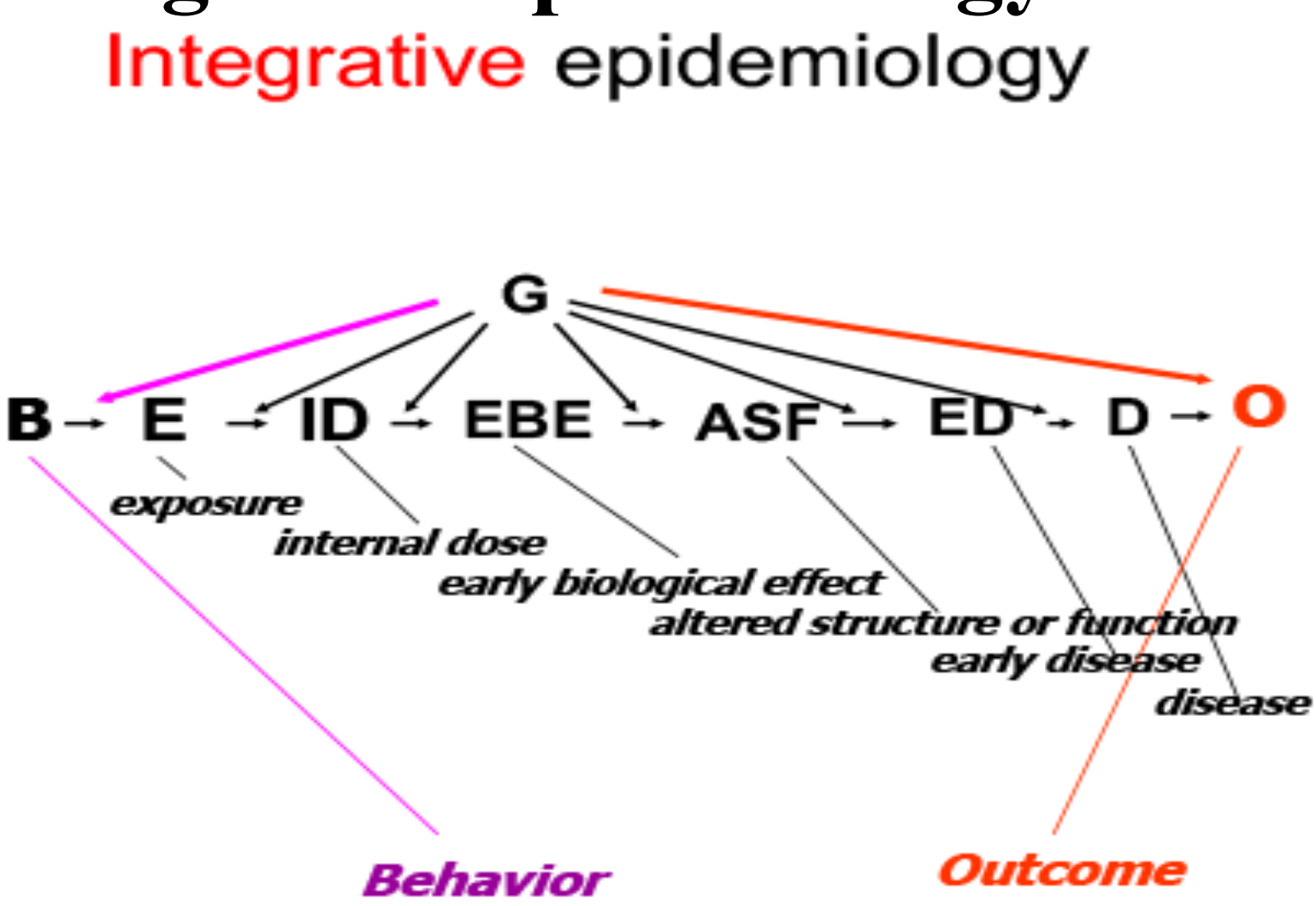


Molecular epidemiology

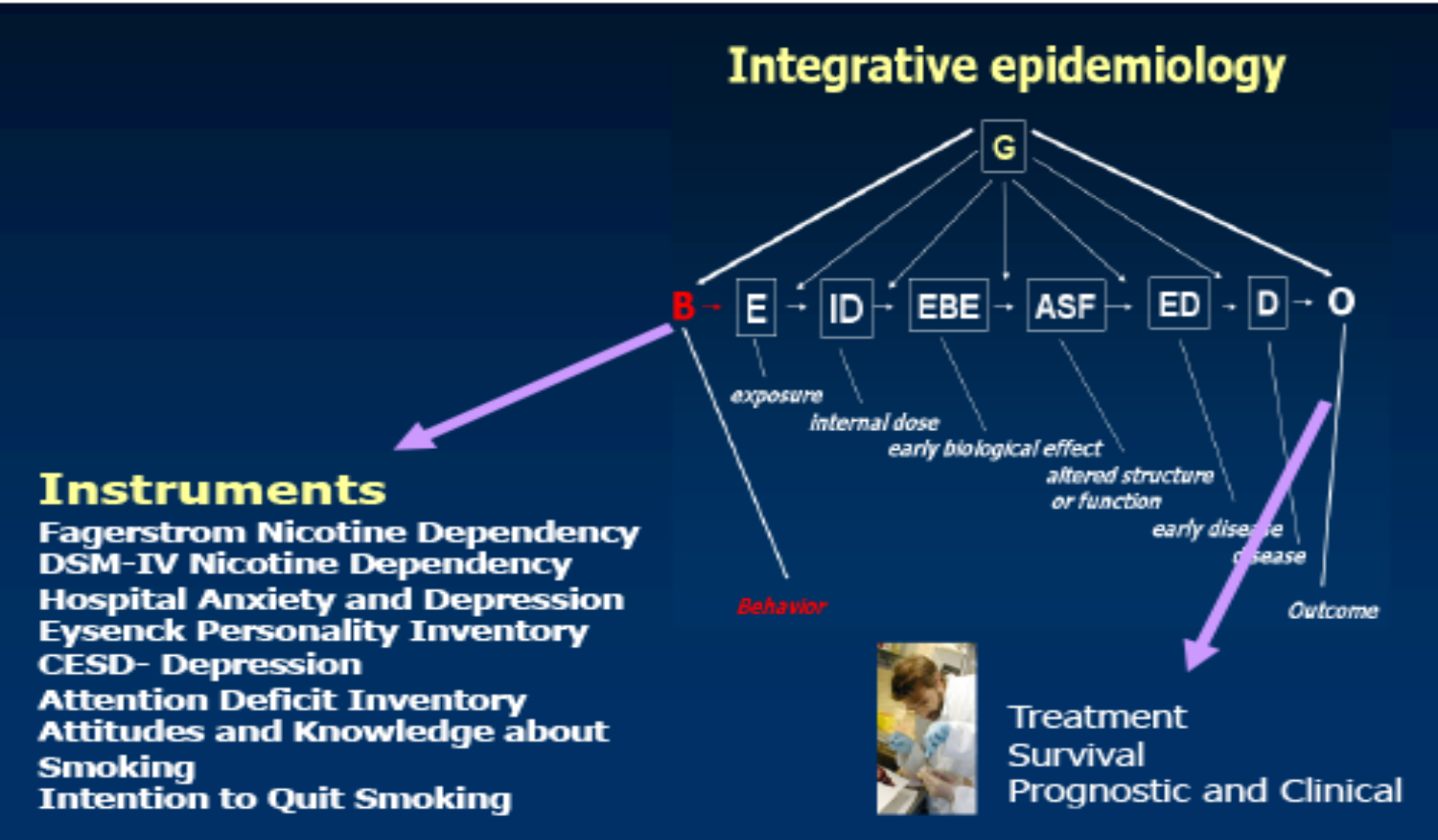


Adding **biomarkers** to investigate genes and mechanisms

Integrative epidemiology



Integrative epidemiology

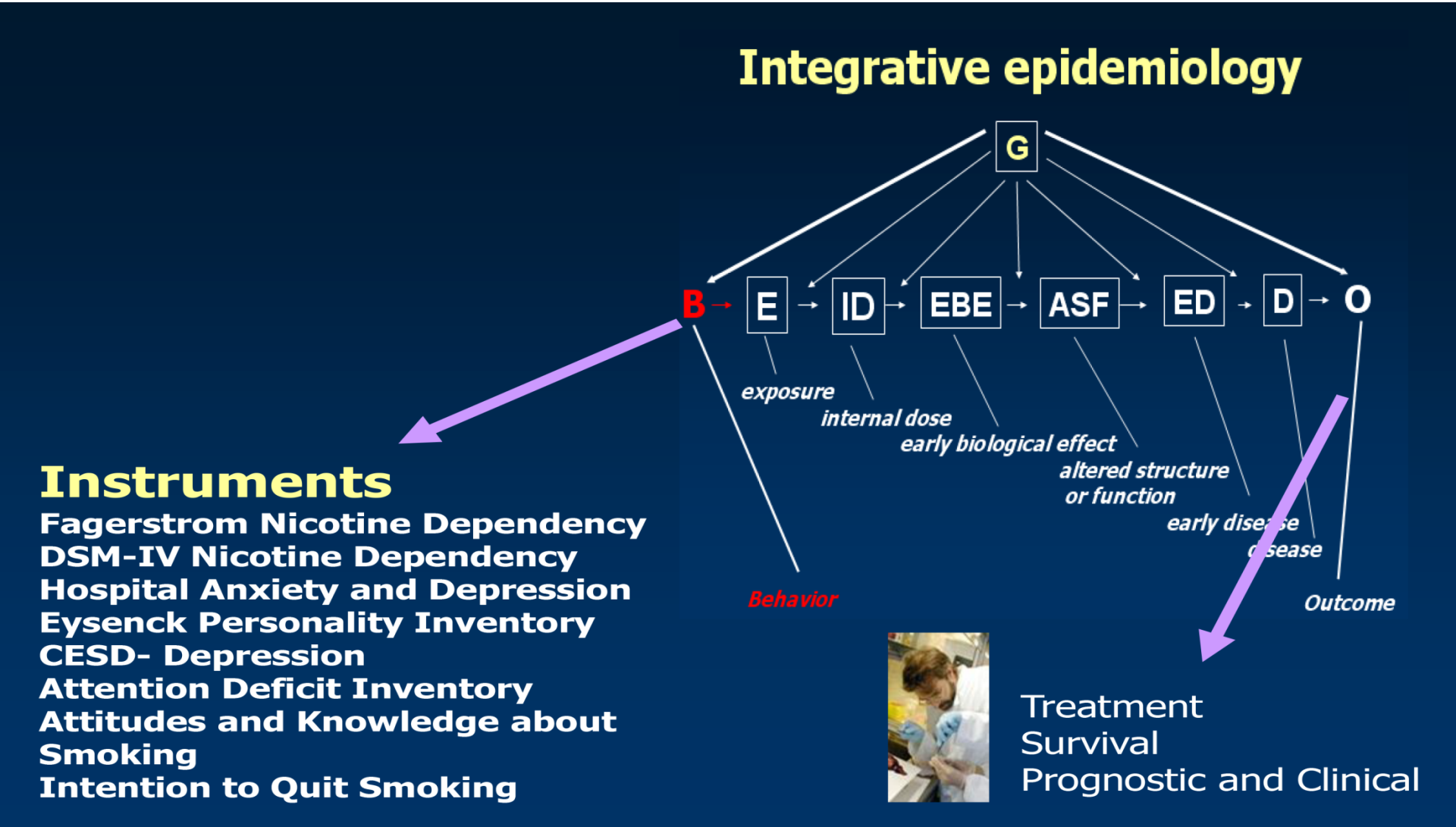


Molecular epidemiology

EAGLE example: molecular epidemiology approach

Epidemiology
'doneness module'

Integrative epidemiology



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…

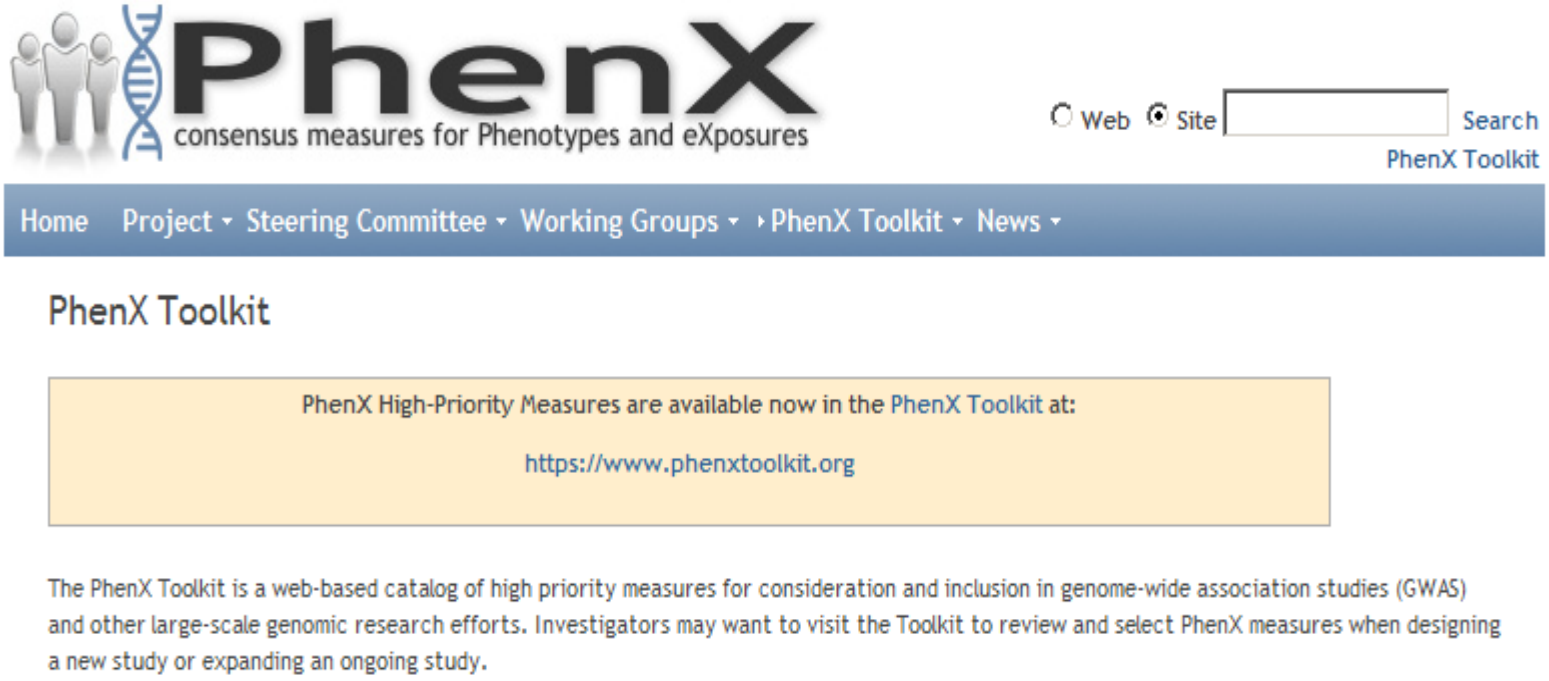
Consortia

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

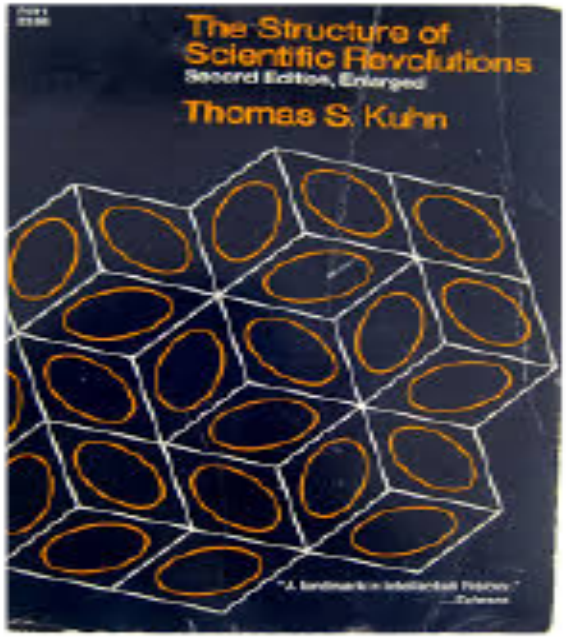
PhenX…approach to expand data collection and reduce misclassification

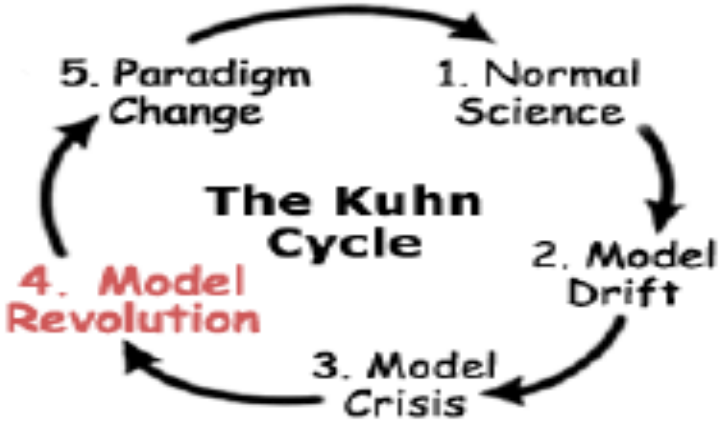


A Population Perspective on Cancer
What is epidemiology?
What has epidemiology accomplished?
What can go wrong?
What can really go wrong?
What next?

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....

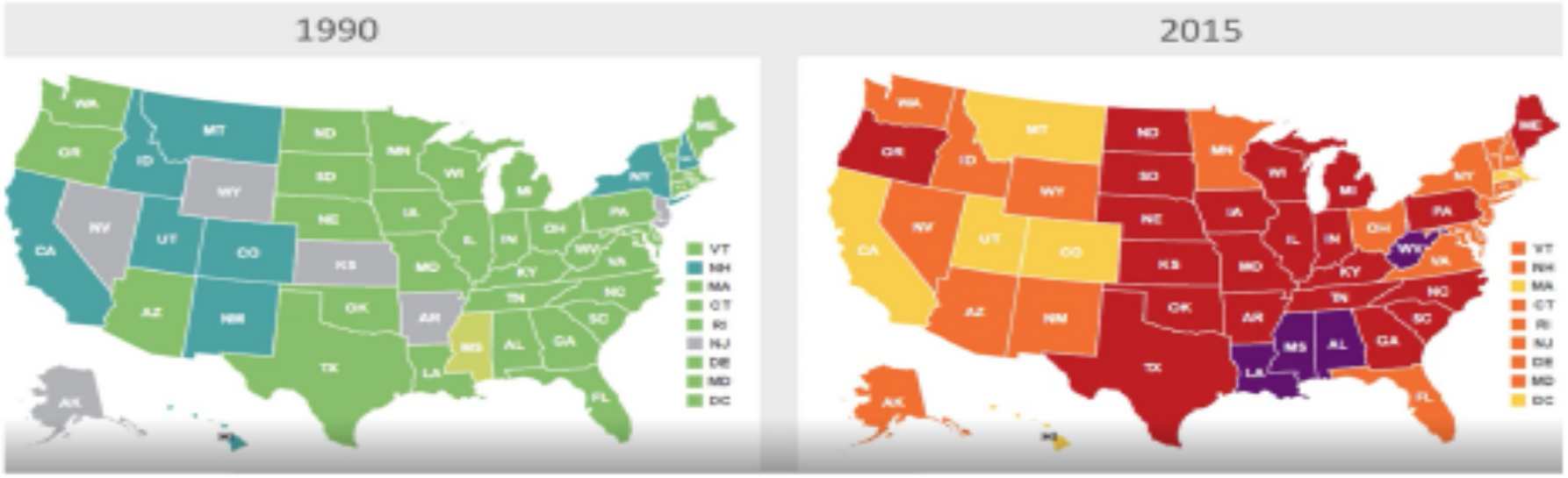
Paradigm shifting

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

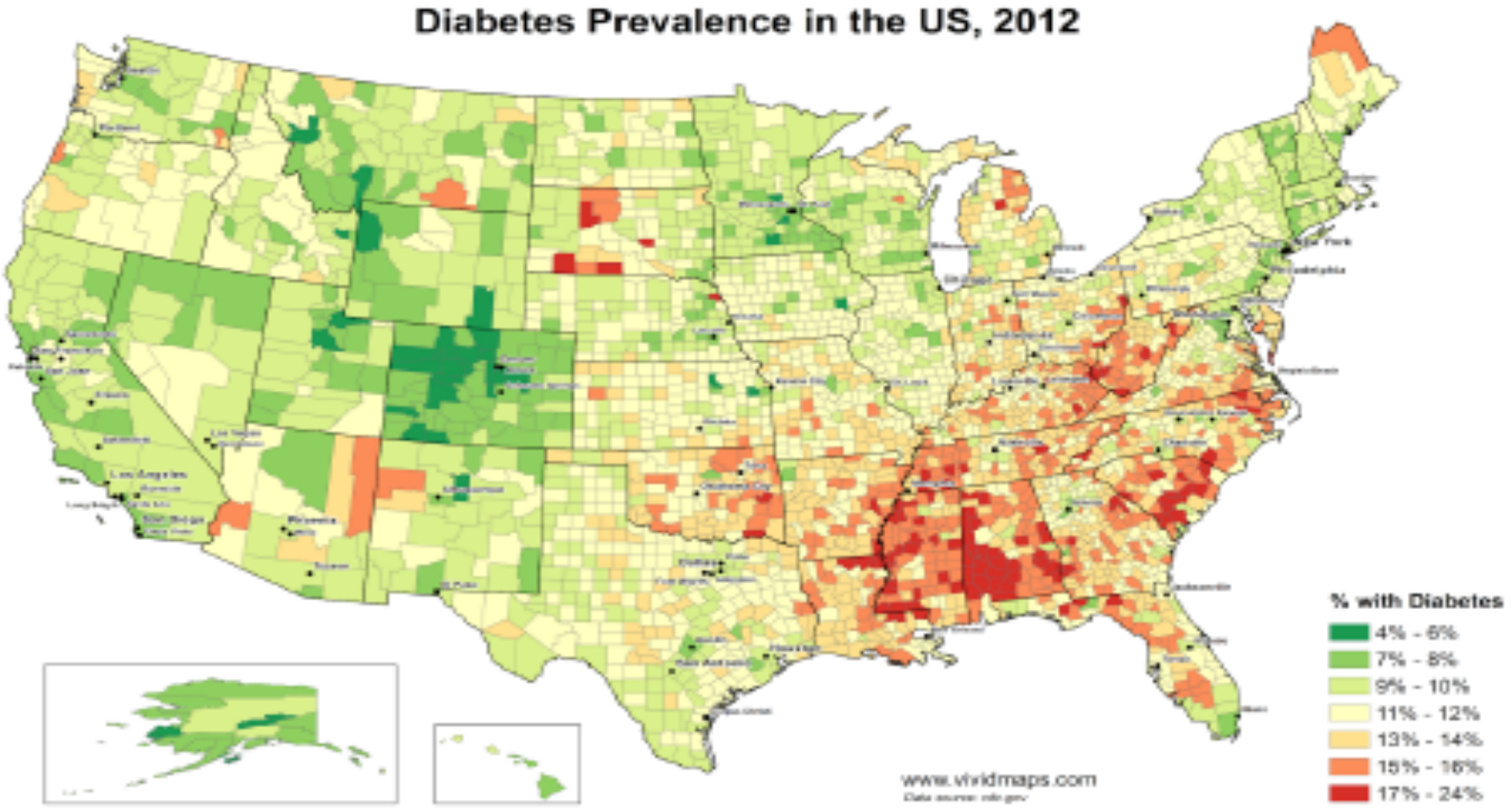
CDC Obesity Rates



No state > 20%

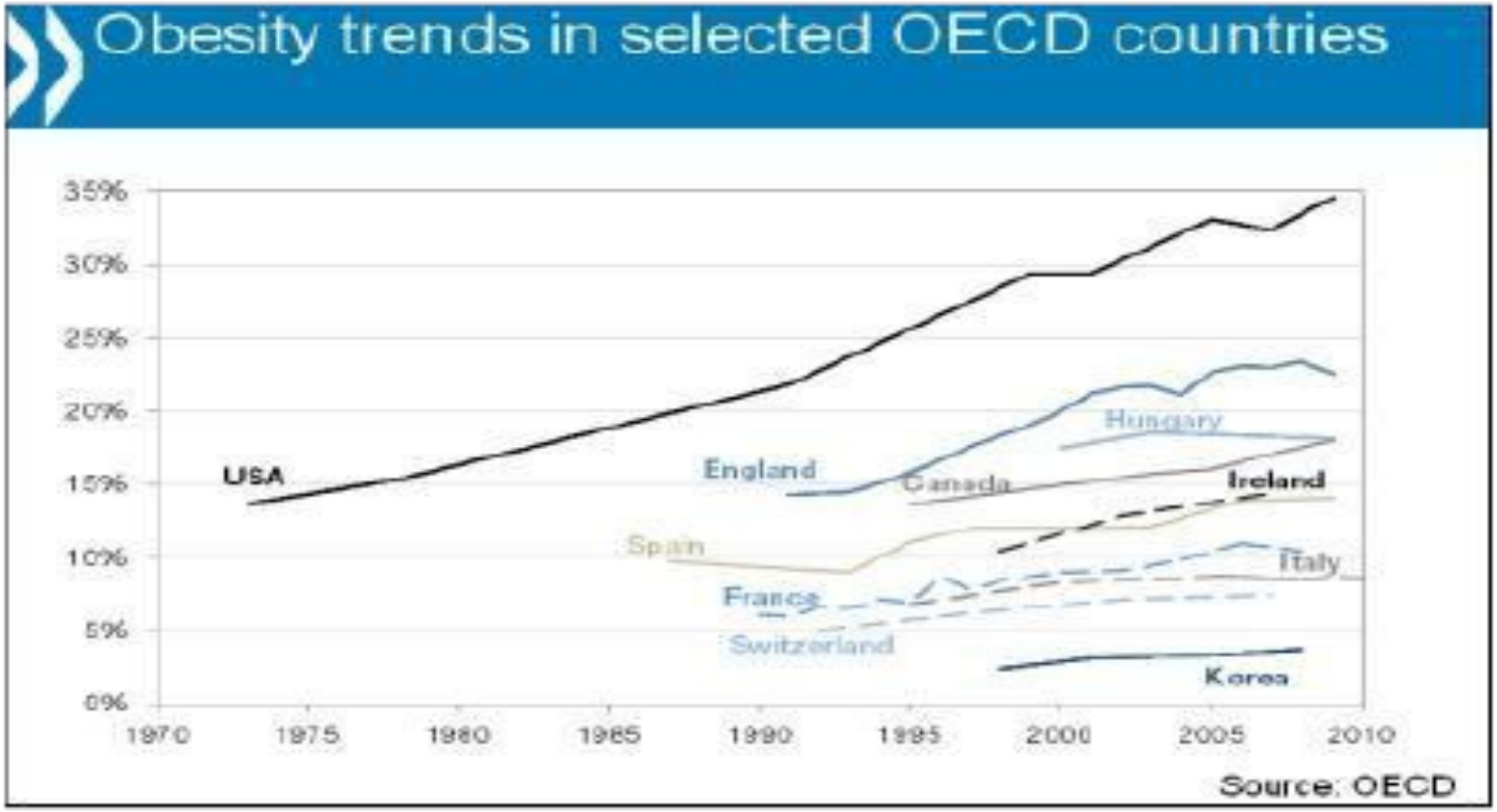
TODAY- no state under 20%

Diabetes in US

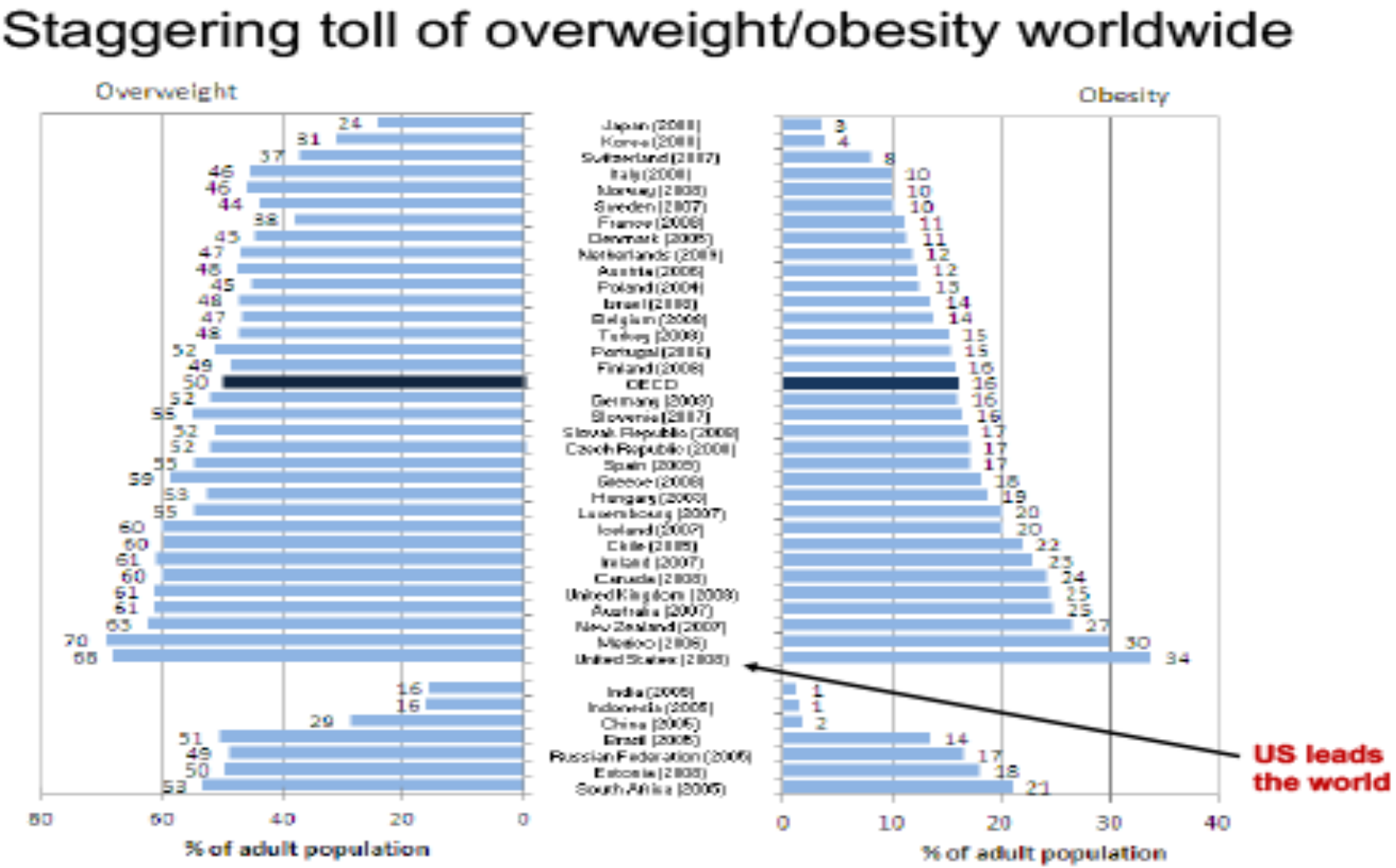


Obesity

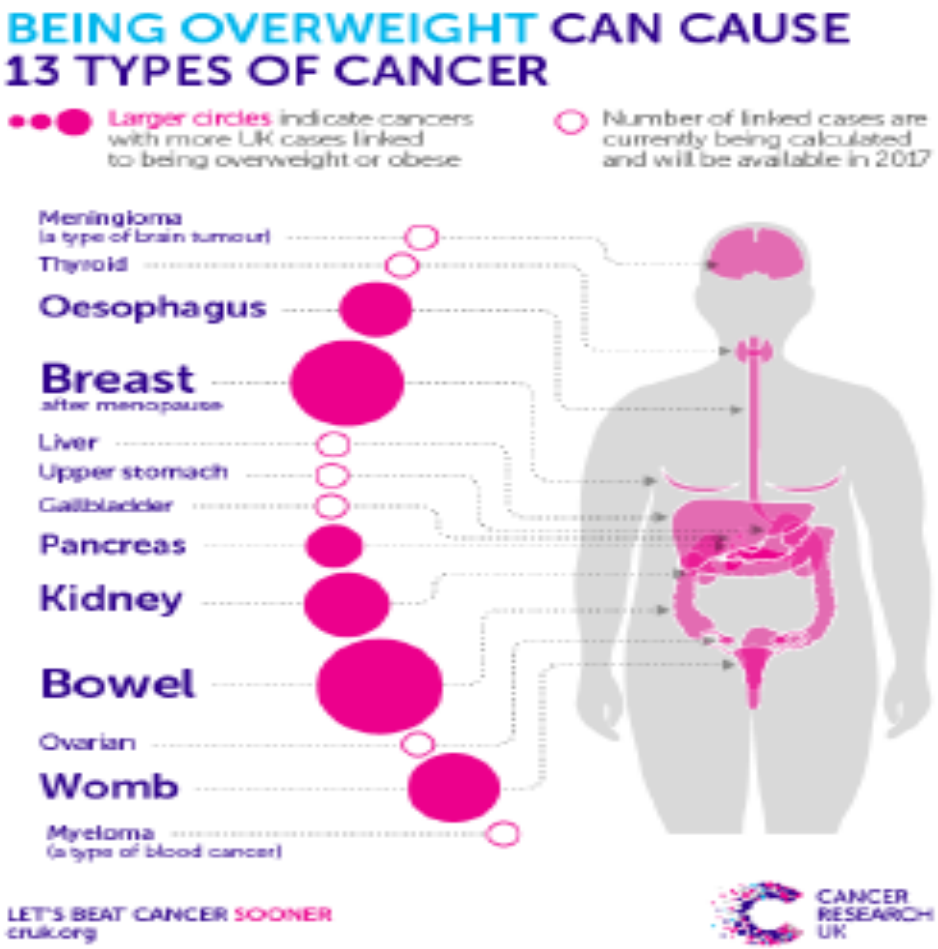
Obesity is an international problem



Obesity worldwide



Being overweight



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

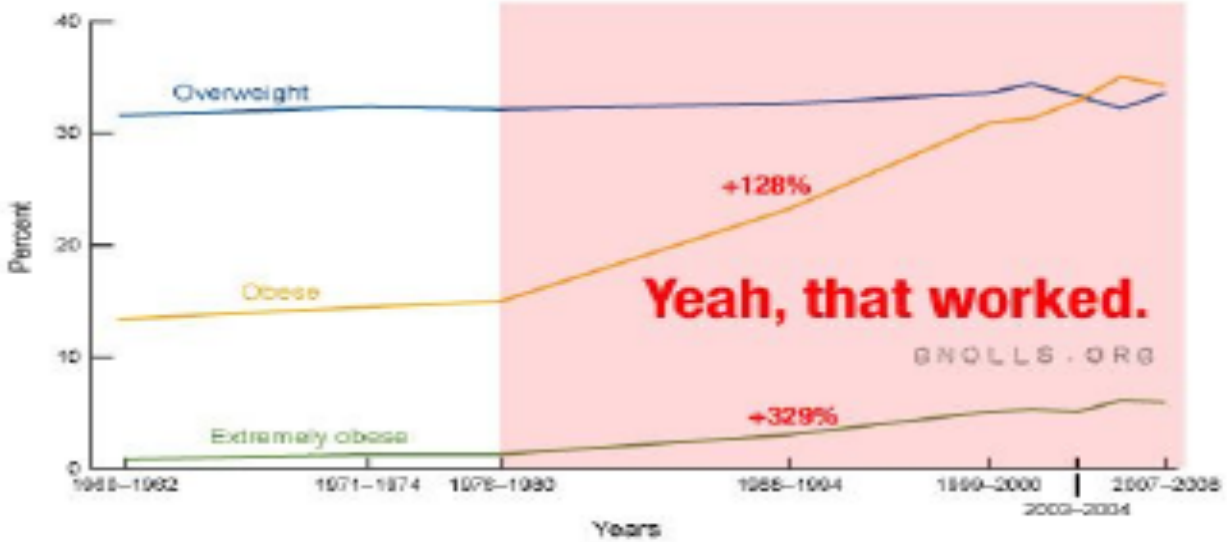
MORE sugar/carbs

MORE processed veg oils

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 (1976–1980), and III (1988–1994), 1999–2000, 2001–2002, 2003–2004, 2005–2006, and 2007–2008.

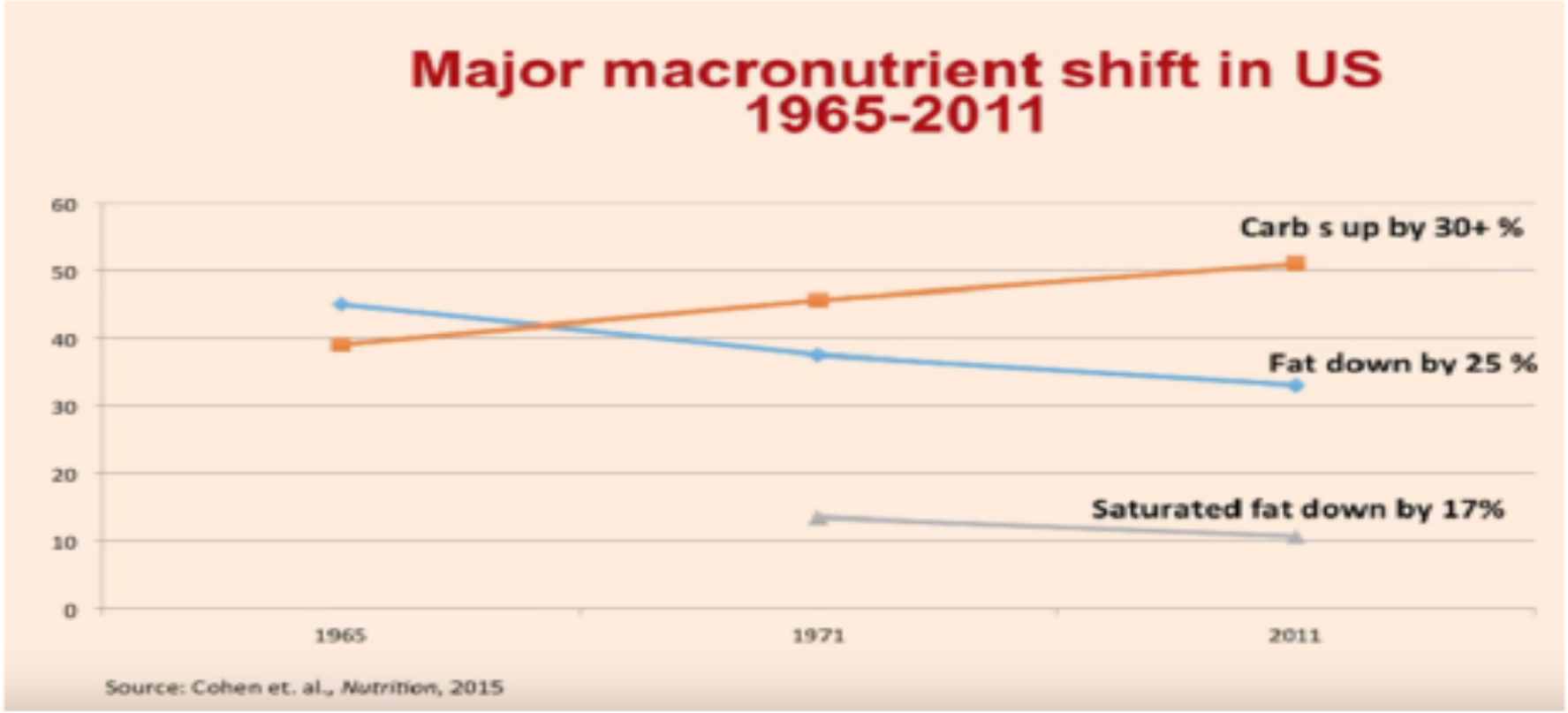
Graph is from "Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1976–1980 Through 2007–2008." Cynthia L. Ogden, Ph.D., and Margaret D. Carroll, M.S.P.H. Available at www.cdc.gov

Food pyramid

Institutional investment

Dietary habits

There has been a massive shift in US dietary habits…



Low fat trials

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

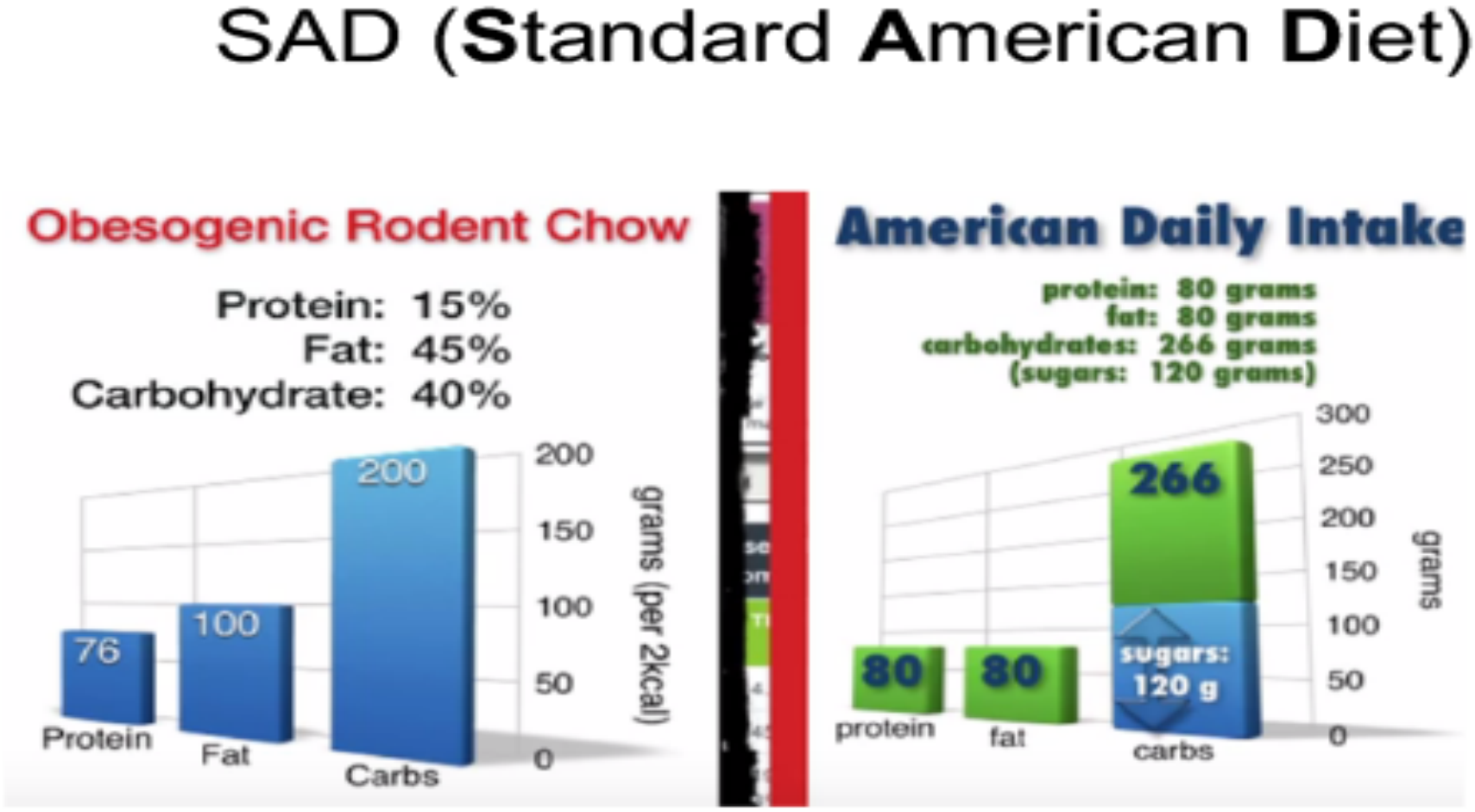
Table 1 Summary of meta-analyses of RCTs and prospective cohort studies

	Studies examined	Studies	People	Measure	Fat	Risk ratio	Conclusion
Skeaff and Miller (2009)[53]	Prospective cohort studies and RCTs	28	280 000	CHD mortality	Total fat	0.94 (0.74 to 1.18)	No significant differe
				CHD events	Total fat	0.93 (0.84 to 1.03)	No significant differe
Siri-Tarino *et al* (2010)[57]	Prospective cohort studies	21	347 747	CHD fatal and non-fatal	Saturated fat (extreme quintiles)	1.07 (0.96 to 1.19)	No significant differe
				CVD fatal and non-fatal	Saturated fat (extreme quintiles)	1.00 (0.89 to 1.11)	No significant differe
Mozaffarian *et al* (2010)[51]	RCTs	8	13 614	CHD events	Replacing SFA with PUFA	0.81 (0.70 to 0.95)	Significant difference
Hooper *et al* (2011)[50]	RCTs	21	71 790	Total mortality	All RCTs	0.98 (0.93 to 1.04)	No significant differe
					Modified fat	1.02 (0.88 to 1.18)	No significant differe
					Reduced fat	0.97 (0.90 to 1.04)	No significant differe
					Reduced and modified fat	0.97 (0.76 to 1.23)	No significant differe
				CVD mortality	All RCTs	0.94 (0.85 to 1.04)	No significant differe
					Modified fat	0.92 (0.73 to 1.15)	No significant differe
					Reduced fat	0.96 (0.82 to 1.13)	No significant differe
					Reduced and modified fat	0.98 (0.76 to 1.27)	No significant differe
				CVD events	All RCTs	0.86 (0.77 to 0.96)	Significant difference
					Modified fat	0.82 (0.66 to 1.02)	No significant differe
					Reduced fat	0.97 (0.87 to 1.08)	No significant differe
					Reduced and modified fat	0.77 (0.57 to 1.03)	No significant differe
Chowdhury *et al* (2014)[54]	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 differe
					Monounsaturated fat	0.99 (0.89 to 1.09)	No significant differe
					Polyunsaturated fat	0.93 (0.84 to 1.02)	No significant differe
					Trans fat	1.16 (1.06 to 1.27)	Significant difference
Schwingshackl and Hoffmann (2014)[55]	RCTs	12	7150	All-cause mortality	Modified fat intake	0.92 (0.68 to 1.25)	No significant differe
				CVD mortality	Modified fat intake	0.96 (0.65 to 1.42)	No significant differe
				CVD events	Modified fat intake	0.85 (0.63 to 1.15)	No significant differe
				MIs	Modified fat intake	0.76 (0.54 to 1.09)	No significant differe
				All-cause mortality	Reduced fat intake	0.79 (0.42 to 1.48)	No significant differe
				CVD mortality	Reduced fat intake	0.93 (0.66 to 1.31)	No significant differe
				CVD events	Reduced fat intake	0.93 (0.65 to 1.34)	No significant differe
				MIs	Reduced fat intake	1.18 (0.88 to 1.59)	No significant differe
Harcombe *et al* (2015)[75]	RCTs to 1977/1983	6	2467	All-cause mortality	Reduced or modified fat	0.99 (0.87 to 1.15)	No significant differe
				CHD mortality	Reduced or modified fat	0.99 (0.78 to 1.25)	No significant differe
Hooper *et al* (2015)[95]	RCTs	12	55 858	Total mortality	Reduced saturated fat	0.97 (0.90 to 1.05)	No significant differe
				CHD mortality	Reduced saturated fat	0.95 (0.80 to 1.12)	No significant differe
				CVD events	Reduced saturated fat	0.83 (0.72 to 0.96)	Significant difference
				MIs	Reduced saturated fat	0.90 (0.80 to 1.01)	No significant differe
				Non-fatal MIs	Reduced saturated fat	0.95 (0.80 to 1.13)	No significant differe
				Stroke	Reduced saturated fat	1.00 (0.89 to 1.12)	No significant differe
				CHD mortality	Reduced saturated fat	0.98 (0.84 to 1.15)	No significant differe
				CHD events	Reduced saturated fat	0.87 (0.74 to 1.03)	No significant differe

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; MIs, myocardial infarctions; PUFA, polyunsaturated fatty acids; RCT, randomised controlled trial; SFA, saturated fatty acids.

Harcombe, 2017
Brit J Sports Med

Standard American diet



Obesity food

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[1] and John PA Ioannidis[1,2,3,4,5,6]

[1]Stanford Prevention Research Center, [2]Meta-Research Innovation Center at Stanford (METRICS), and [3]Departments of [4]Medicine, [5]Health Research and Policy, [6]Biomedical Data Science, and [7]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[1]

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 questionaire

Food Questionnaires have limitations

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…….

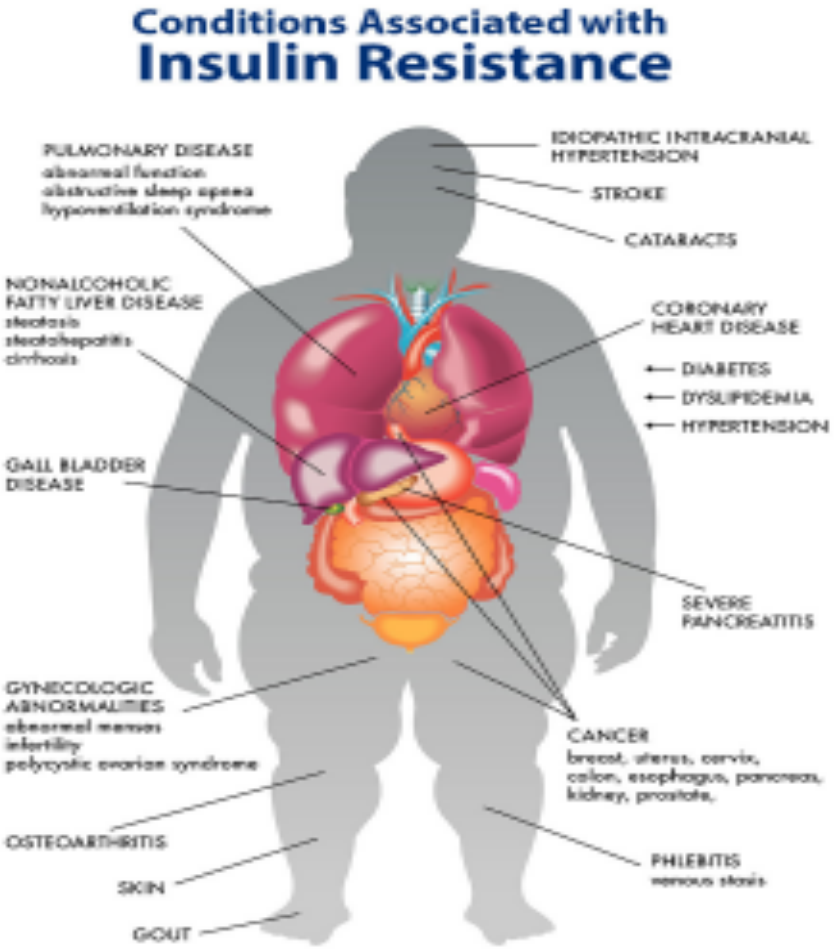
Stevens, 1987

Insulin resistance

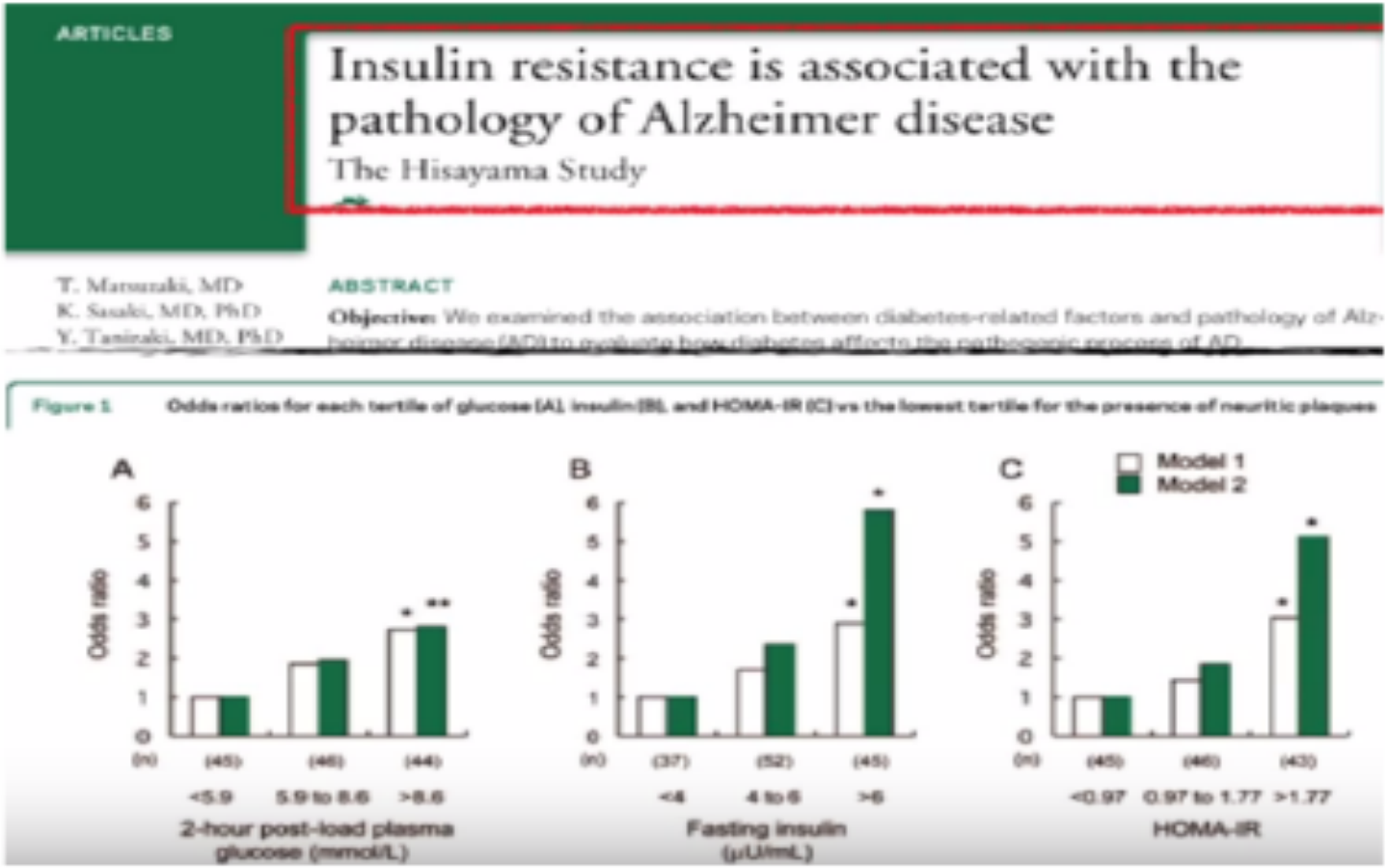
Before we develop diabetes…..

Insulin resistance

Is present for many years and does damage



Insulin resistance



ARTICLES

Insulin resistance is associated with the pathology of Alzheimer disease

The Hisayama Study

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

ABSTRACT

Objective: We examined the association between diabetes-related factors and pathology of Alz-
heimer 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[1]
EDWARD J. BOYKO, MD, MPH[2]
GEORGE N. IOANNOU, BMBCH, MS[1,3]

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.

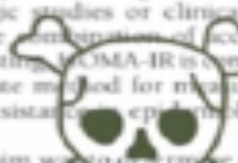
RESEARCH DESIGN AND METHODS — We determined the association between HOMA-IR and death certificate–based mortality among 5,311 nondiabetic, adult participants of the third U.S. National Health and Nutrition Examination Survey (1988–1994) during up to 12 years of follow-up, after adjustment for potential 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^2 (the median value) but not in subjects with BMI ≥25.2 kg/m^2. 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 [illegible] of accuracy and ease of testing, HOMA-IR is considered an appropriate method for measurement of insulin resistance in epidemiologic studies (12).

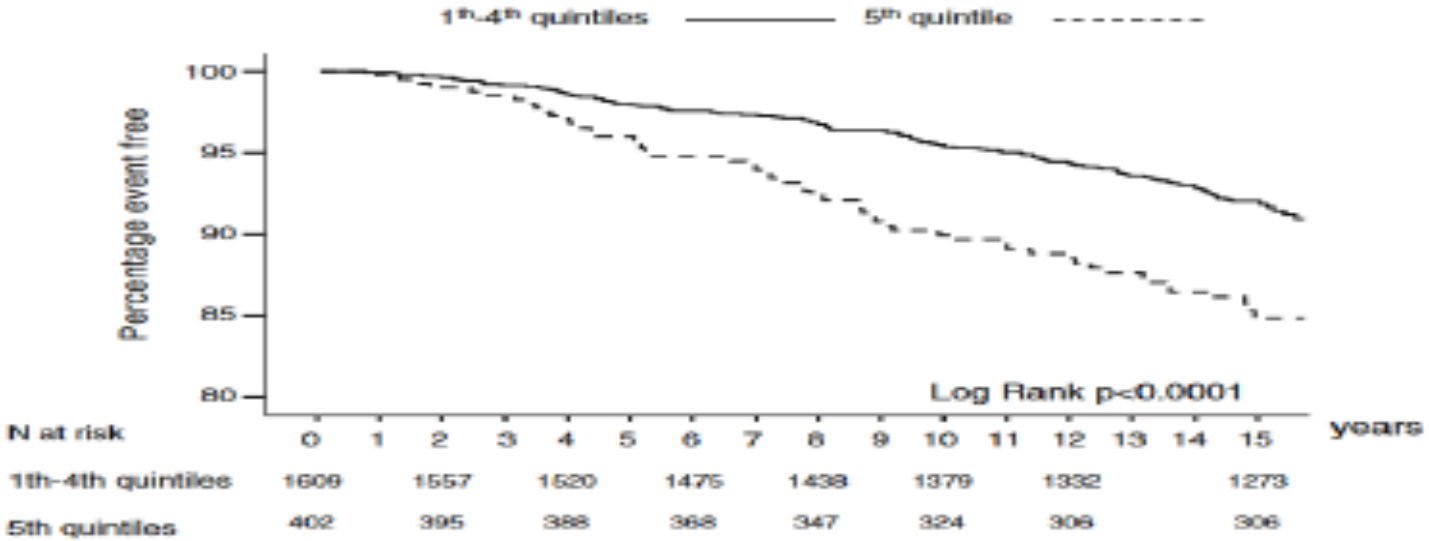
Our aim was to determine the association between [illegible] and mortality in nondiabetic participants in the U.S. independently of other important predictors of mortality. This finding would be impor-



ONCLUSIONS — HOMA-IR is associated with all-cause mortality in the nondiabetic U.S. pulation but only among persons with normal BMI. HOMA-IR is a readily available measure t 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

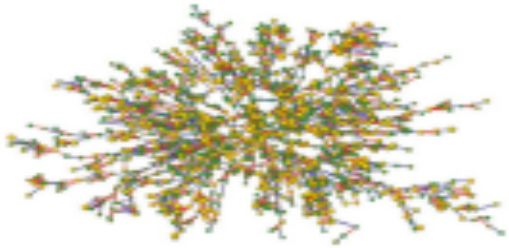
Traditional lung cancer risk factors used to assess utility of screening

- 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	35%	25%	18%	19%
Alcohol (> 1d/day)	15%	14%	13%	15%
Diabetes	8%	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

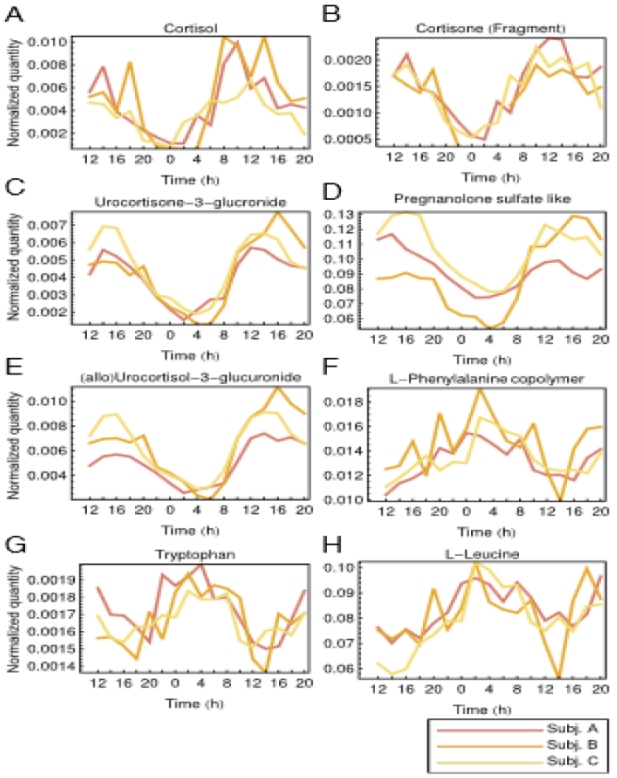
Circadian variation

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



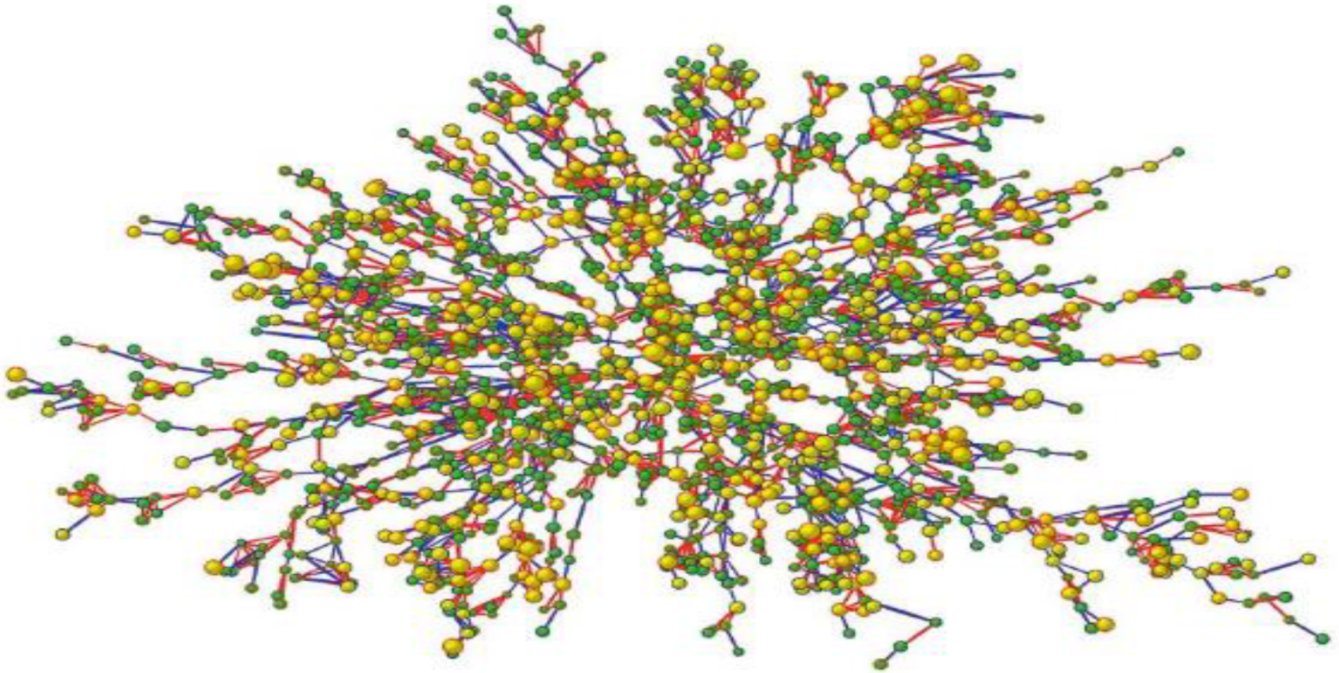
Human body metabolite timetable indicates internal body time.
PNAS 11sept2012 Kasukawa T et al.

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)

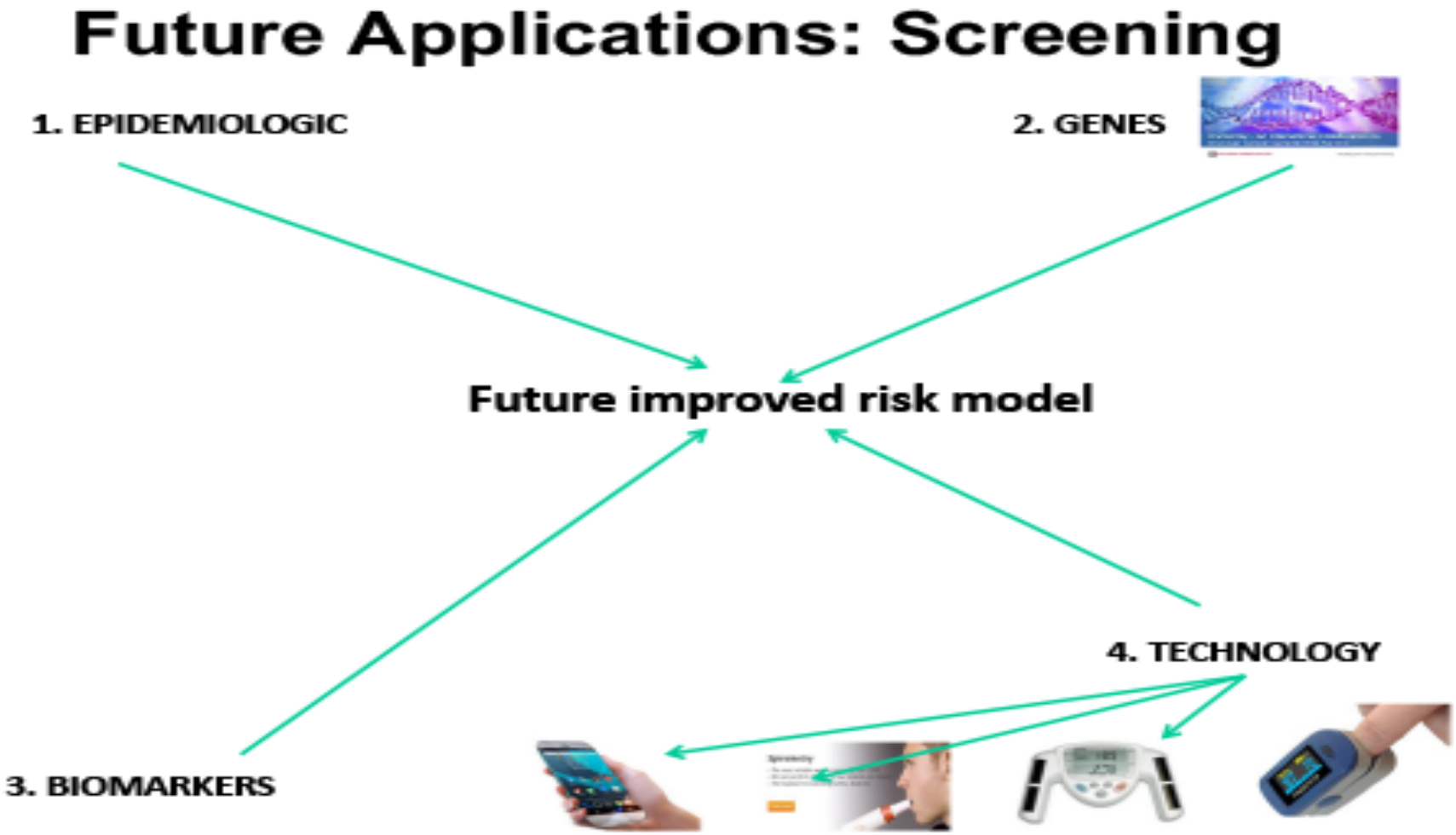
Ref SpO2 > 96%

BMC 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[1,2], Aasebø U[3,4], Wilsgaard T[5], Melbye H[6].

Future applications



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