NEOPLASIA (II)

APPROVED

Cancer Epidemiology

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Epidemiology in the news…from just 1 week..about just one cancer!

- Collards and carrots may ward off breast cancer! (Boston University)
- Hormones may raise breast cancer death risk! (JAMA)
- Soy intake may reduce breast cancer recurrence! (Canadian Medical Journal)
- Brisk walkers have lower breast cancer risk! (Arch Internal Med)

We get a lot of cancer news in the media

Objectives: Neoplasia 2

1. Describe the role of epidemiology in generating hypotheses about cancer causes
2. Describe relative frequency of major cancers in U.S.
3. Identify several cancers with varying geographic incidence
4. Discuss epidemiologic evidence for the role of environmental factors and diet in cancer
5. Describe the major types of heritable cancer syndromes
6. List several occupational cancers and their causes.
7. Define carcinogen and give examples of several types of carcinogens
8. Describe the differences between initiators and promoters

Epidemiology

When you're studying epidemiology, you're not looking at individuals, you're looking at populations

"The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems"

-Stedman's Medical Dictionary

Epidemiology of Cancer

- **Has had a profound influence on our understanding of cancer historically**
- **Continues to be source of new hypotheses on cancer causes**
- **Helps us understand the social and economic costs of cancer**

Cancer Epidemiology

- U.S. statistics
- Geographic and general environmental factors
- Inherited cancer syndromes
- Medical predisposing factors
- Occupational cancers and carcinogens
- Initiation and Promotion

Useful Sources of Data

- **NCI-Surveillance Epidemiology and End Results (SEER)**
  - http://seer.cancer.gov
- **American Cancer Society**
  - http://caonline.amcancersoc.org/cgi/content/full/60/5/277
- **WHO-International Agency for Research on Cancer (IARC) Globcan**
  - http://globocan.iarc.fr

NOTE: Most analyses do not include non-melanoma skin cancers; these are extremely common but rarely cause death.

Cancer Epidemiology

- **Incidence = how many people are diagnosed with a cancer in a given time period**
  - Given time period is often 1 year
- **Mortality = how many people die from cancer in a given time period**
  - Incidence is usually higher than mortality because not everyone dies from cancer
- **Prevalence = how many people (total) have the cancer**
  - Also during a given time period
  - **Prevalence depends on cancer incidence, length of survival, and mortality rates.**

Prevalence is greater than mortality and greater than incidence

CANCER FAST FACTS—U.S.

- **How Many People Alive Today Have Had Cancer?**

  18.6 million Americans have been diagnosed with cancer (8.2%).
- **How Many New Cases Are Expected to Occur in 2009 ?**

  1,479,350 new cancer cases in 2009.
- **How Many People Are Expected to Die of Cancer This Year?**

  In 2009, about 562,340 Americans are expected to die of cancer. Cancer is the second most common cause of death in the US, exceeded only by heart disease. In the US, cancer accounts for about 1 of every 5 deaths (23% of deaths).
- **What Percentage of People Survive Cancer?**

  The 5-year relative survival rate for all cancers diagnosed between 1996-2004 is 66%, up from 50% in 1975-1977. The improvement in survival reflects progress in diagnosing certain cancers at an earlier stage and improvements in treatment.
- **What Are the Costs of Cancer?**

  $228 billion in 2008.

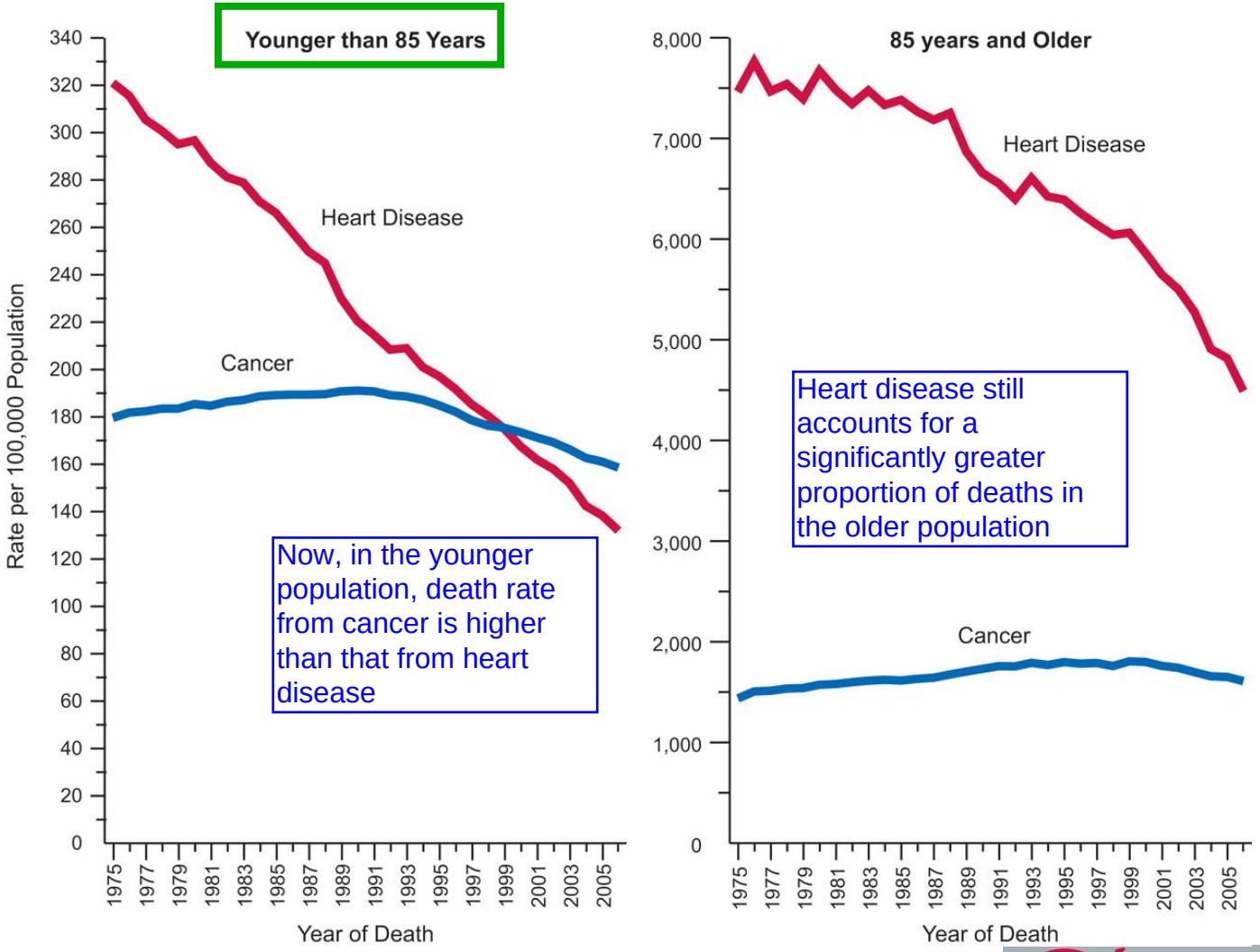
US Mortality, 2007

Heart disease and cancer together account for almost half of all deaths

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	616,067	25.4
2.	**Cancer**	**562,875**	**23.2**
3.	Cerebrovascular diseases	135,952	5.6
4.	Chronic lower respiratory diseases	127,924	5.3
5.	Accidents (unintentional injuries)	123,706	5.1
6.	Alzheimer disease	74,632	3.1
7.	Diabetes mellitus	71,382	2.9
8.	Influenza & pneumonia	52,717	2.2
9.	Nephritis*	46,448	1.9
10.	Septicemia	34,828	1.4

***Includes nephrotic syndrome and nephrosis.**
Source: US Mortality Data 2007, National Center for Health Statistics, Centers for Disease Control and Prevention, 2010.

FIGURE 6 Death Rates* For Cancer and Heart Disease for Ages Younger Than 85 Years and 85 Years and Older, 1975 to 2006



We've been doing a good job reducing the death rate from heart disease but not as good of a job in reducing death rate from cancer

Now, in the younger population, death rate from cancer is higher than that from heart disease

Heart disease still accounts for a significantly greater proportion of deaths in the older population

From Jemal, A. et al.
CA Cancer J Clin 2010;60:277-300.

CA
A Cancer Journal for Clinicians

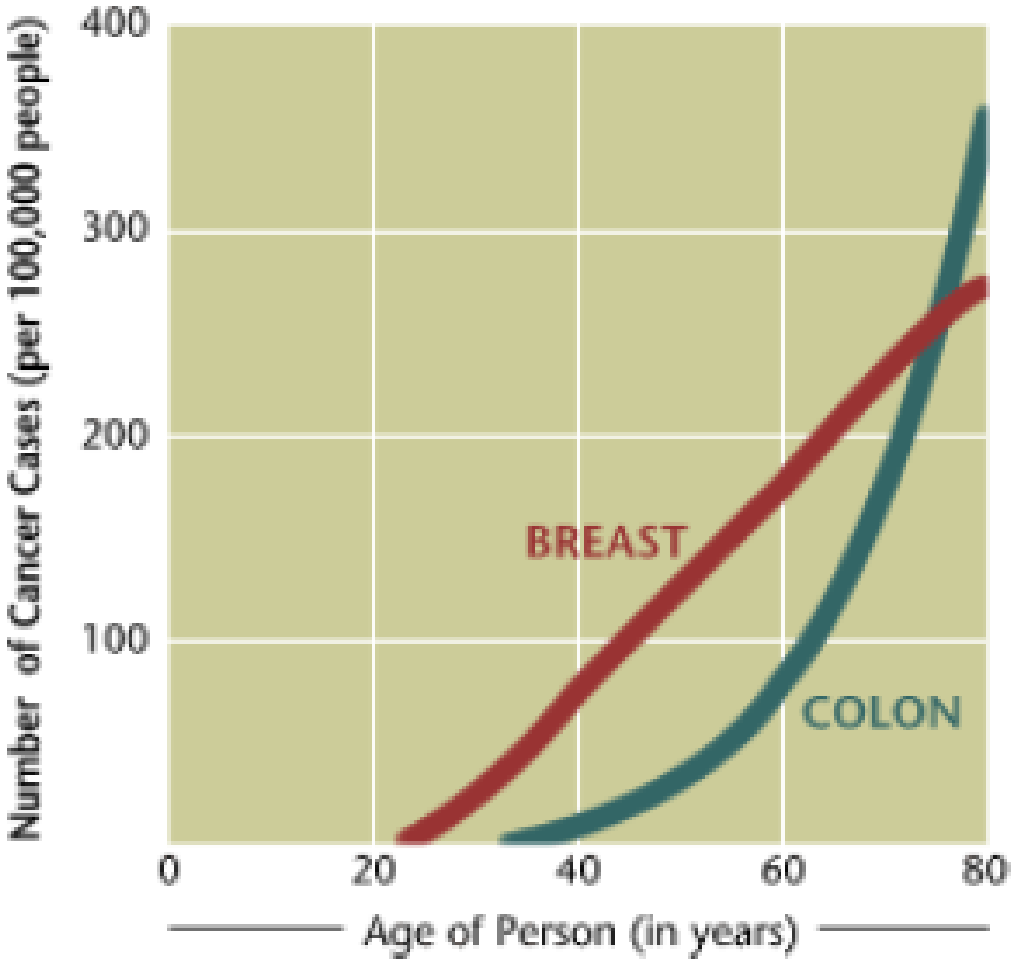
Lifetime Probability of Developing Cancer, Women, US, 2004-2006*

Site	Risk
All sites†	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 16
Colon & rectum	1 in 20
Uterine corpus	1 in 40
Non-Hodgkin lymphoma	1 in 52
Urinary bladder‡	1 in 84
Melanoma§	1 in 56
Ovary	1 in 71
Pancreas	1 in 72
Uterine cervix	1 in 145

*** For those free of cancer at beginning of age interval.**
† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
§ Statistic for white women.
Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.4.0 Statistical Research and Applications Branch, NCI, 2009. http://srab.cancer.gov/devcan

CANCER RISK AND AGING

Cancer is largely a disease of the older population



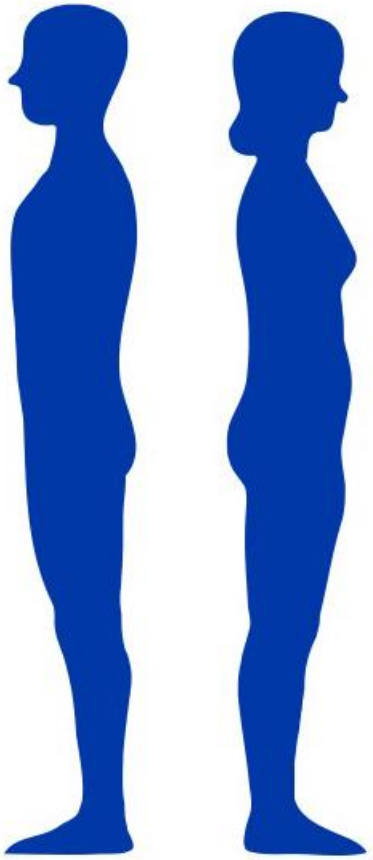
Most cancers have a similar graph as this one in terms of incidence vs. age

2010 Estimated US Cancer Deaths*

Men	
Lung & bronchus	29%
Prostate	11%
Colon & rectum	9%
Pancreas	6%
Liver & intrahepatic bile duct	4%
Leukemia	4%
Esophagus	4%
Non-Hodgkin lymphoma	4%
Urinary bladder	3%
Kidney & renal pelvis	3%
All other sites	23%

Source: American Cancer Society, 2010.

Men 299,200 **Women 270,290**



Women	
26%	Lung & bronchus
15%	Breast
9%	Colon & rectum
7%	Pancreas
5%	Ovary
4%	Non-Hodgkin lymphoma
3%	Leukemia
3%	Uterine corpus
2%	Liver & intrahepatic bile duct
2%	Brain/Other nervous system
24%	All other sites

Source: American Cancer Society, 2010.

YOUR TOP FOUR!!!!!

(Apologies to Ryan Seacrest….)

- **LUNG**
- **COLON**
- **BREAST**
- **PROSTATE**

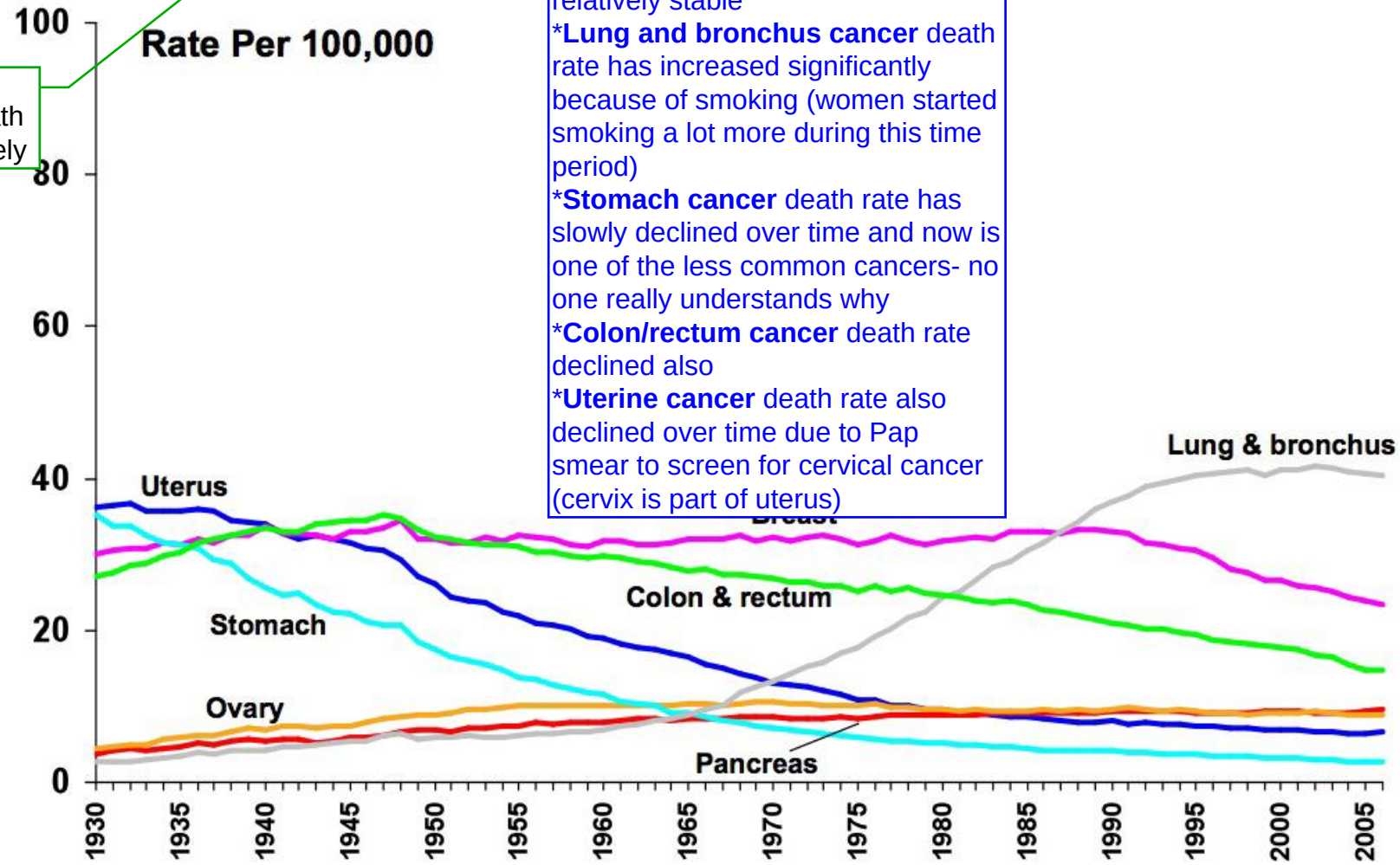
Account for >50% of cancer diagnoses and deaths in U.S.*

*Not including non-melanoma skin cancers, which are the single most commonly diagnosed cancer (>1 million/yr)

Cancer Death Rates* Among Women, US,1930-2006

Incidence rates match these death rates pretty closely

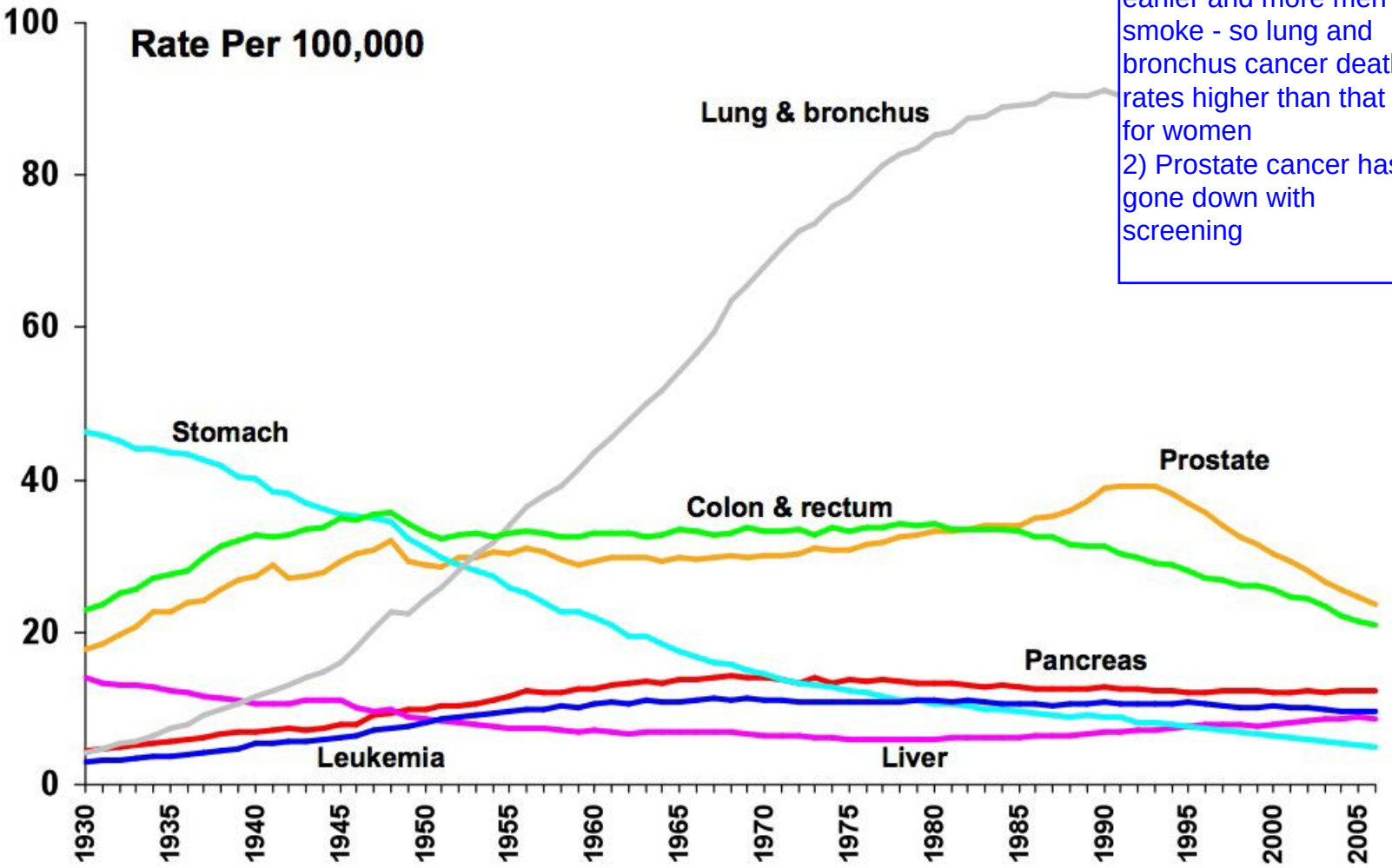
*__Breast cancer__ death rate has been relatively stable
*__Lung and bronchus cancer__ death rate has increased significantly because of smoking (women started smoking a lot more during this time period)
*__Stomach cancer__ death rate has slowly declined over time and now is one of the less common cancers- no one really understands why
*__Colon/rectum cancer__ death rate declined also
*__Uterine cancer__ death rate also declined over time due to Pap smear to screen for cervical cancer (cervix is part of uterus)



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Trends in females and males are similar (see previous slide)

Cancer Death Rates* Among Men, US,1930-2006



Some differences between men and women:
1) Men started smoking earlier and more men smoke - so lung and bronchus cancer death rates higher than that for women
2) Prostate cancer has gone down with screening

*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Cancer Survival*(%) by Race, 1999-2005

Site	White	African American	Absolute Difference
All Sites	69	59	10
Breast (female)	91	79	12
Colon	67	56	11
Esophagus	20	13	7
Leukemia	55	46	9
Non-Hodgkin lymphoma	70	60	10
Oral cavity	64	46	18
Prostate	100	98	2
Rectum	69	61	8
Urinary bladder	83	68	15
Uterine cervix	73	65	8
Uterine corpus	87	62	25

This difference may be due to genetic differences, ability to get care/screening, etc. (there are multifactorial reasons for these differences)

***5-year relative survival rates based on cancer patients diagnosed from 1999 to 2005 and followed through 2006. Source: Surveillance, Epidemiology, and End Results Program, 1975-2006, Division of Cancer Control and Population Sciences, National Cancer Institute, 2009.**

Geographic and General Environmental Factors

Geographic variability

There are different patterns of cancer at different places and different times. These patterns relate both to habits and to environmental hazards.

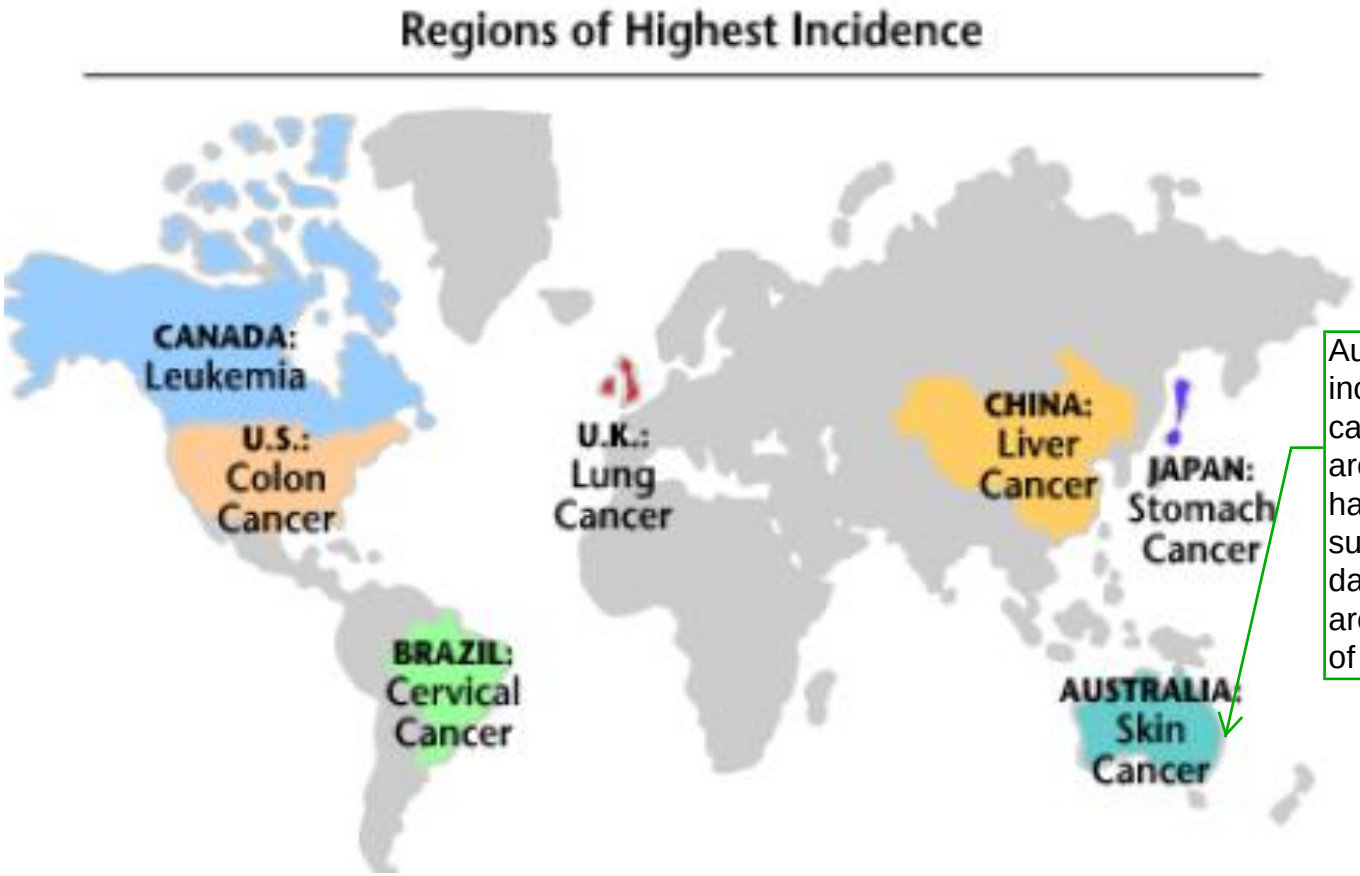
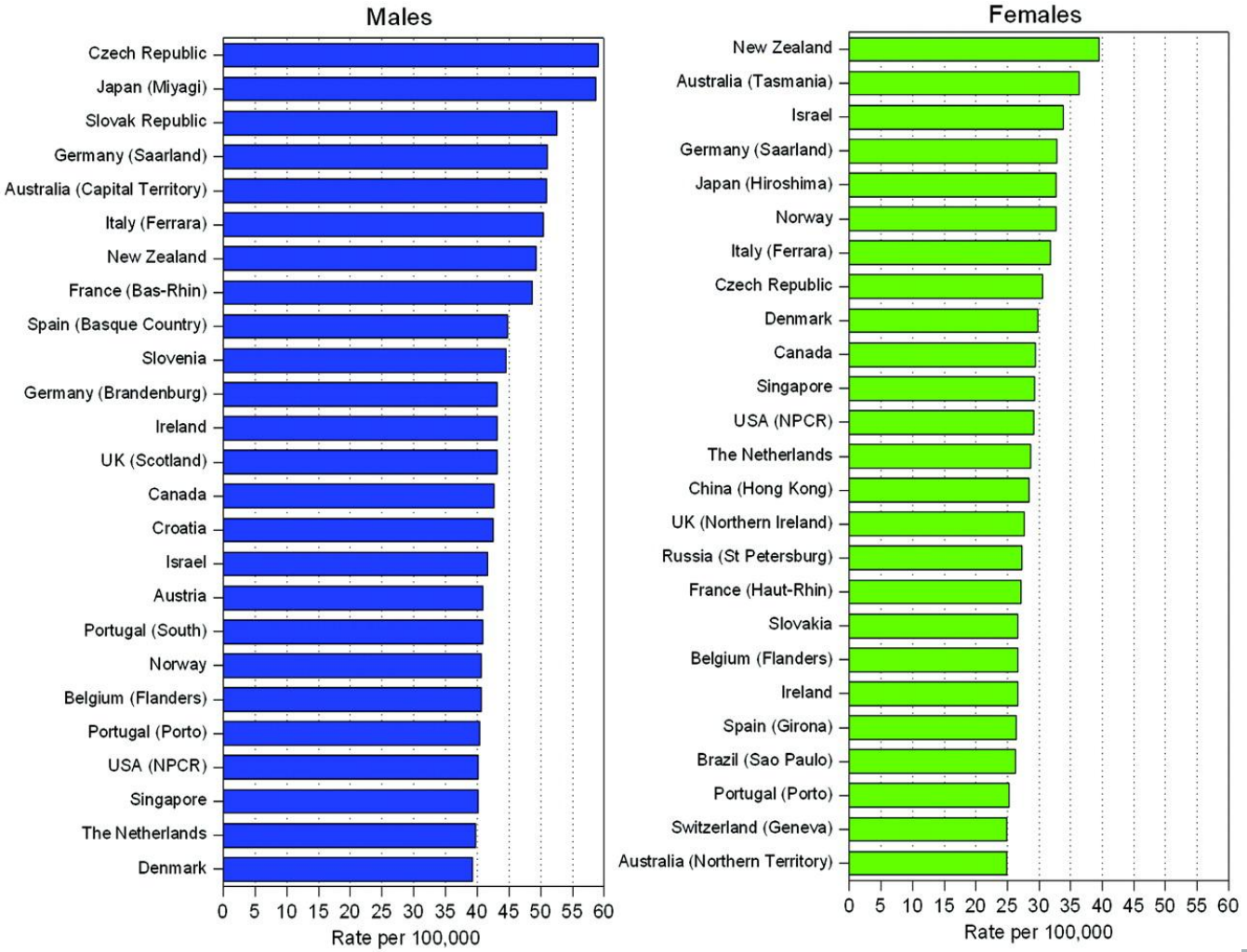
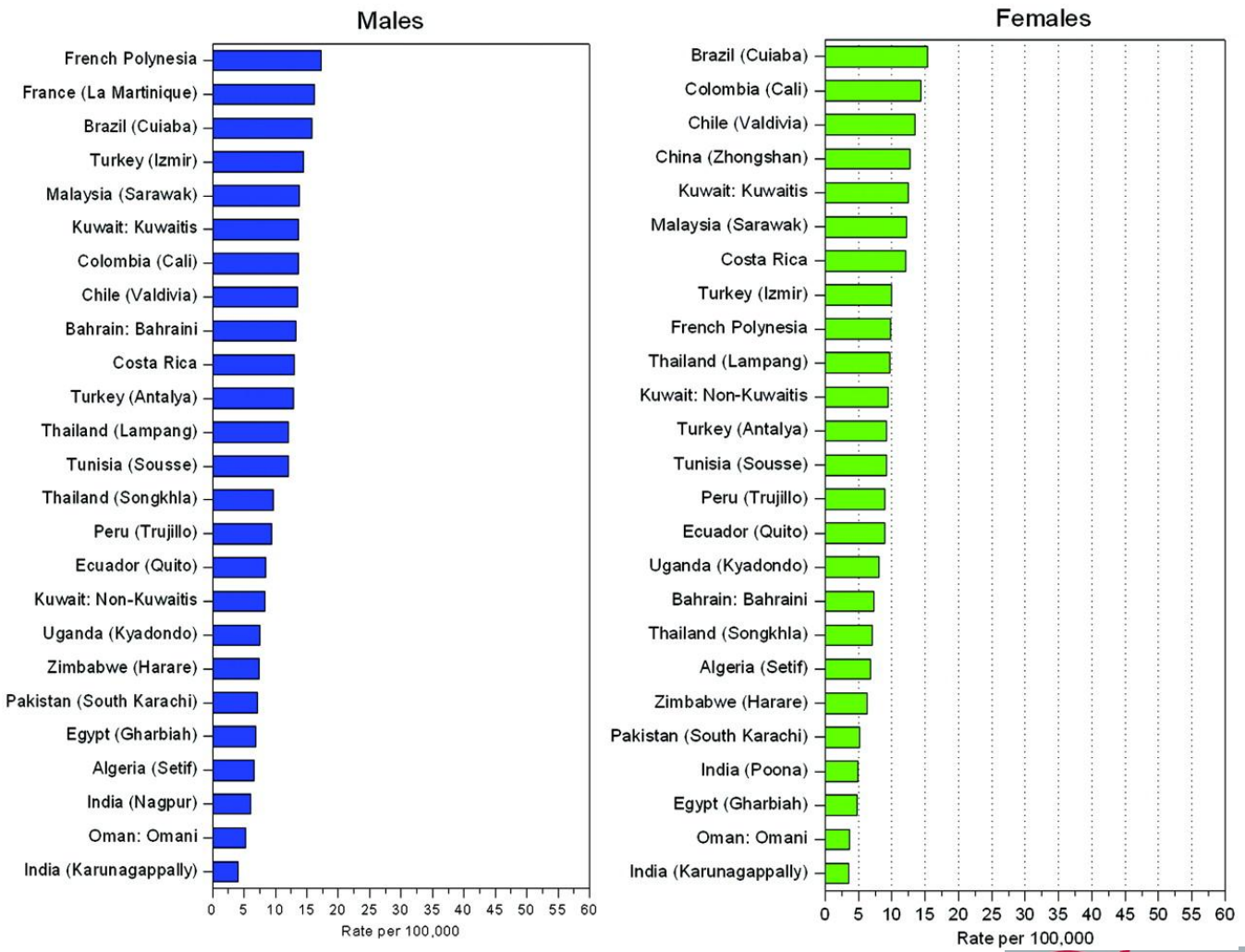


FIGURE 1 Registries with the Highest Age-Standardized Colorectal Cancer Incidence Rates by Sex, 1998-2002



From Center, M. M. et al.
CA Cancer J Clin 2009;59:366-378.

FIGURE 2 Registries with the Lowest Age-Standardized Colorectal Cancer Incidence Rates by Sex, 1998-2002



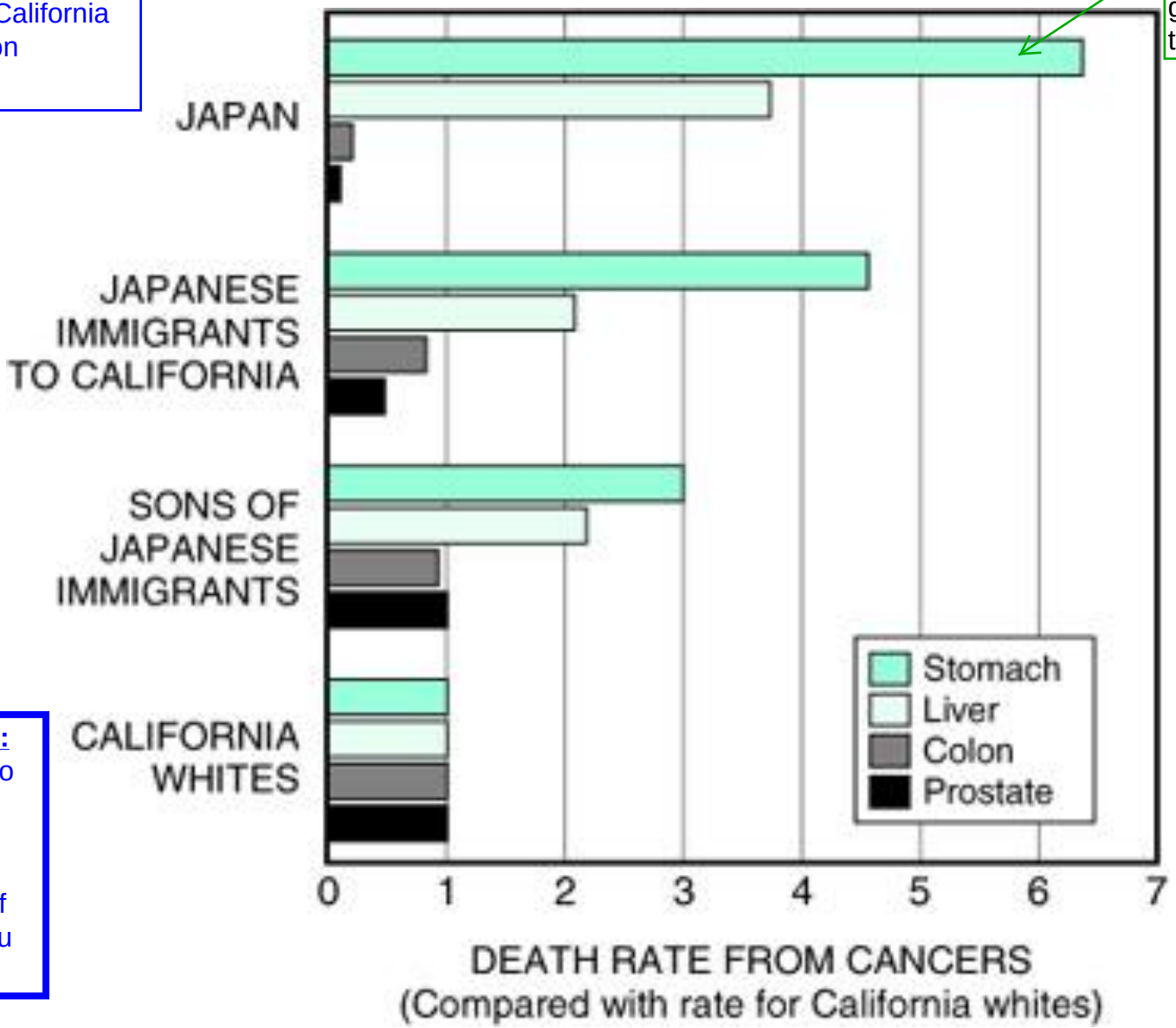
There are very big differences in colon cancer incidence rates depending on location

From Center, M. M. et al.
CA Cancer J Clin 2009;59:366-378.

CA
A Cancer Journal for Clinicians

Everything was normalized to California white population

6 fold more likely to get stomach cancer than CA whites



Point of Slide:
As you move to a certain country, you acquire the cancer rates of the country you move to

Epidemiology says most cancers caused by "environment"

- Incidence and specific cancers varies widely by geographic region, even within single countries
- Cancer rates within a population can change rapidly
- Migrant populations acquire the cancer incidence of their new environment in 1-2 generations

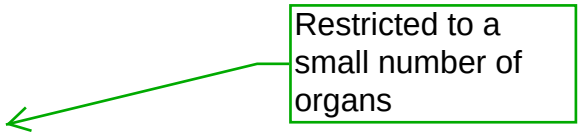
This is faster than the migrant populations could genetically change

The majority of cancers are preventable!

Majority of cancers are preventable because the majority of cancers are caused by the environment

GENETIC PREDISPOSTION TO CANCER

- **"Inherited Cancer Syndromes"**
  - **Cancer develops in a large proportion of the afflicted patients**
  - **Usually early onset**
  - **Often site restricted**



- **In sporadic cancer, hereditary influence is indirect and subtle**
  - **Variations in P450 can determine how quickly a carcinogen can be eliminated, for example**

Inherited Cancer Syndromes

- **Uncommon (5-10% of all cancers)**
- **Important because they help identify specific genes that are often involved in sporadic cancers**
- **Three categories:**
  - **Autosomal Dominant**
  - **Autosomal Recessive**
  - **Unclassified familial clusters**
    - **High rate of cancer within family, but unclear mechanism of inheritance, and no genetic defect identified**

AUTOSOMAL DOMINANT CANCER SYNDROMES

Inheritance of a mutated allele of a single tumor suppressor gene increases the risk of cancer

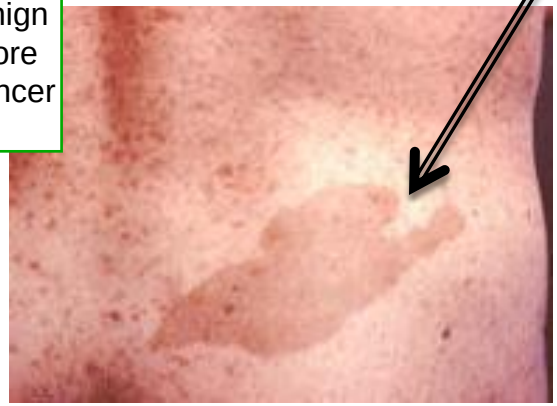
- **Retinoblastoma: Rb**
- **Li-Fraumeni syndrome: p53**
- **Neurofibromatosis 1 and 2: NF1, NF2**
- **Melanoma: p16INK4A**
- **Breast and Ovarian: BRCA1,BRCA2**
- **Multiple endocrine neoplasia 1 and 2: MEN1, RET**
- **Basal cell carcinoma: PATCH**
- **Familial adenomatous polyposis (FAP): APC**
- **Just to name a few!**

FEATURES OF AUTOSOMAL DOMINANT CANCERS

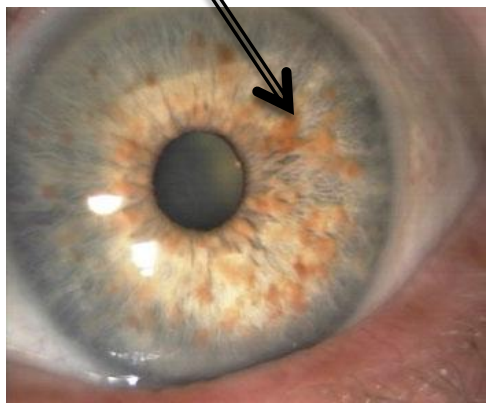
- Usually have specific sites or tissues affected by cancer
  - BRCA1—breast and ovarian cancer
- Can have incomplete penetrance and variable expressivity
  - BRCA-1: 40-80% penetrance
- Can have multiple benign tumors in the target tissue
  - Colon polyps in familial polyposis, endocrine tumors in MEN
- Can have characteristic non-neoplastic lesions in other tissues (Café au lait spots and Lisch nodules in neurofibromatosis)

Because these cancers are autosomal dominant, patients have one abnormal copy of the gene and can have incomplete penetrance depending on how knocked out that gene is

Hundreds or thousands of benign colon polyps before patients have cancer



Multiple endocrine neoplasia - benign endocrine tumors in many endocrine sites



Non-neoplastic lesions important for screening because if you recognize these things, you can catch cancer before it develops

Retinoblastoma

Pupillary reflex here is completely white = not good

- Carriers of **mutated Rb gene** have 10,000X increase in **risk of retinoblastoma**, which are often bilateral. Also develop **osteosarcomas.**

A patient with a mutated Rb gene doesn't get cancers all over his/her body

- 40% of all retinoblastomas are in patients with the syndrome.

Retinoblastomas are fairly uncommon

- One of the **first inherited cancer syndromes** to be understood on the molecular level—led to **discovery of the Rb gene** and the **concept of tumor suppressor genes**, which play an **important role in sporadic cancers** of many types.


White thing = tumor. The tumor here explains why the pupillary reflex looked white in the previous slide
Pupil

FEATURES OF AUTOSOMAL RECESSIVE CANCERS

- Rare in comparison
- Usually have complete penetrance
- Tumors arise in sites exposed to mutagens (UV light, radiation, etc)
- Typically have complex multisystem effects in addition to neoplasms.

Autosomal Recessive Cancer Syndromes

Mostly defects in DNA repair

- **Xeroderma Pigmentosum**
- **Ataxia-telangiectasia**
- **Bloom Syndrome**
- **Fanconi Anemia**

Defective DNA repair syndromes

Defective in DNA repair and resultant DNA instability

- **Examples of DNA damage**
  - **Base modifications** by alkylating agents
  - **Pyrimidine dimers** by ultraviolet radiation
  - **Gamma** and **X-rays**

- **A cell that has accumulated a large amount of DNA damage, or one that no longer effectively repair damage incurred by its DNA, can enter :**
  - **Senescence**, an irreversible state of dormancy
  - **Apoptosis**, programmed cell death
  - **Unregulated cell division**, leading to the formation of a tumor

Cell can't divide anymore

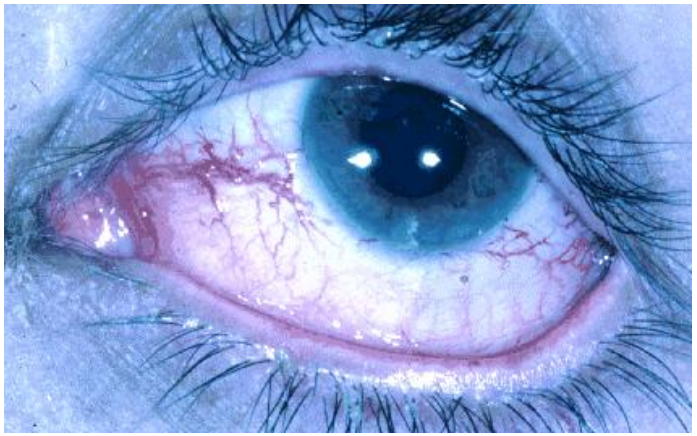
This is what we're concerned about for cancer

Defective DNA repair syndromes

Ataxia telangiectasis

- Autosomal recessive, multisystem disorder characterized by progressive neurologic impairment, cerebellar ataxia, variable immunodeficiency with susceptibility to sinopulmonary infections, impaired organ maturation, x-ray hypersensitivity, ocular and cutaneous telangiectasia, and a predisposition to malignancy in multiple tissue types.
- ATM gene: senses DNA double-strand breaks caused by radiation and oxygen free radicals. Its physiological function is to phosphorylate p53, leading to cell cycle arrest or cell death.

DNA repair mechanism is defective all over the body



Defective DNA repair syndromes

Xeroderma pigmentosum (or XP)

Normally, damage to DNA in epidermal cells occurs during exposure to UV light. The absorption of the high energy light leads to the formation of pyrimidine dimers. The normal repair process entails nucleotide excision. The damage is excised by endonucleases, then the gap is filled by a DNA polymerase and "sealed" by a ligase.

In XP, the nucleotide excision repear (NER) enzymes are mutated. Cells are deficient in repairing of damage DNA caused by ultraviolet (UV) light. This leads to basal cell carcinoma and other skin malignancies at a young age.

CLINICAL PRESENTATION:

This allows this syndrome to be diagnosed early in life

- **An unusually severe sunburn after a short sun exposure. The sunburn usually occurs during a child's first sun exposure.**
- **>1000 times more susceptible to develop skin cancer only when exposed to sun**

Hereditary Nonpolyposis Colon Cancer (HNPCC)

- Aka “Lynch Syndrome”
- Most common inherited colon cancer, and probably most common of any inherited cancer syndrome
- Cancers of the colon, endometrium, and ovary
- Exception to the rule…an autosomal dominant inheritance pattern, but caused by a DNA repair defect.

Unclassified Familial Cancers

- **Virtually all common cancers have familial forms that are not well defined**
  - **Cancers in multiple close relatives**
  - **Multiple cancers in individuals**
  - **Persistence over several generations**
- **Most have unclear (?multigene?) inheritance patterns**
- **Many more genetic causes of familial cancer remain to be discovered!**

To show it has a genetic component

It is not clearly autosomal dominant or recessive - often multifactorial

Interactions between heritable genetic and non-genetic causes

- Different individuals inheriting the same genetic defect develop different cancers at different times
- Environment and interactions with other genes has strong influence on development of cancer even in patients with a heritable cancer syndrome
- Example: BRCA1 and BRCA2 carriers born after 1940 have 3 times more breast cancer than carriers born before 1940.

We don't understand why this is, but clearly there is an environmental factor

Non-hereditary Predisposing Medical Conditions

- In addition to environmental, occupational, and lifestyle risks, some medical conditions increase cancer risk.
- Chronic inflammation is common denominator.
- Important to be aware of—enhanced cancer screening may be necessary.

Chronic inflammation and Cancer

- **Associated with infection**
  - **Helicobacter Pylori gastritis (gastric cancer)**
  - **Chronic osteomyelitis (cancer in fistula tracts)**
  - **Viral hepatitis (liver cancer)**
- **Autoimmune**
  - **Ulcerative colitis of the colon (colon cancer)**
  - **Sclerosing cholangitis (bile duct cancer)**
- **Medically induced**
  - **Long term bladder catheterization (bladder cancer)**

Fistula tracts go to the skin to drain infected bone. These fistula tracts have a high propensity to develop squamous cell carcinoma

Chronic bone infection

Immune system attacks bile duct, and you get a lot of inflammation

Bladder cath was in place to help with urinary retention problems

However, bladder cath caused inflammation

Pre-cancerous lesions

- For some cancers, precursor lesions have been identified—pre-cancerous lesions:
  - "In-situ carcinoma" (non-invasive)
  - "Dysplasia"
  - "Intraepithelial neoplasia"
  - Some (but certainly not all!) benign neoplasms (adenomas of the colon, for example)
- Marked increase in cancer at the site
- Obligate precursor (remove it and you prevent cancer!)
- Not all will progress to cancer.

On pathway to developing tumor, they increase risk of cancer

Occupational Cancers and Carcinogens

Definition of Carcinogen

Carcinogen: Anything that increases the cancer rate/risk

An external agent that increases the incidence of malignant neoplasms, reduces their latency, or increases their severity or multiplicity--WHO

http://monographs.iarc.fr/ENG/Preamble/currenta2objective0706.php

Occupational Cancers--Historic

- **Identification of scrotal cancer in chimmney sweeps in the 1700's led to the discovery of tar and soot as a carcinogen (Sir Percival Pott).**
  - **First public health measure to prevent occupational cancer—bathing!**
- **Study of occupational cancers has identified many chemical carcinogens.**

Bathing eliminated scrotal cancer

Bathing is one of the single most important public health measures to eliminate cancer

OCCUPATIONAL CANCERS

Allow us to find specific carcinogens in different occupations

Examples of occupational cancers (approximately 20,000 cancer deaths and 40,000 new cases of cancer each year in the U.S. are attributable to occupation)

- Arsenic (metal smelting, herbicide)

  lung and skin cancers

- Asbestos (fire-resistant textile, brake lining, tiles)

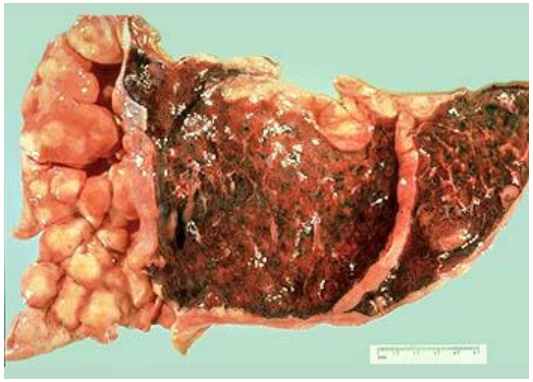
  lung, mesothelioma and GI tract cancers

- Benzene (light oil, paint, dry cleaning)

  leukemia, Hodgkin lymphoma

- Vinyl chloride (refrigerant and plastics)

  Angiosarcoma and liver cancer



mesothelioma

Carcinogens

Thousands of proposed carcinogens.
IARC accepts 107 class 1 carcinogens

- **Chemical/occupational**
- **Radiation (including UV)**
- **Infectious**
- **Dietary exposures**
- **Therapeutic/iatrogenic**
- **Social Habits**

The WHO has a ranking as to how good a carcinogen in. A Class 1 carcinogen is one for which there is outstanding evidence that it is really a carcinogen

http://monographs.iarc.fr/ENG/Classification/index.php

CHEMICAL CARCINOGENS

- Many chemical carcinogens are highly reactive electrophiles (have electron deficient atoms) that can react with nucleophilic (electron rich) sites in the cell, including DNA, RNA and protein.
  - Direct carcinogens
  - Indirect carcinogens (aka procarcinogens)
    - Metabolite is the active carcinogen

A procarcinogen is not a carcinogen. Our body metabolizes procarcinogens into active carcinogens. Most of the carcinogens we know are probably procarcinogens

Types of Procarcinogens

Indirect carcinogens

- Polycyclic aromatic hydrocarbons: the most potent carcinogen, produced in combustion of tobacco, can cause lung and bladder cancers
- Tobacco smoke contains over 4000 chemical compounds

We're not sure which ones out of the 4000 are the worst procarcinogens

- Aromatic amines (in dye and rubber) and azo dye (food color)
- Naturally occurring carcinogens: aflatoxin B in stored peanuts and grains, cause liver cancer

Mold that grows on peanuts

- Nitrosamines and amides: nitrate preservatives are converted by bacteria in gastrointestinal tract and may contribute to gastric cancer

Metabolic Activation of Procarcinogens

Enzymes that convert procarcinogen into carcinogen can affect cancer risk

Particularly the polycyclic aromatic hydrocarbons

People have different versions of the enzymes in the P450 dependent pathway (which occurs in the liver)

- **Most known carcinogens are metabolized and activated by cytochrome P-450 dependent mono-oxygenases**
- **A P-450 gene product, CYP1A1 metabolize polycyclic aromatic hydrocarbons**
- **Cytochrome P-450 enzymes are polymorphic**
- **A highly inducible form of CYP1A1 is associated with higher risk to develop lung cancer in smokers.**

This highly inducible form allows more conversion of procarcinogen to carginogen = more cancer

If you block conversion of procarcinogen to carcinogen, you can block the cancer progression

Inactivation of procarcinogen or its derivatives

- **Glutathione-S-transferase (GST)** inactives polycyclic aromatic hydrocarbons
- **GST is deleted** in many patients, who incur a **higher risk** of lung and bladder cancer if exposed to tobacco smoke.

Radiation

- **Ultraviolet light**

  Skin cancers

- **Ionizing radiation (X-rays, gamma rays)**

  Leukemia, thyroid, and many others

Infectious agent carcinogens

- **Viruses:**
  - **Human papilloma virus (HPV)--Cervical cancer**
  - **Epstein-Barr Virus (EBV)--Lymphoma**
  - **Hepatitis B and C viruses--Liver Cancer**
  - **Human T-cell lymphotrophic virus-1--Leukemia/lymphoma**
- **Bacteria:**
  - **Helicobacter Pylori--Stomach Cancer**
- **Parasites:**
  - **Shistosoma haematobium--Bladder Cancer**
  - **Opisthorchis viverrini-- Bile duct cancer**

Parasites are a more significant cause of cancer globally than in the US

Dietary carcinogens

- **Aflatoxins (product of mold on peanuts, etc)**

  Liver cancer

- **Arsenic**

  Lung and skin cancer

Therapeutic/iatrogenic carcinogens

- **Many chemotherapy agents (lymphomas and leukemias).**
- **Estrogenic hormone(trium, breast).**

Chemotherapy agents not uncommonly cause additional cancers which are usually lymphomas or leukemias

Estrogenic hormones cause low rates of cancer

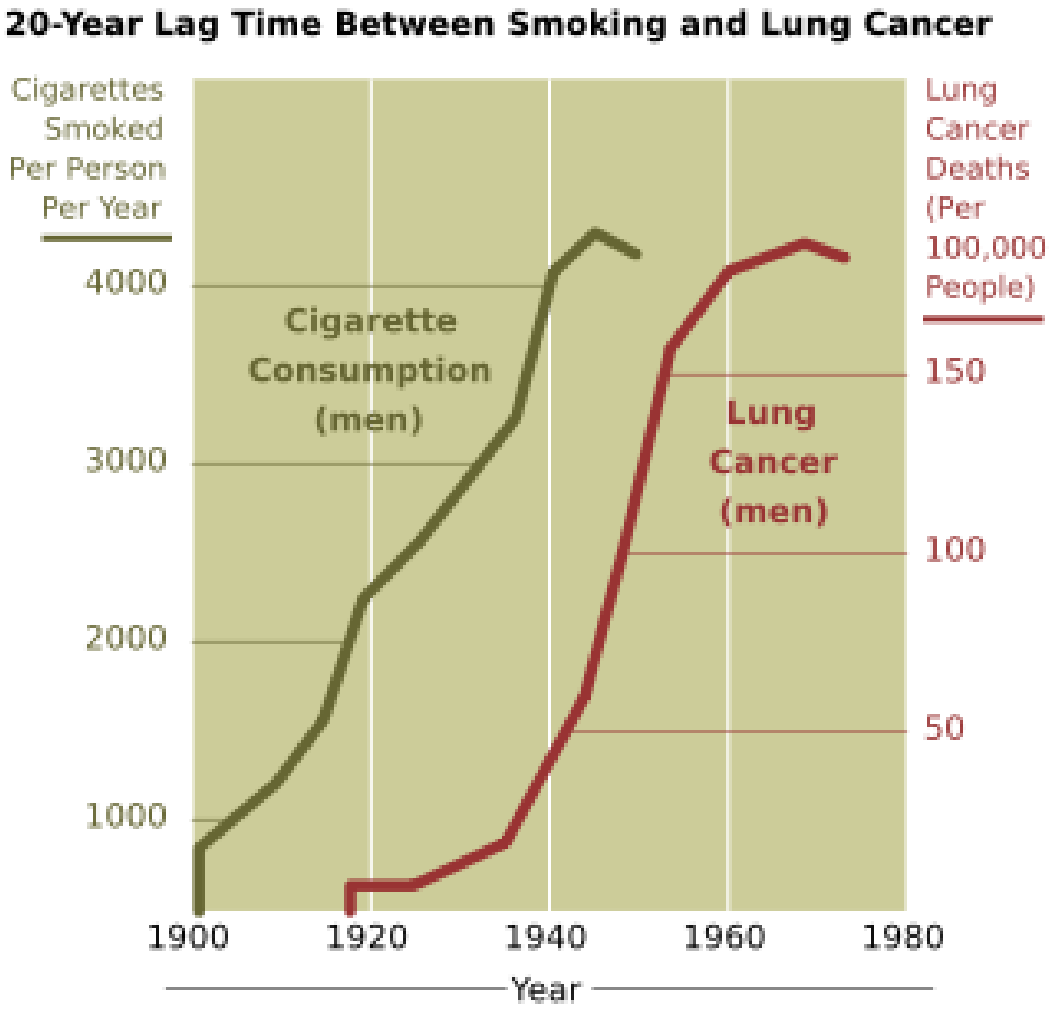
Cultural and Lifestyle Habits

- Tobacco smoke – Lung and respiratory tract, kidney, bladder, and pancreas cancers
- Ethanol – Liver, upper aerodigestive tract cancers
- Betel quid – Mouth cancer
- Smokeless tobacco – Mouth cancer
- Salted fish, chinese style – Nasopharyngeal cancer
- Obesity – Colon, endometrial, breast cancer

25% of U.S. cancers are caused by tobacco smoke!

Obesity - Colon, endometrial, breast cancer

The incidence of lung cancer is highly correlated with smoking



There is almost a perfect 20-25 year lag time between these two curves

“Lifestyle” Risk Factors and Prevention

Over a third of cancer deaths worldwide are due to potentially modifiable risk factors. The leading modifiable risk factors worldwide are tobacco smoking and ethanol use, and diet low in fruit and vegetables; in developed countries obesity is also a leading cause of cancer, and in low-and-middle-income countries sexual transmission of human papillomavirus is a leading risk factor for cervical cancer.

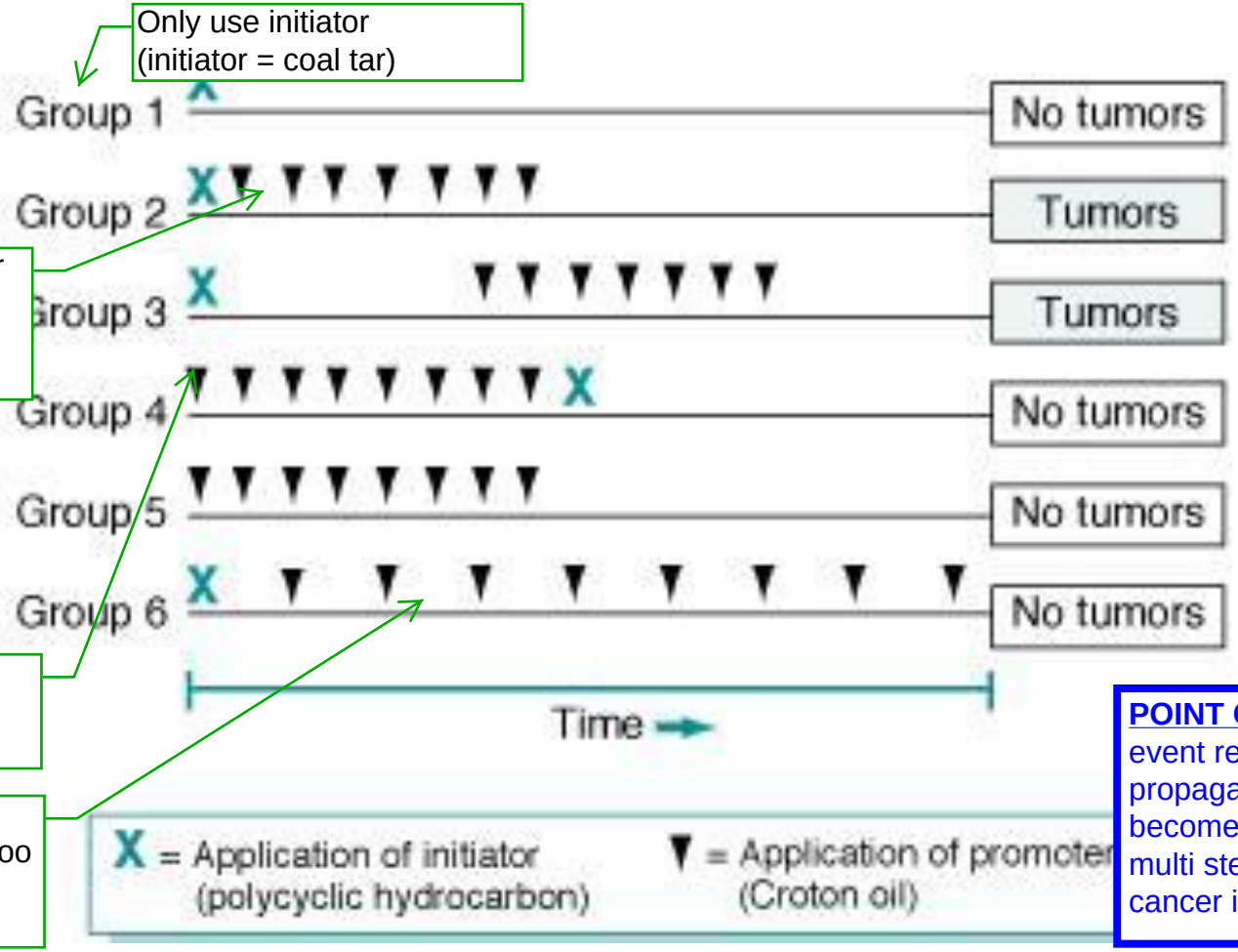
Environmental Causes of Cancer

- Although specific known carcinogens are important, much of the observed variation in cancer rates cannot be attributed to specific carcinogens
- Dietary and lifestyle/cultural contributions to carcinogenesis are complex and multifactoral
- We are constantly exposed to a wide variety of potentially carcinogenic agents

"All the good things in life are fattening, immoral, illegal, or oncogenic"

you pick which one you want! yay! :D

Carcinogenesis is a multi-stepped process of initiation and promotion



Initiator + Promoter (Promoter = irritant that causes inflammation)

Promoter before initiation = no tumor

Initiator and then promoter that is too spaced out = no tumor

Experiment: try to induce cancer in rabbits by applying coal tar
*if you paint the tar on ears of rabbits - nothing happens
*found out you have to add tar + promoter to have cancer

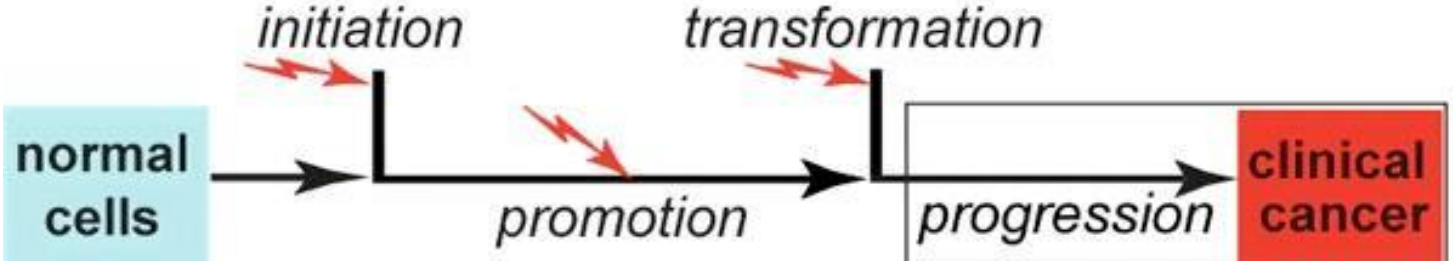
POINT OF SLIDE: Initiation event requires something to propagate (usually mutations) to become a neoplasm. There is a multi step progression to cancer, cancer is not one hit

Painted onto ears of rabbits

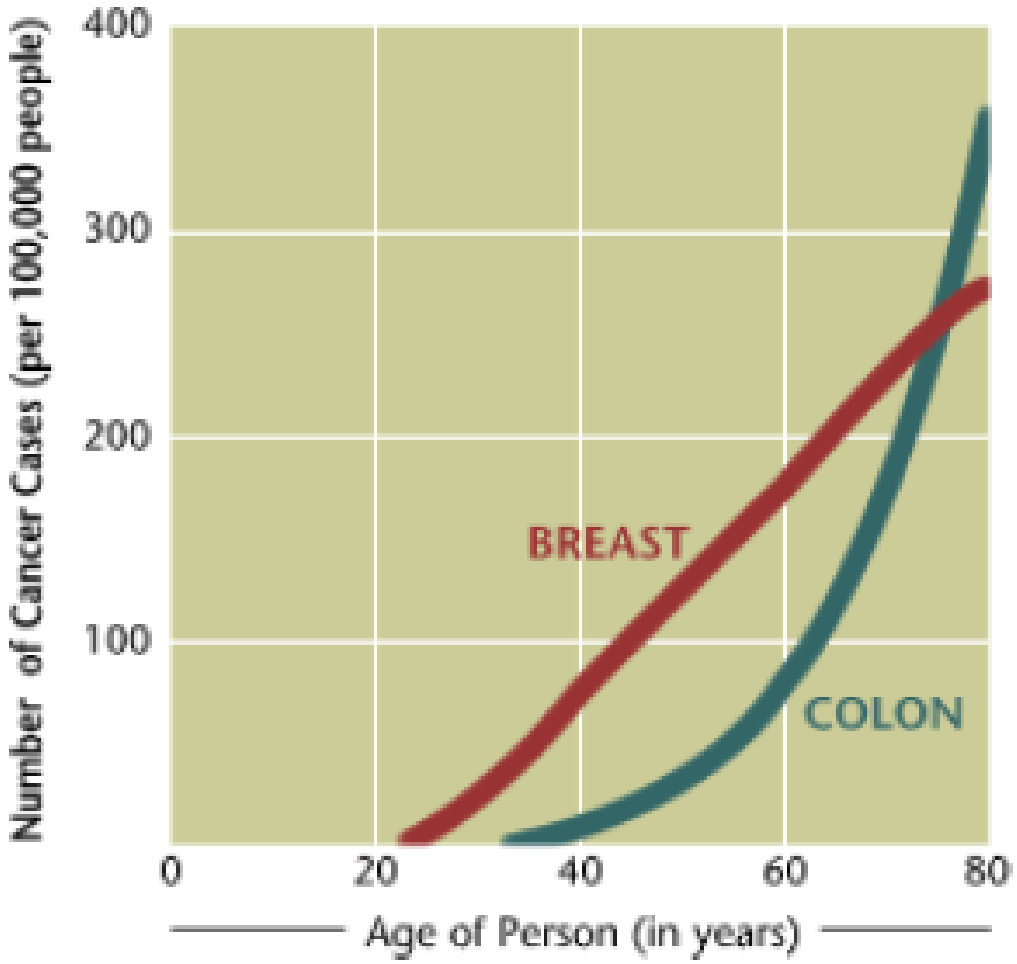
Rules of Initiation and Promotion

Initiation and promotion are both needed but their functions are different.

- Neoplasia appears only when initiators are administered prior to promoters; initiator or promotor itself is not sufficient
- Generally, **initiators are agents that cause DNA damage/mutations.**
- **Promoters cause cellular proliferation** (thereby expanding the number of cells with damage or mutations and increasing the chance of additional mutations.
- Lead to **"multi-step" model of carcinogenesis**



CHILDHOOD CANCER



There are childhood cancers even though it looks like 0 on this graph. Colon and breast cancer is extraordinarily rare in children.

CHILDHOOD CANCER

- Childhood cancers **rare** overall--1% of all new cancer.
  - **#2 leading cause of death** before age 15 (accidents #1)
- 10,730 new cases among children aged 0 to 14 years in 2009.
- 80% of children and adolescents with cancer survive 5 or more years.
- Cancer types **differ dramatically** from adults
  - **Leukemias, primitive brain tumors** 60%
  - "Small round blue cell" tumors of solid organs
  - Adult type carcinomas exceedingly rare

Better survival rates than that for adult cancers

Very primitive and recapitulate embryological development

THE END—NEOPLASIA 2

I didn't catch the questions, but here are the responses he gave:

Answer to 1st question: None of the artificial sweeteners are class 1 carcinogens. There is not strong evidence for these sweeteners in human populations. Saccharine got a lot of press because it caused bladder cancer in lab animals. Not everything that is carcinogenic in animals is carcinogenic in humans because we have different metabolic pathways. Also in labs, they gave very high doses to lab animals to be able to see enough cancer to get statistical significance. The experiment with saccharine involved giving animals enough saccharine to equal something like 1000 diet cokes each day for a year. Artificial sweeteners are a concern but haven't been proven epidemiologically in humans.

Answer to 2nd question: (question was something about how often radiation/chemotherapy ends up causing cancer) Depending on the chemotherapeutic agent, how much agent was given, age of patient - probably several percent. However, there are situations that could significantly increase this rate. If you radiate the chest wall and catch the breast tissue during puberty, these patients have almost 100% incidence of breast cancer later on in life.