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Introduction to Epidemiologic Concepts, Study Design, and Radiation Epidemiology

Radiation Epidemiology & Dosimetry Course

National Cancer Institute www.dceg.cancer.gov/RadEpiCourse

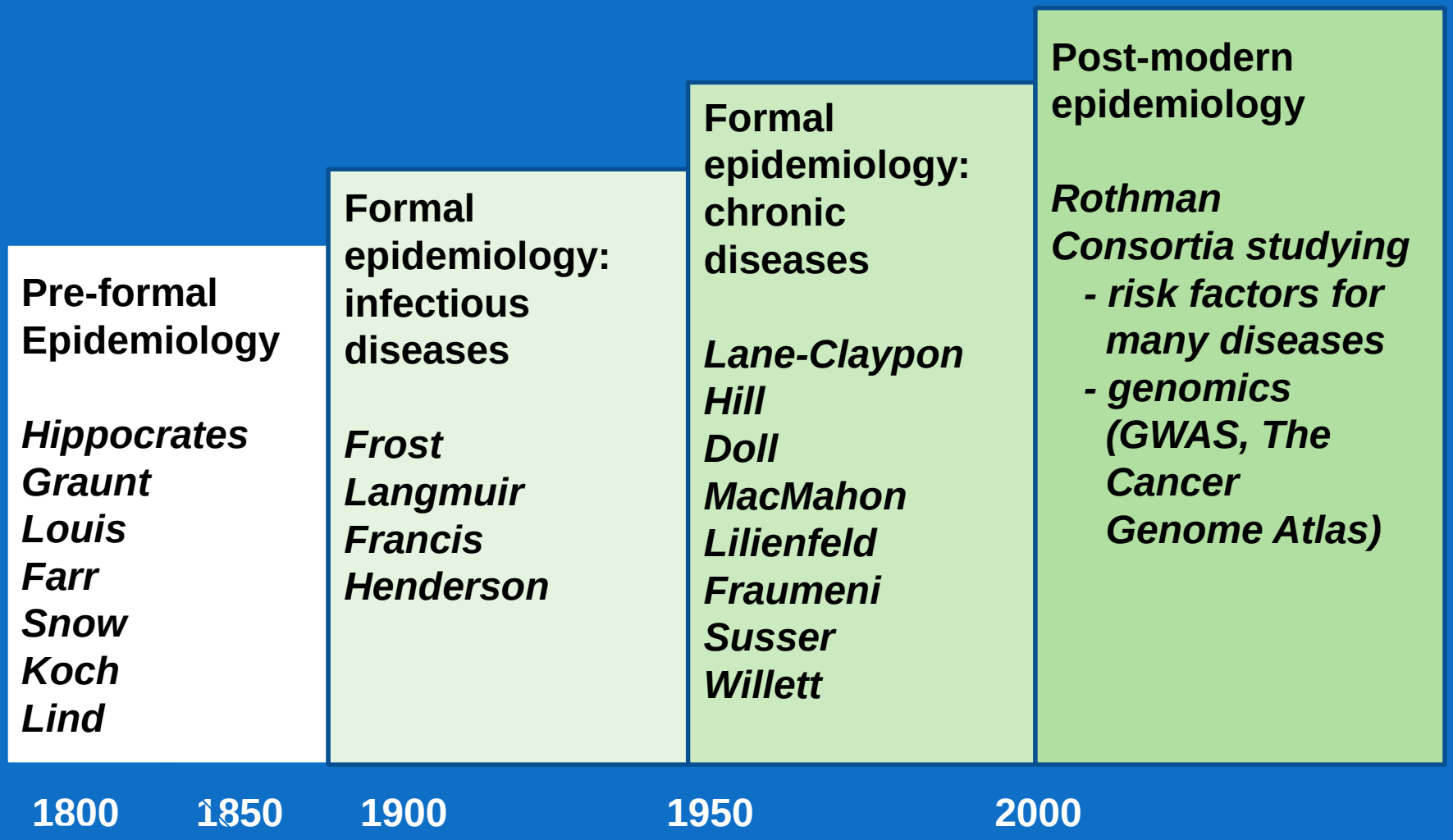
Outline

- Introduction to epidemiology: history & definitions
- Descriptive patterns
- Disease models and causation
- Sources of exposure & outcome information
- Study designs
- Introduction to radiation epidemiology

Epidemiology: A scientific discipline that provides quantitative information about human health risks associated with specific exposures

History and Definitions

History: Epidemiology from 1850 - present



Modified from AJ McMichael, 2005

Key definitions

- **Epidemiology:** the study of the distribution of a disease or conditions in human populations and the factors that influence the distribution
- **Endemic:** usual prevalence of a given disease within a defined geographic area
- **Epidemic:** excess occurrence of a group of illnesses of a similar nature in a defined area

Exposure and Outcomes

- **Exposure:** an agent or substance presumed to be causal of a disease or event (exposure surrogate is a factor indicating exposure potential, *e.g.*, job title)

- **Outcome:** a disease or precursor to a disease

Rates

- **Rate: a measure of change in a quantity per unit time**

  Incidence: the total number of new-onset disease events divided by the total person-time at risk during a given period of time

  Mortality: the total number of deaths from a disease divided by the total person-time at risk during a given period of time

Measures of Risk

- **Risk: the probability of disease developing in a population in a specified time interval**

Relative risk: the incidence of disease in an exposed group divided by the incidence of disease in a non-exposed group

Attributable risk: the maximum proportion of a disease attributable to a given exposure

Absolute risk: the observed or calculated probability of occurrence of an event in a population related to a specific exposure

Correlation, Association, Causation

- **Correlation:** the degree to which variables change together (no direction assumed)
- **Association:** a disease occurs more (or less) frequently in the presence of an exposure than in its absence & varies by exposure level
- **Causation:** in an individual, an exposure caused a given disease; within a population, at least some cases of the disease would not have occurred in the absence of the exposure

Descriptive Patterns & Trends and Disease Classification

Descriptive Epidemiology

Why study disease patterns and trends?

- Explain occurrence and natural history
- Provide guidance for health services
- Suggest hypotheses to elucidate causal inferences and mechanisms

What is the purpose of disease classification?

- Group ill persons into categories to distinguish one category from another
- Arrange diseases into groups with common characteristics

International Classification of Childhood Cancer

I. Leukemia

II. Lymphomas and reticuloendothelial neoplasms

III. CNS and other intracranial and intraspinal neoplasms

IV. Sympathetic nervous system tumors

V. Retinoblastoma

VI. Renal tumors

VII. Hepatic tumors

VIII. Malignant bone tumors

IX. Soft tissue sarcomas

X. Germ cell, trophoblastic, & other gonadal neoplasms

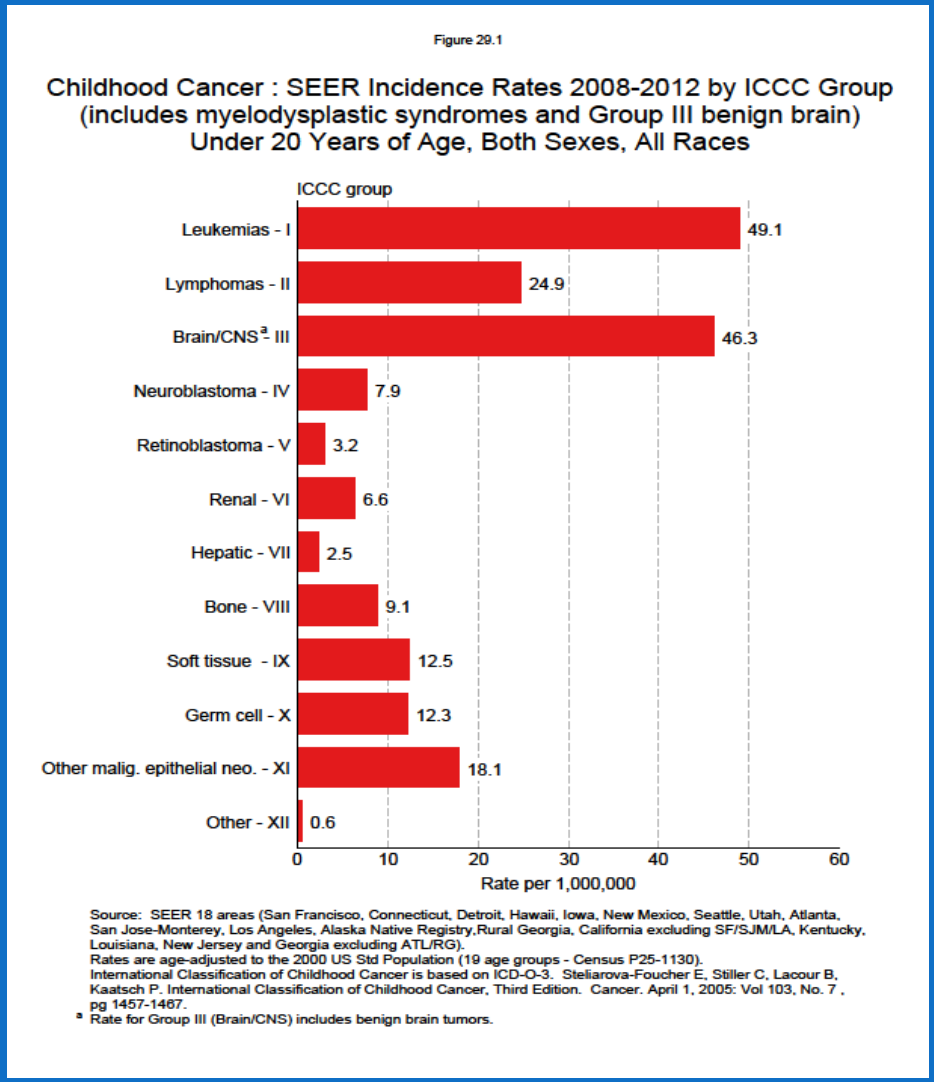
XI. Carcinomas & other malignant epithelial neoplasms

XII. Other and unspecified malignant neoplasms

Childhood Cancer Statistics

Total childhood cancer (ages 0-19) for 2014:

- **15,780 incident cases**
- **1,960 deaths**
- **5-yr survival 78%**

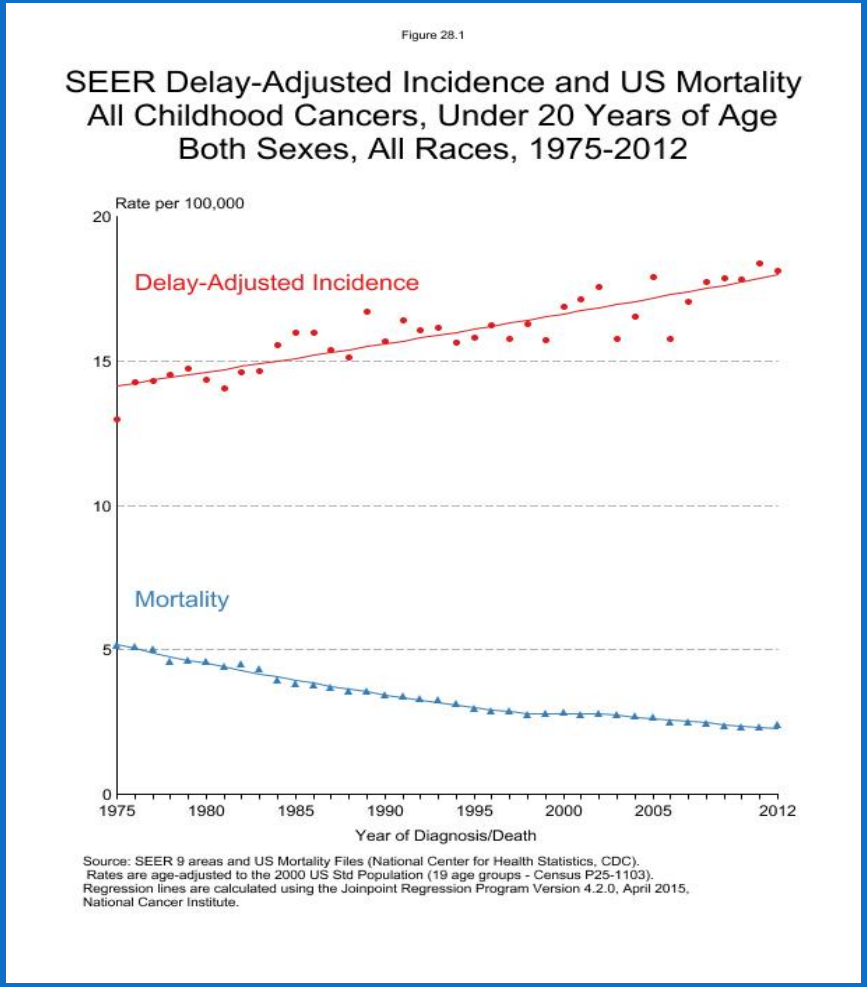


Pediatric Cancer Types Vary in Age, Gender, and Race Patterns

Characteristic	Subgroup	↑ Risk by Cancer Types
- Age	infancy	neuroblastoma, CNS, leukemia, retinoblastoma
	adolescence	Hodgkin lymphoma, germ cell cancers, CNS, leukemia
- Gender	male	lymphoma
- Race	Caucasian	Ewing's sarcoma, acute lymphoblastic leukemia
	African-American	Wilms' tumor, retinoblastoma
	African	endemic Burkitt's lymphoma

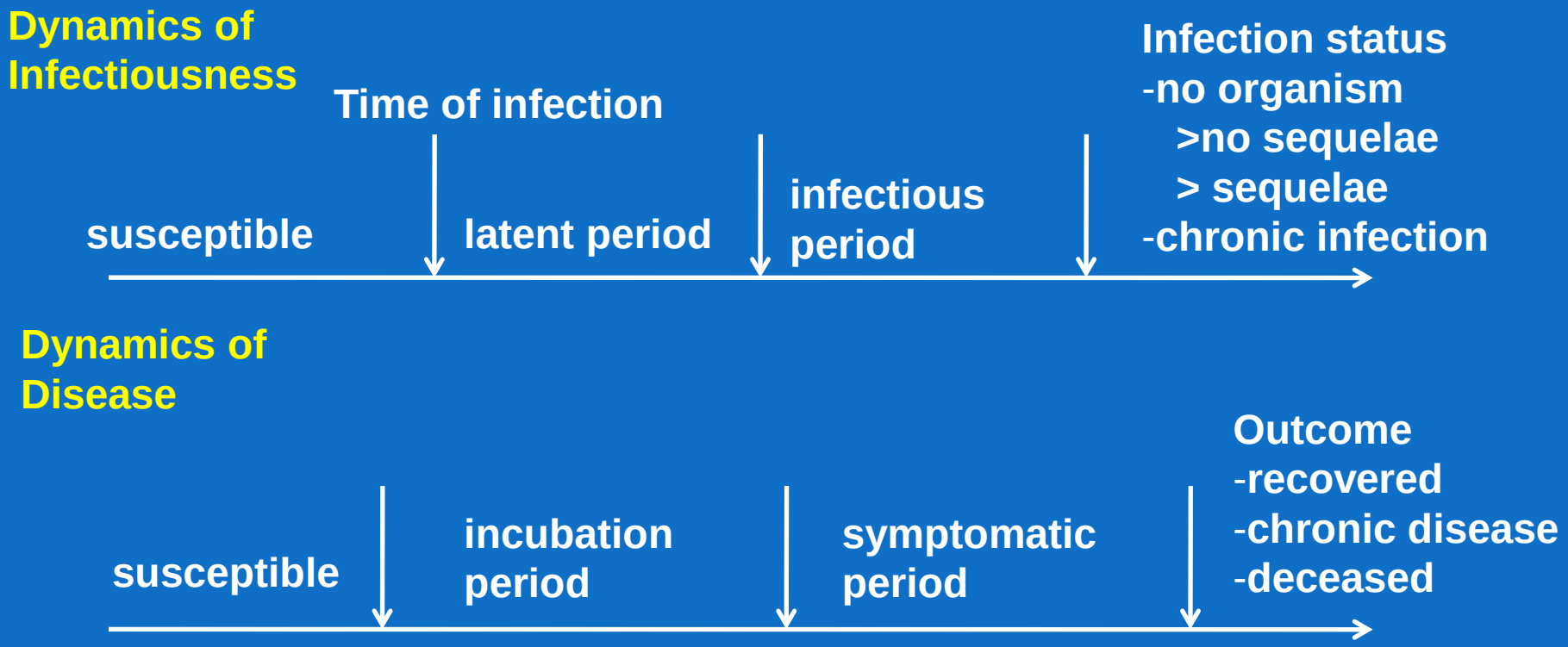
Trends in Total U.S. Childhood Cancer Incidence Children ≤ 20 Years Old, 1975-2012

- Incidence rose about 1% per year for all childhood cancers, 1975-2012
- Rate of increase was lower (*e.g.*, 0.2% per year) during 1990-2006, but subsequently rose
- Mortality steadily declined since chemotherapy in 1960s, but decrease has leveled off



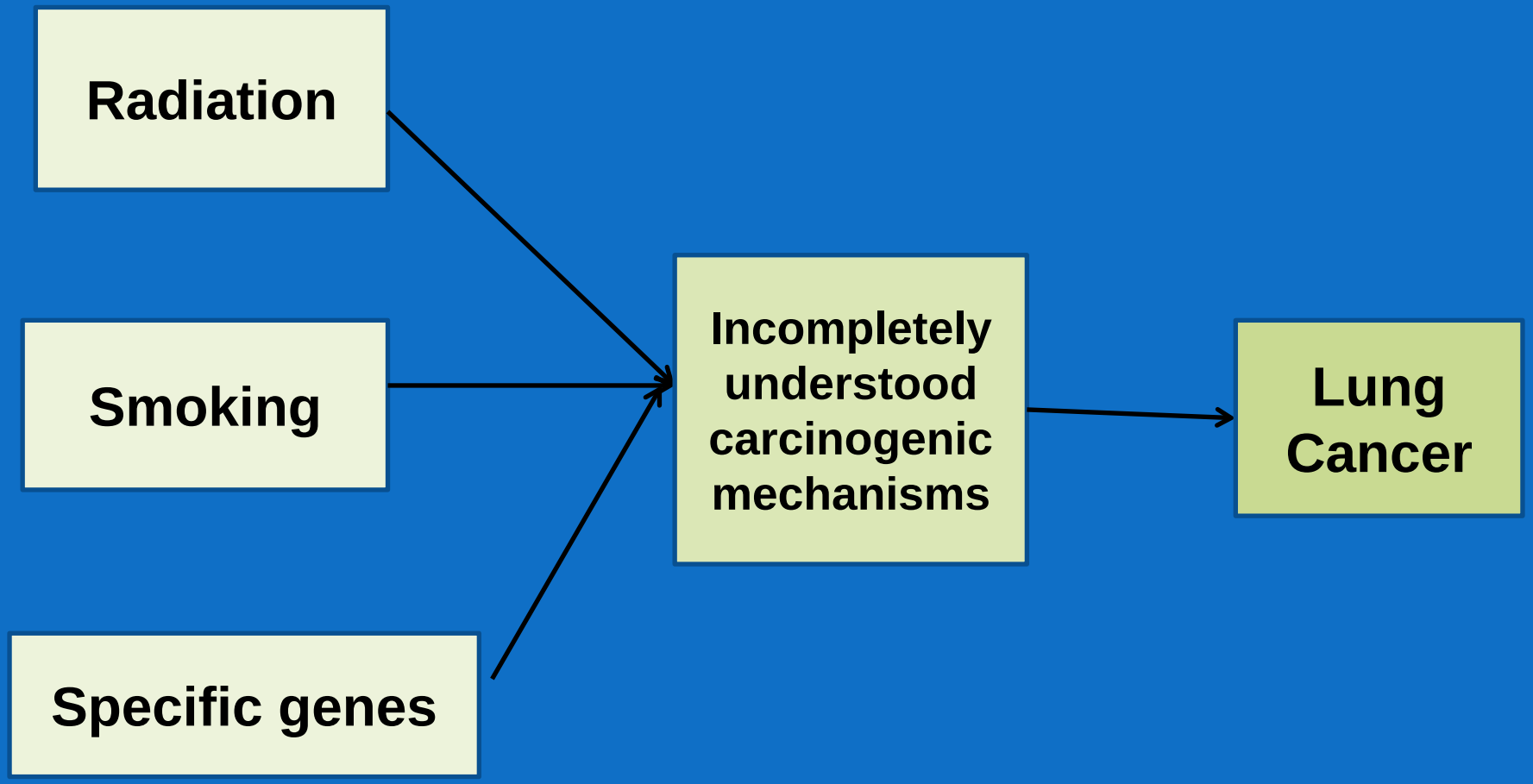
Disease Models

Dynamics of Infection and Disease

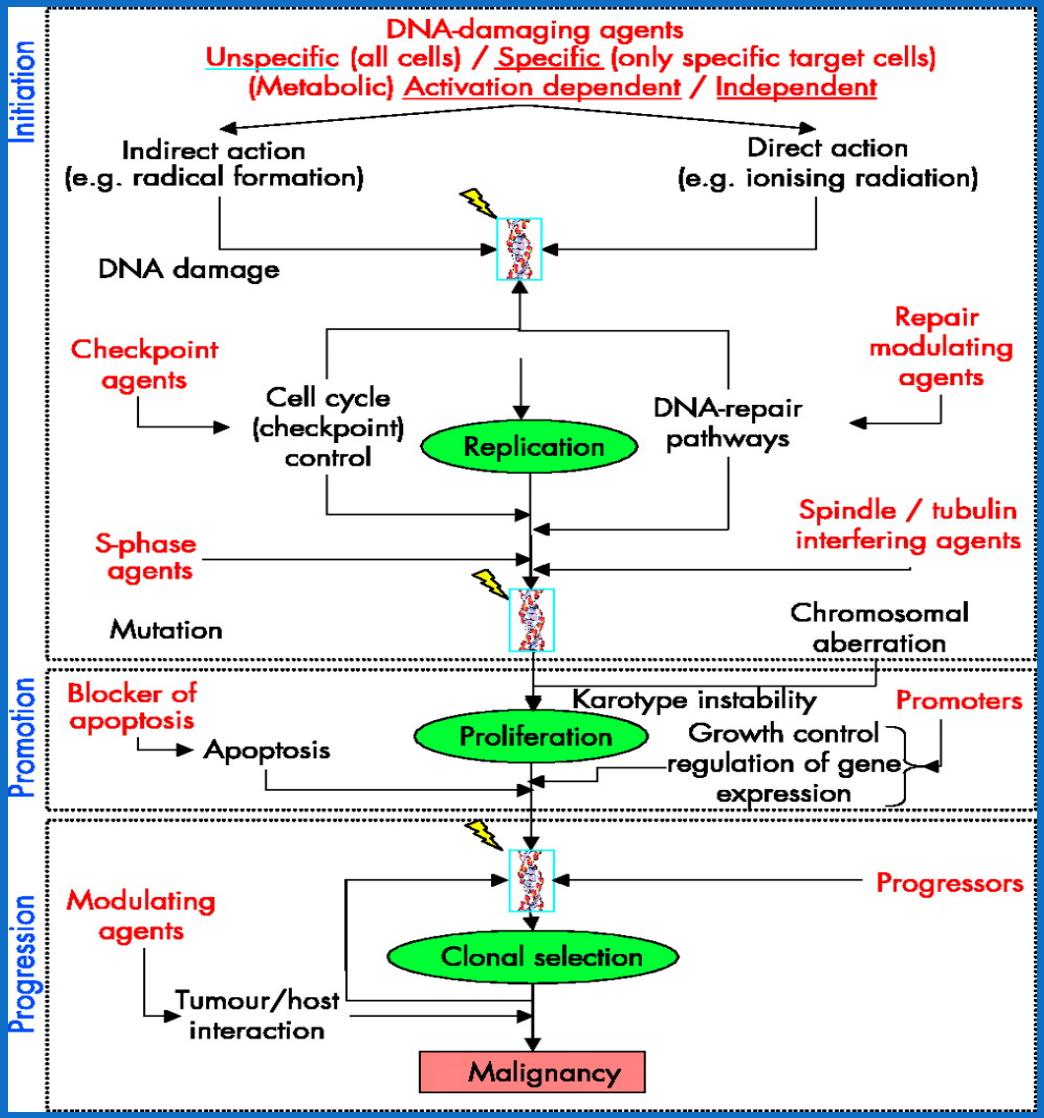


Rothman KJ, Greenland S. Modern Epidemiology, 2nd Edition, 1998

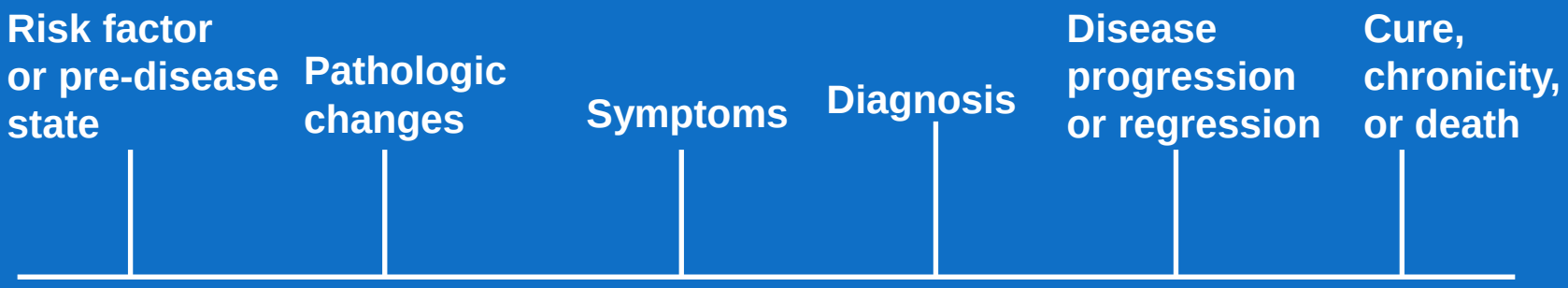
Chronic Diseases



Steps in Malignant Transformation



Natural History of Chronic Disease



- Time periods vary among different steps in process
- Time periods may vary for different exposures and different outcomes

Diseases with Familial Occurrence

Familial occurrence

- > Rare diseases that are common within affected families (X-linked lymphoproliferative syndrome)
- > Rare genetic syndrome with multiple cases of different phenotypes within affected families (Li-Fraumeni)
- > Small increase in risk within families (sibs with childhood leukemia)

Onset of some familial cases occur at notably younger ages than sporadic cases

Approaches to Identifying Genes Associated with Disease Occurrence or Progression

Population-based association studies

- > Genetic pathways
- > Genome-wide association studies
- > New generation genomic studies
  - - germline
  - - somatic

Familial aggregation/segregation analysis

Multi-Factorial Disease Causation

Societal Factors

- Neighborhood
- Cultural
- Economic
- Social

Individual – Level Factors

- Sex
- Race/ethnic group
- Lifestyle, behavioral
- Environmental
- Occupational
- Medical
- Genetic predisposition

Statistical Association versus Disease Causation

Statistical Association

Definition of association:* **Statistical dependence between two or more events, characteristics or other variables. An association is present if the probability of occurrence of an outcome, depends upon the occurrence of one or more exposures or characteristics .**

A statistical association does not imply causation

***Modified from Last JM. A Dictionary of Epidemiology, 4th Edition. 2001**

Criteria for Causation* - 1

- **Strength of the association**
  - Level of risk
- **Consistency of the association**
  - Repeatedly observed in different populations
- **Specificity of the association**
  - "If…limited to specific workers and to specific types of disease…then clearly that is a strong argument in favor of causation"
- **Plausibility**
  - "What is biologically plausible depends on the biological knowledge of the day"

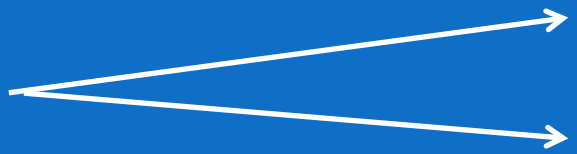
*Hill AB. The Environment and Diseases. Association or Causation? Proc R Soc Med 1965:58:295-300

Criteria for Causation* - 2

- **Coherence**
  - "…the cause and effect interpretation… should not…conflict with the…known… natural history and biology of the disease"
- **Experiment**
  - "Occasionally is it possible to appeal to experimental or semi-experimental evidence?"
- **Analogy**
  - "With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy"

*Hill AB. The Environment and Diseases. Association or Causation? Proc R Soc Med 1965:58:295-300

Types of Causal Associations



Causal Model

- **Necessary vs sufficient**
  - Necessary: must be present to cause disease
    (more common with infections: HIV → AIDs
  - Sufficient: can independently cause disease
  - Example: smoking is neither a necessary or sufficient cause of lung cancer

	Sufficient (S+)	Not sufficient (S-)
Necessary (N+)	N+S+ (necessary & sufficient)	N+S- (necessary but not sufficient)
Not necessary (N-)	N-S+ (sufficient but not necessary)	N-S- (neither necessary nor sufficient)

Non-Causal Associations

- **Types of non-causal associations**
  - **Chance association**
  - **Bias**
    - **> Selection bias (differential selection or participation of exposed vs. unexposed or controls vs. cases)**
    - **> Recall bias (differential recall by exposed vs. unexposed or controls vs. cases)**
    - **> Confounding (association of disease and an exposure with a third variable may introduce spurious associations)**

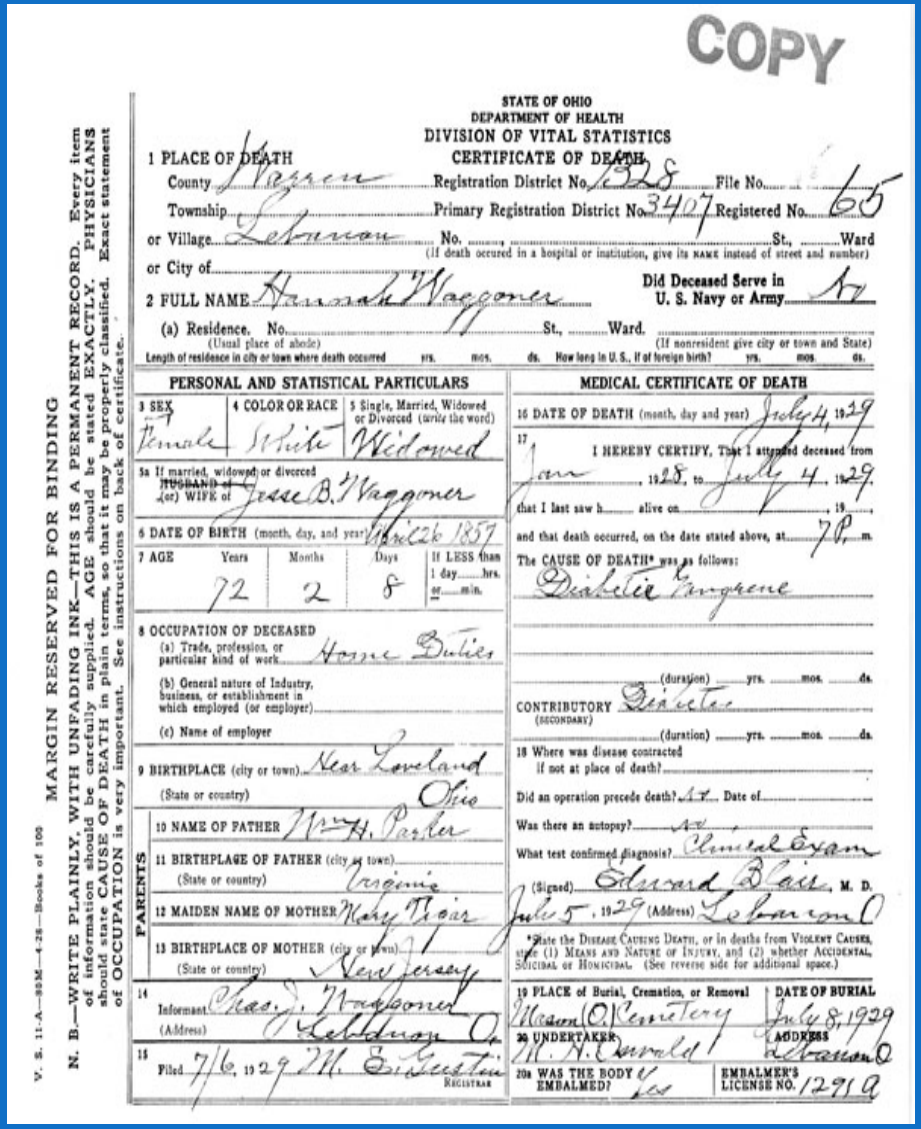
Sources of Exposure & Outcome Information

Sources of Exposure Information

- **Measurements**
  - > Group: air levels
  - > Individual
    - External: badge
    - Internal: blood
- **Questionnaires**
  - > Medical history
  - > Work history
- **Administrative records**
  - > birth certificates
  - > job records

Sources of Outcome Information

- **Vital records**
  - > death certificates
  - > birth certificates
- **Morbidity surveys**
  - > Health Interview Survey
  - > Health Examination Survey
- **Disease notification & registration**
  - > cancer registries
  - > infection notification



COPY

STATE OF OHIO
DEPARTMENT OF HEALTH
DIVISION OF VITAL STATISTICS
CERTIFICATE OF DEATH

1 PLACE OF DEATH
County Warren Registration District No. 1528 File No. 65
Township Lebanon Primary Registration District No. 3407 Registered No.
or Village Lebanon No. St., Ward
(If death occured in a hospital or institution, give its NAME instead of street and number)
or City of
2 FULL NAME Hannah Waggoner Did Deceased Serve in U. S. Navy or Army No
(a) Residence. No. St., Ward.
(Usual place of abode) (If nonresident give city or town and State)
Length of residence in city or town where death occurred yrs. mos. ds. How long in U. S., if of foreign birth? yrs. mos. ds.

PERSONAL AND STATISTICAL PARTICULARS

3 SEX: Female
4 COLOR OR RACE: White
5 Single, Married, Widowed or Divorced (write the word): Widowed
5a If married, widowed or divorced (HUSBAND of) (or) WIFE of: Jesse B. Waggoner
6 DATE OF BIRTH (month, day, and year): April 26 1857
7 AGE: Years 72 Months 2 Days 8 If LESS than 1 day hrs. or min.
8 OCCUPATION OF DECEASED
(a) Trade, profession, or particular kind of work: Home Duties
(b) General nature of Industry, business, or establishment in which employed (or employer)
(c) Name of employer
9 BIRTHPLACE (city or town): Near Loveland (State or country) Ohio
PARENTS
10 NAME OF FATHER: Wm H. Parker
11 BIRTHPLACE OF FATHER (city or town) (State or country): Virginia
12 MAIDEN NAME OF MOTHER: Mary Friar
13 BIRTHPLACE OF MOTHER (city or town) (State or country): New Jersey
14 Informant: Chas. J. Waggoner (Address) Lebanon O.
15 Filed 7/6, 1929 M. E. Geeting REGISTRAR

MEDICAL CERTIFICATE OF DEATH

16 DATE OF DEATH (month, day and year): July 4, 1929
17 I HEREBY CERTIFY, That I attended deceased from Jan 1928, to July 4, 1929
that I last saw h alive on
and that death occurred, on the date stated above, at 7 P. m.
The CAUSE OF DEATH* was as follows:
Diabetic Gangrene
(duration) yrs. mos. ds.
CONTRIBUTORY (SECONDARY) Diabetes
(duration) yrs. mos. ds.
18 Where was disease contracted if not at place of death?
Did an operation precede death? No Date of
Was there an autopsy? No
What test confirmed diagnosis? Clinical Exam
(Signed) Edward Blair M. D.
July 5, 1929 (Address) Lebanon O
*State the DISEASE CAUSING DEATH, or in deaths from VIOLENT CAUSES, state (1) MEANS AND NATURE OF INJURY, and (2) whether ACCIDENTAL, SUICIDAL or HOMICIDAL. (See reverse side for additional space.)
19 PLACE of Burial, Cremation, or Removal: Mason (O.) Cemetery DATE OF BURIAL: July 8, 1929
20 UNDERTAKER: M. A. Oswald ADDRESS Mason O
20a WAS THE BODY EMBALMED? Yes EMBALMER'S LICENSE NO. 1291

MARGIN RESERVED FOR BINDING

N. B.—WRITE PLAINLY, WITH UNFADING INK—THIS IS A PERMANENT RECORD. Every item of information should be carefully supplied. AGE should be stated EXACTLY. PHYSICIANS should state CAUSE OF DEATH in plain terms, so that it may be properly classified. Exact statement of OCCUPATION is very important. See instructions on back of certificate.

V. S. 11-A—30M—4-28—Books of 100

Epidemiologic Study Designs

Cohort Studies

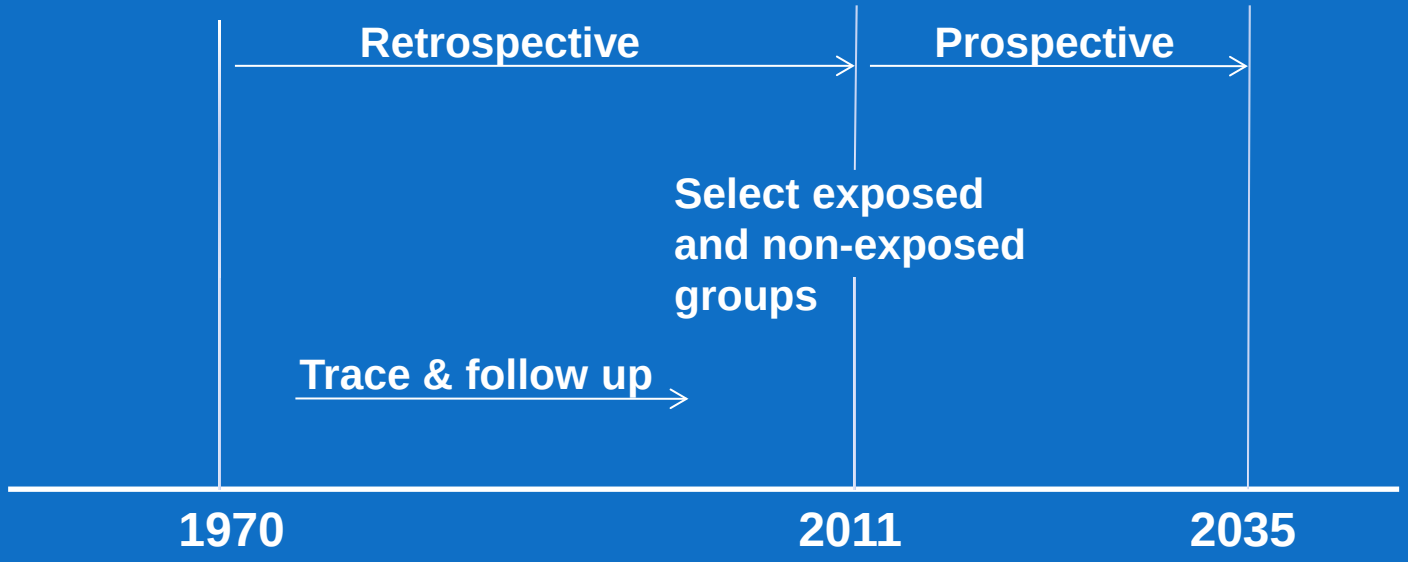
- **Distinguishing features**

  > population defined by exposures prior to onset of disease

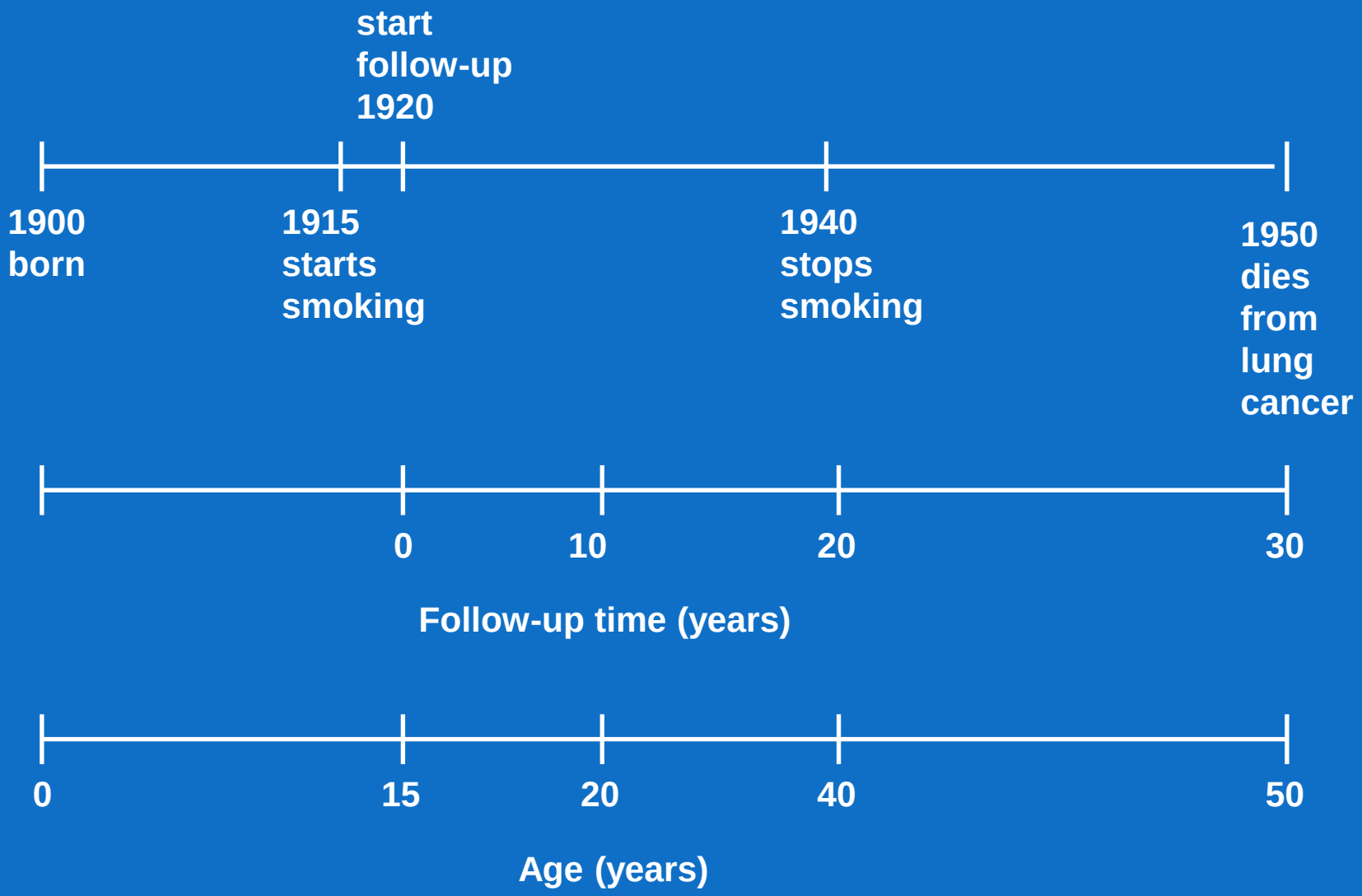
  > population followed over time to estimate disease/death rate

  > compare rates in exposed vs unexposed groups

- **Retrospective vs prospective follow-up**



Follow-up: Multiple Axes of Time



Case-Control Studies

Definition: compare proportion with exposures in diseased cases vs controls

Study base: composed of population at risk of exposure during period of risk of exposure; cases and controls should emerge from same study base & have same exposure opportunity

Associations identified from case-control studies: smoking and lung cancer, DES and vaginal adenocarcinoma, post-menopausal estrogen and endometrial cancer

Case-Control Studies

- **Distinguishing features**

  > determine exposures prior to diagnosis/referent date using interviews, medical records or other records

  > compare proportion of cases with exposure to proportion of controls with exposure

  > estimate risk using odds ratio = a x d/ b x c

- **Framework**

Characteristics	With disease	Without disease	Total
With exposure	a	b	a + b
Without exposure	c	d	c + d
Total	a + c	b + d	a + b + c + d

Cross-Sectional Studies

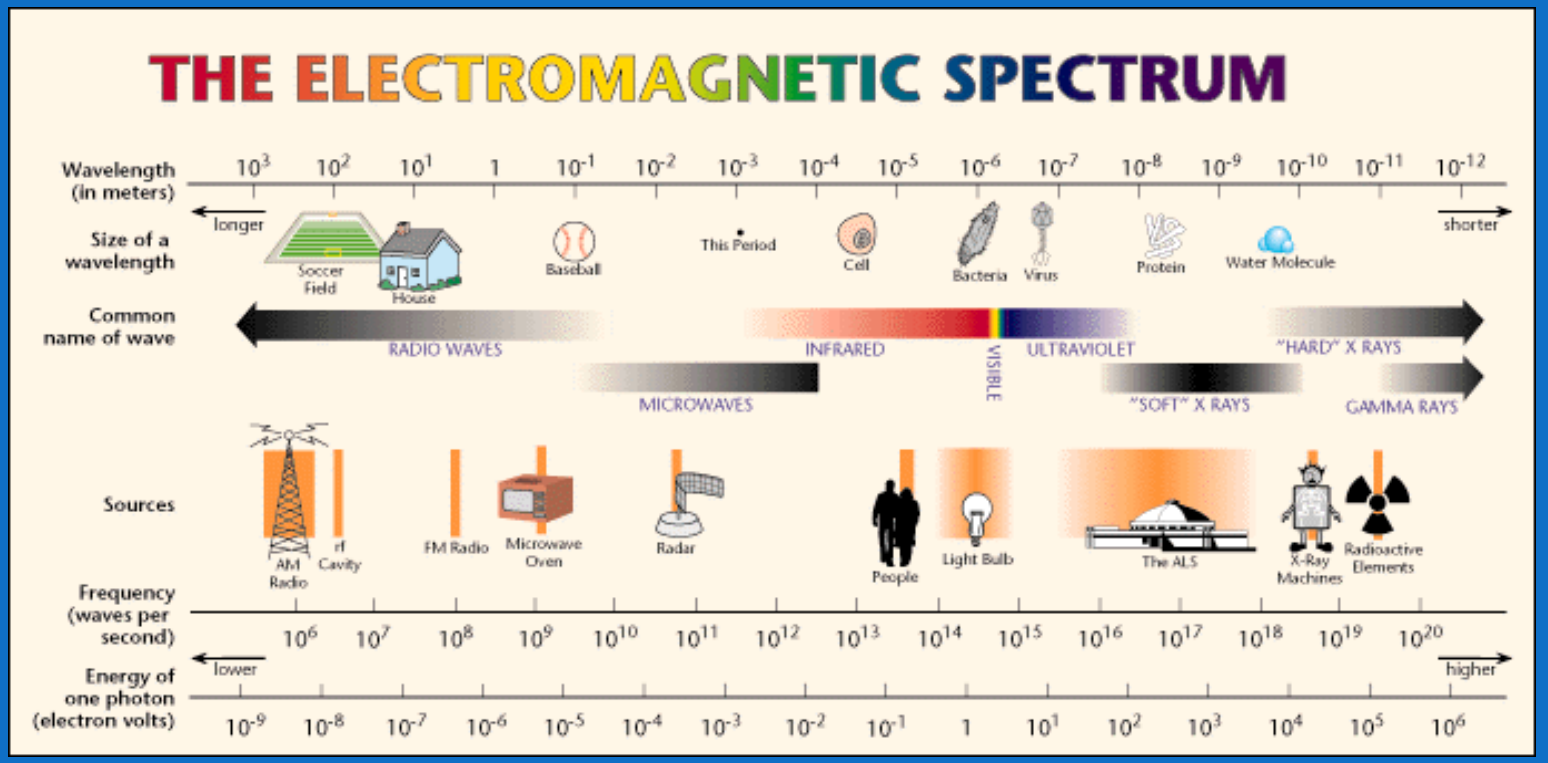
- **Distinguishing features**
  - > compare exposures in cases and controls
  - > compare proportion of cases with exposure to proportion of controls with exposure at the time of the study

Introduction to Radiation Epidemiology

Types of Ionizing Radiation

- **γ-rays / X-rays:**
  - **similar properties**
- **α-particles:**
  - **nuclei of helium atoms**
  - **major source of natural background radiation (*e.g.* radon)**
- **β-particles:**
  - **Electrons (^{131}I)**
- **Neutrons:**
  - **nuclei with no electrical charge**
  - **flight crews and frequent flyers**
- **Heavy charged particles:**
  - **nuclei of elements (carbon, neon, iron)**
  - **cosmic radiation, space travel, astronauts**

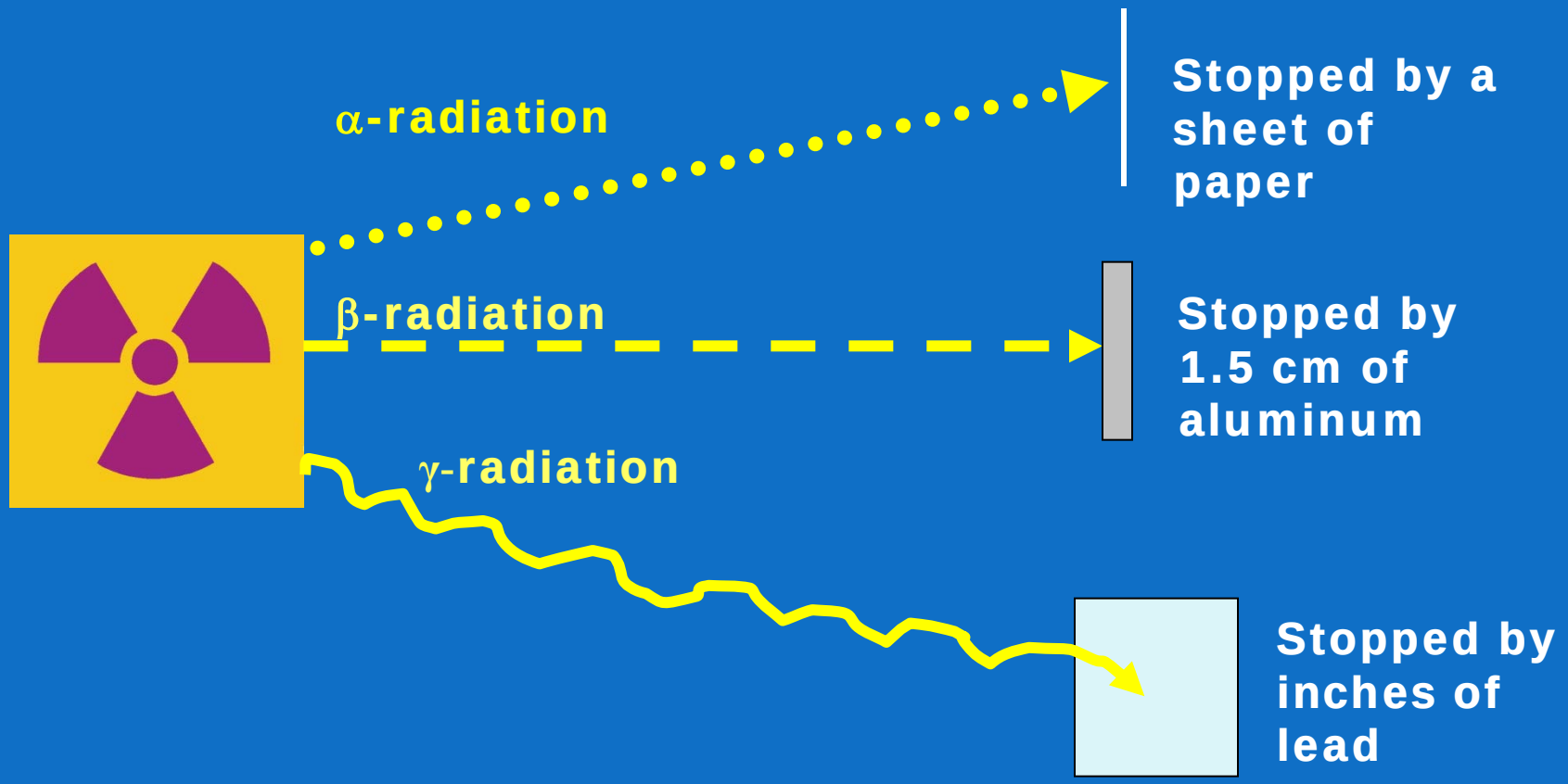
Differ in their penetrating ability & biological effectiveness



Source: http://www.lbl.gov/MicroWorlds/ALSTool/EMSpec/EMSpec2.html

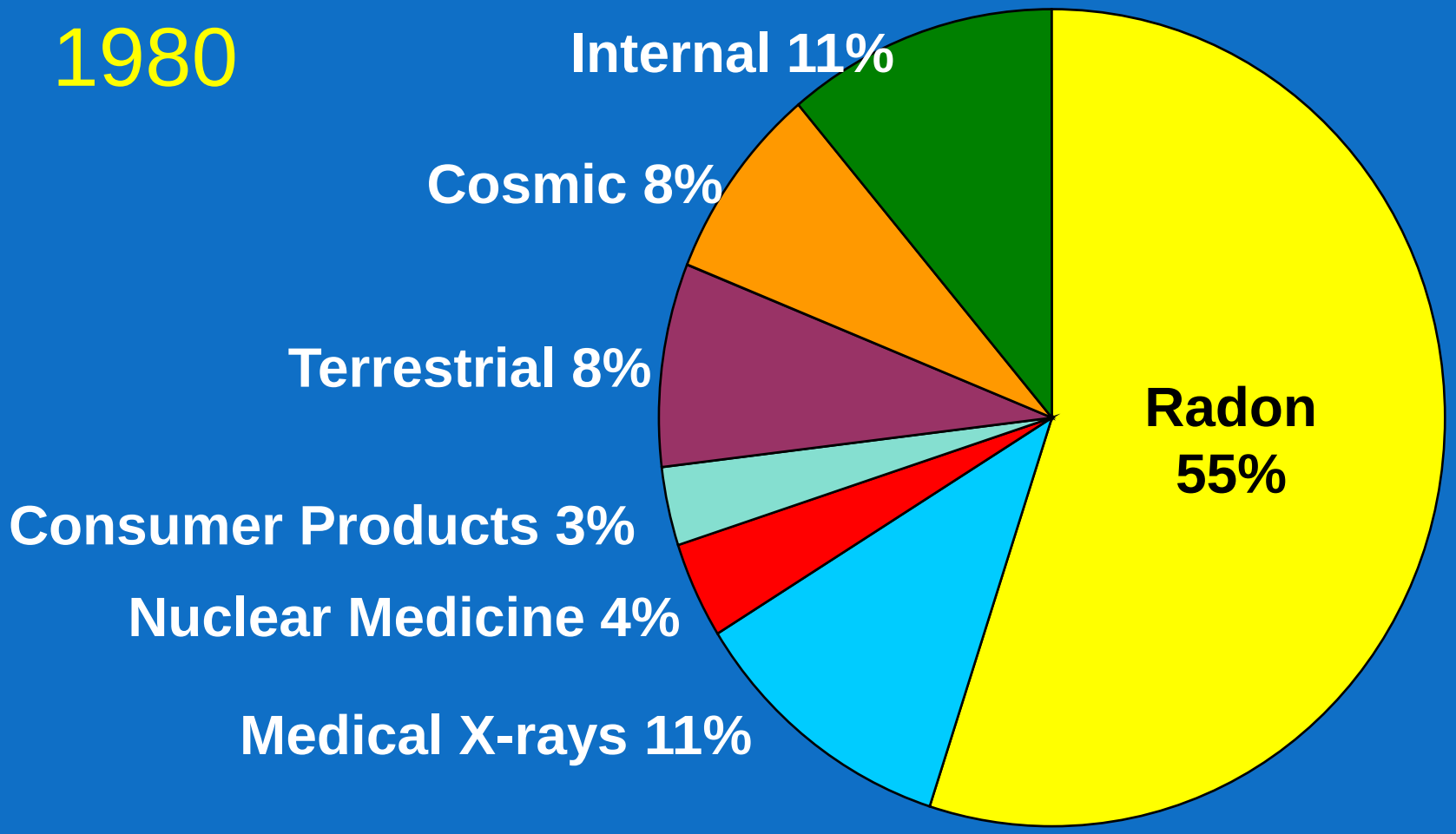
- **Extremely low frequency magnetic fields/radiofrequency/**
- **microwaves: low energy; radiofrequency/microwave heats tissue, not established carcinogens**
- **Ultraviolet (UV): low energy; skin carcinogen**
- **Ionizing: high energy, penetrates tissue easily, dislodges electrons creating ions, carcinogen**

Penetrating Power



Sources of Ionizing Radiation

1980

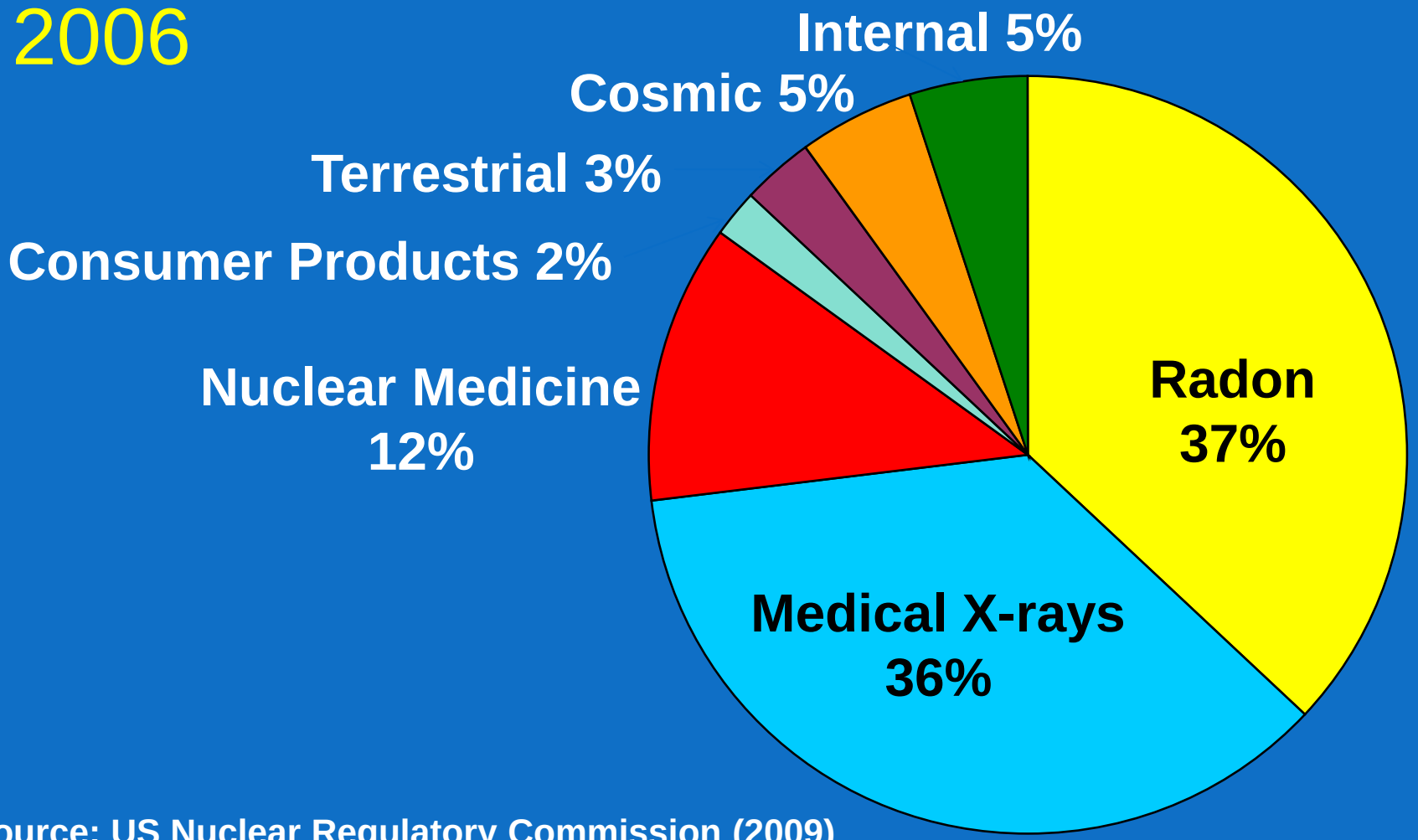


Source: US Nuclear Regulatory Commission 1987

http://www.nrc.gov/reading-rm/basic-ref/glossary/exposure.html

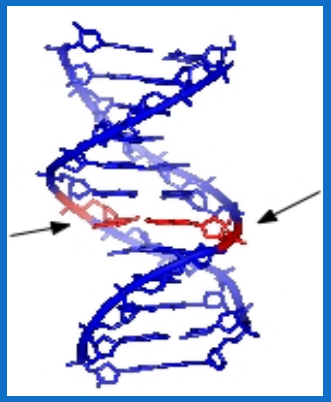
Sources of Ionizing Radiation

2006



Source: US Nuclear Regulatory Commission (2009)
http://www.nrc.gov/reading-rm/basic-ref/glossary/exposure.html

Radiation Carcinogenesis



- **Hallmark of radiation damage**
  - DNA double strand breaks (DSB)
  - Clustered complex lesions
  - DNA repair processes
    - non-homologous end-joining (NHEJ): error prone, can lead to chromosome aberrations
    - homologous recombination (HR): error free
- **Non-targeted effects**
  - Effects in tissues far from ‘in-field radiation’
  - Genomic instability: manifests after several generations of cell division

Comparing Doses
Gray – energy deposited/kg

Activity	Level
US Average, all sources*	6.2 mSv (annual)
Fallout	0.005 mSv (annual)
Chest x-ray	0.1 mGy
Mammogram	0.7 mGy
CT scan	10 mGy
A-bomb	100 mSv
Cancer treatment (tumor)	10,000–70,000 mGy

*US Nuclear Regulatory Commission (2010)
http://www.nrc.gov/about-nrc/radiation/around-us/doses-daily-lives.html#1

Radiation Epidemiology Studies

Environmental

- Nuclear discharges
  - > A-bomb
  - > Nuclear testing
  - > Nuclear accidents
- Radon
- Cosmic radiation
- Other natural background

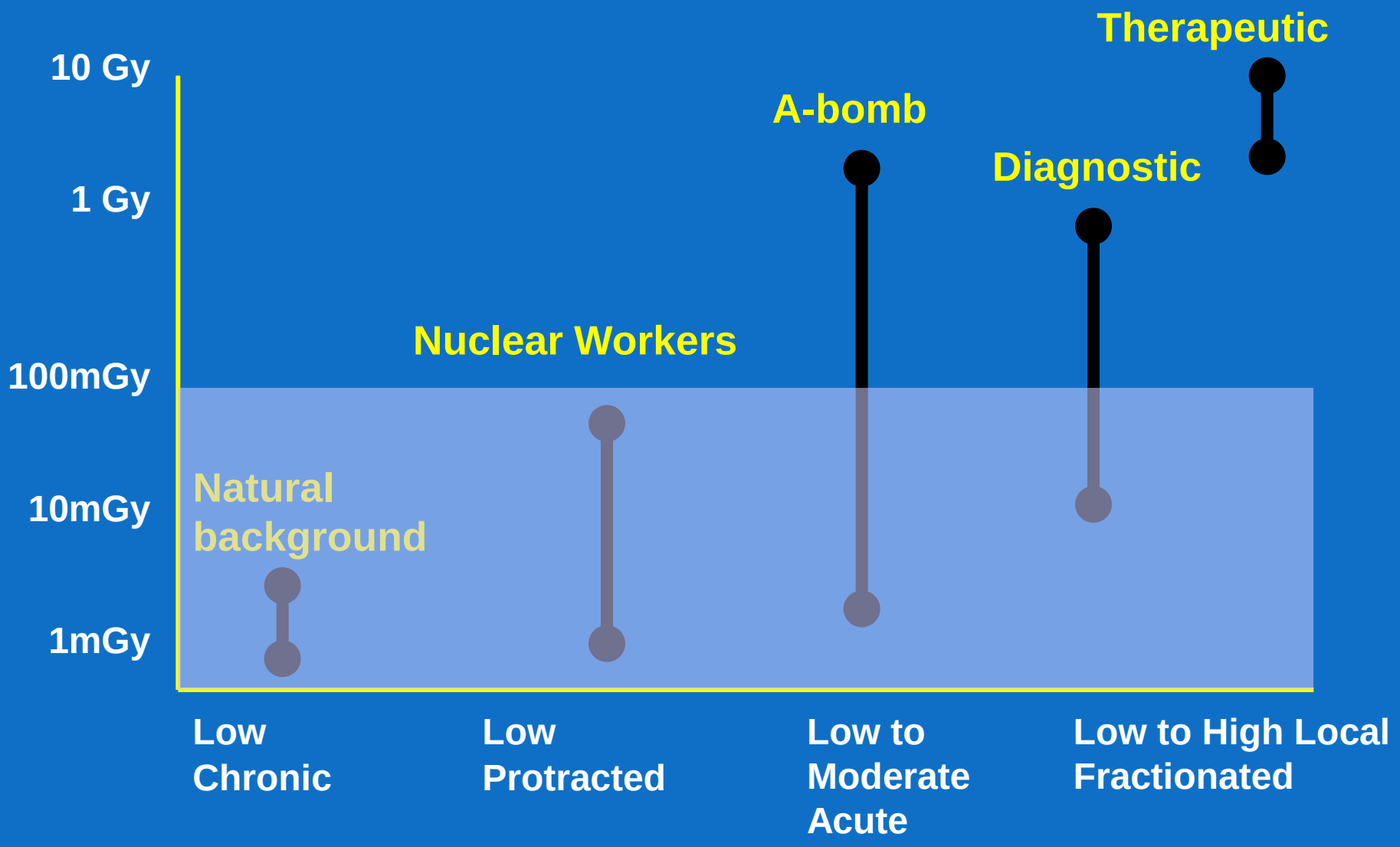
Medical

- Diagnostic
- Therapeutic

Occupational

- Radiologists & radiologic techs
- Uranium miners
- Nuclear facilities
- Chernobyl clean-up workers

Ranges of Effective Dose Levels in Major Study Categories



Environmental Sources of Radiation

- Protracted exposure to all (natural background) or acute or shorter-term (nuclear discharges)

- Military and nuclear discharges: ↑understanding radiation carcinogenesis & non-cancer diseases
  - A-bomb: 'gold-standard' for understanding radiation dose-response and basis of radiation protection
  - Chernobyl: internal exposures and thyroid cancer

- Generally low doses (moderate-to-high in some exposed A-bomb and Chernobyl exposed)

Medical Sources of Radiation

- Fractionated, partial body exposures to growing percent of population with underlying conditions
- Types
  - Diagnostic: x-rays (radiography, CT, fluoroscopy), radionuclides (nuclear heart scans, PET)
  - Therapeutic (low to high doses)
- Cancer and non-cancer outcomes evaluated
- Low, moderate, and high doses

Occupational Sources of Radiation

- Protracted, generally low-dose exposures during working life to millions of workers
- Workers wear monitoring badges to capture exposures for radiation protection purposes
- Epidemiologic studies: risks of all and specific cancers, cataracts, circulatory diseases
- Generally low doses (moderate-to-high exposures before 1950)

Summary - 1

- Epidemiology: provides quantitative information about exposures and associated human health risks
- Key definitions: rates, risks, correlation, statistical association
- Descriptive epidemiology: importance of evaluating patterns and trends
- Disease classification: purpose & importance

Summary-2

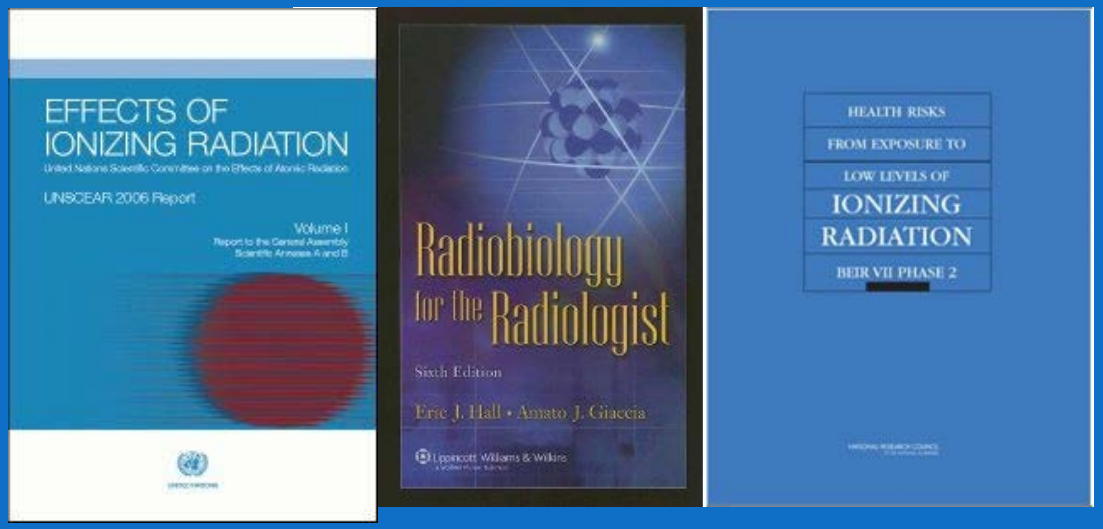
- Disease models: infectious & chronic disease
- Natural history of disease: implications for epidemiologic study designs
- Familial occurrence and genetic components of disease
- Multi-factorial disease causation
- Statistical association vs causation; causal criteria; non-causal associations

Summary-3

- Sources of exposure and outcome information
- Epidemiologic study designs: cohort, case-control and cross-sectional studies
- Introduction to radiation epidemiology
  - > types of radiation
  - > sources and levels of radiation exposures
  - > major categories of radiation epidemiologic studies (environmental, medical, occupational)

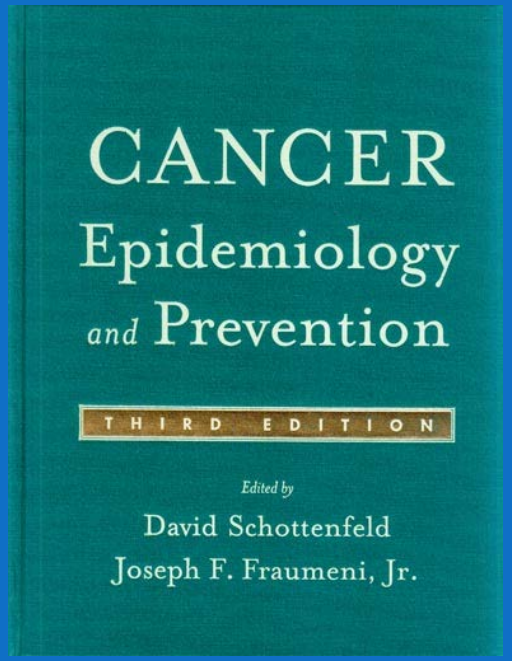
References

- Radiobiology for the Radiologist, 7th Edition (Eric Hall)
- Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR VII Report - NAS)
- Effects of Ionizing Radiation (UNSCEAR reports)



References

- Radiation Epidemiology Branch, DCEG, NCI
  http://dceg.cancer.gov/reb
- Radiation Effects Research Foundation (RERF)
  http://www.rerf.or.jp/index_e.html
- Cancer Epidemiology and Prevention
  (Schottenfeld and Fraumeni)



Questions and Answers

U.S. Department of Health and Human Services
National Institutes of Health | National Cancer Institute
www.dceg.cancer.gov/RadEpiCourse
1-800-4-CANCER
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