National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Division Of Cancer Epidemiology And Genetics
Radiation Epidemiology Branch

The Carcinogenic Effects of Radiation: Experience from Recent Epidemiologic Studies

Elaine Ron
Columbia University Radiation Course
June 15, 2007

Epidemiology is the study of the distribution and determinants of disease in human populations

Epidemiologic Studies

- **Conducted on Humans**
- **Real Exposure Conditions**

Epidemiologic Studies

- Observational rather than Experimental
- Possibility of confounding or bias
- Uncertainties in dose estimation
- Problem of multiple comparisons
- Low statistical power can limit detection of effects

Types of Epidemiologic Studies

- Clinical Trial
- Cohort
- Case-Control
- Ecologic

Methodological Issues

- Appropriate study population
- Statistical power to detect radiation effects
- Reliable individual dose estimates
- Accuracy and completeness of outcome measure
- Information on potential confounders and risk modifiers

Radiation Epidemiology

To characterize and quantify the risk of cancer in populations exposed to radiation, alone or in combination with other agents or risk factors

Why Study Radiation?

- To recommend or regulate protection standards for workers and the general public
- To modify radiotherapy
- To better understand individual susceptibility
- To learn more about carcinogenesis

Ionizing Radiation: Some History

- X-rays discovered in 1895
- First used medically in 1896
- Identified as a human carcinogen at turn of century
- Since then, extensively studied and quantified carcinogen
- In last few decades, occupational exposure declined, medical exposure increased

Radiation Epidemiology: Some History

- 1920s: Bone cancer excess among radium dial painters
- 1940s: Leukemia excesses among radiologists
- 1950s: Leukemia in A-bomb survivors
- 1960s: Lung cancer risk from underground mine exposure to radon

Radiation Exposures

- Medical
- Environmental
- Occupation
- Military

Epidemiologic Studies

Atomic bomb survivors

Medical exposure
- *Diagnostic*
- *Radiotherapy*

Environmental exposure
- *Radon*
- *Radiation accidents*
- *Fallout from nuclear testing*
- *Emissions from nuclear plants*
- *High background areas*

Occupational exposure
- *Medical and nuclear workers*
- *Miners*

Background

- Radiation cancer risks derive mostly from:
  - Acute single-dose A-Bomb survivors' exposures
  - Fractionated, high-dose radiotherapy exposures
- Protracted low-dose radiation less studied:
  - Ongoing public concern
  - Medical, environmental, occupational, military exposures
  - Most quantitative data from nuclear worker studies and now Techa River

Magnitude of Doses (Sv)

Radiotherapy: up to 80 (tumor)
50% survival probability: 4
A-bomb survivors: mean ~ 0.25
Occupational limit: 0.02 per yr
Nuclear worker study: mean ~0.004 per yr
Background radiation: 0.003 per yr
Diagnostic medical exams: 0.00001-0.01*
Round-trip flight, NY – London: 0.0001

** Lower doses for screening x-rays higher for CT*

Describing Radiation Risks

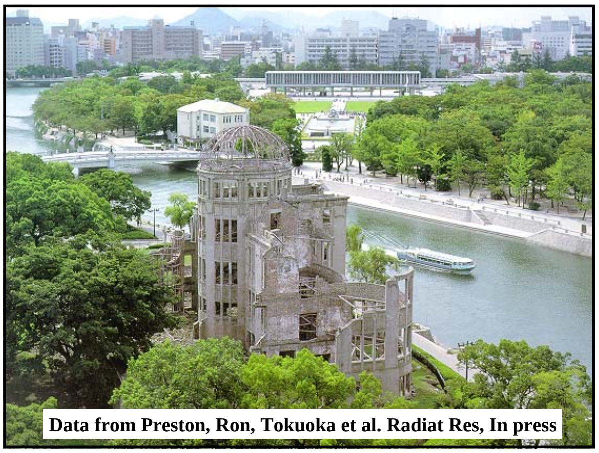
- Excess Relative Risk (ERR)
  - Percentage change in risk for a unit dose, Gy (Relative change in rate)
- Excess Absolute Rate (EAR)
  - Absolute change in rates for a unit dose, Gy (Rate difference)
- ERR and EAR can vary with age, time and gender; provide complementary information

RERF Atomic Bomb Survivor Studies

RERF

Life Span Study (LSS)
Second Solid Cancer Incidence Report 1958-1998

Preston, Ron, Tokuoka, Funamoto, Nishi, Soda, Mabuchi, Kodama. Radiat Res, In press



Data from Preston, Ron, Tokuoka et al. Radiat Res, In press

Objectives of Incidence Report

- Quantify cancer risks attributable to radiation
- Explore the shape of the dose response
- Assess how the risk is modified by age, time, gender and other factors
- Help clarify site specific differences in risk patterns
- Highlight issues and cancer sites needing more research

LSS Cohort

- Survivors within 2.5 km of the bombings
- Survivors within 2.5-10 km
- Not-in-city (NIC)

TOTAL PEOPLE 120,321

Atomic Bomb Survivors: LSS Cancer Incidence

- 105,427 people; 2.8 million PYR
- Follow-up 1958-1998
  - *>50 years after bombings*
  - *48% alive in 1998*
  - *86% alive of those <20 at exposure*
- Hiroshima and Nagasaki tumor registries
- 17,448 first primary tumors
- DS02 organ dose estimates

Preston et al. Radiat Res, In Press

Strengths of LSS Cohort

- Large, healthy non-selected population
- All ages and both sexes
- Wide range of well characterized dose estimates
- Mortality follow-up virtually complete
- Complete cancer ascertainment in tumor registry catchment areas
- More than 50 years of follow-up

Limitations of LSS Cancer Incidence Data

- Inadequate solid cancer data from 1945-1958 and leukemia data from 1945-1950
- Cancer data limited to Hiroshima and Nagasaki area residents
- Limited treatment data

LSS Cancer Incidence Cohort

Dose (Gy)	Person Years	Subjects	%
Not in city	680,744	25,247	23.9
< 0.005 in city	918,200	35,545	33.7
0.005 - 0.1	729,603	27,789	26.4
0.1 - 0.2	145,925	5,527	5.2
0.2 - 0.5	153,886	5,935	5.6
0.5 - 1	81,251	3,173	3.0
1-2	41,412	1,647	1.6
2+	13,711	564	0.5

Distribution of Solid Cancers

TOTAL	17,448
Digestive system	10,052
Respiratory system	2,001
Female genital	1,457
Breast	1,082
Urinary system	741
Thyroid	471
Skin	347
Male genital	420
Nervous system	281
Oral cavity	277

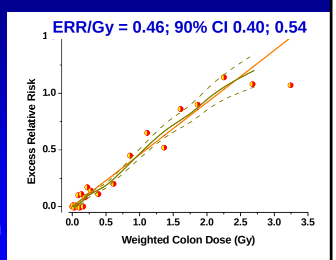
Solid Cancer Incidence

Dose (Gy)	Observed	Excess	AR%
< 0.005	9,597	3	0.0
0.005 - 0.1	4,406	81	1.8
0.1 - 0.2	968	75	7.6
0.2 - 0.5	1,144	179	15.7
0.5 - 1	688	206	29.5
1-2	460	196	44.2
2+	185	111	61.0
Total	***17,448***	***853***	**10.7***

***Attributable risk % among people with dose >0.005 Gy.**

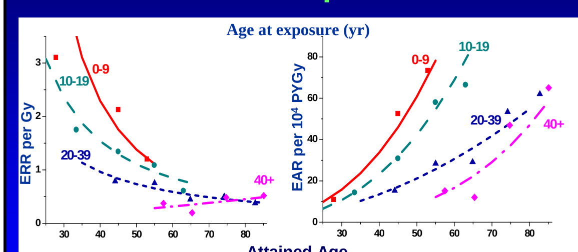
Solid Cancer Incidence Dose Response

- No evidence of non linearity in the dose response
- Statistically significant trend on 0 – 0.15 Gy range
- Low dose range trend consistent with that for full range



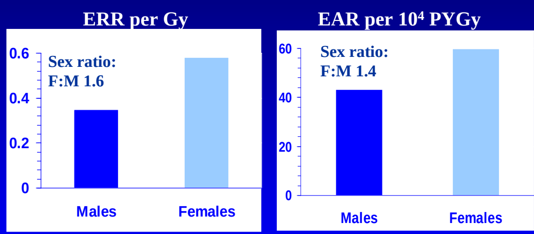
Sex-averaged at age 70 for exposure at age 30

Solid Cancer Temporal Patterns



For person age 70 exposed at age 30

Solid Cancer Risks by Gender



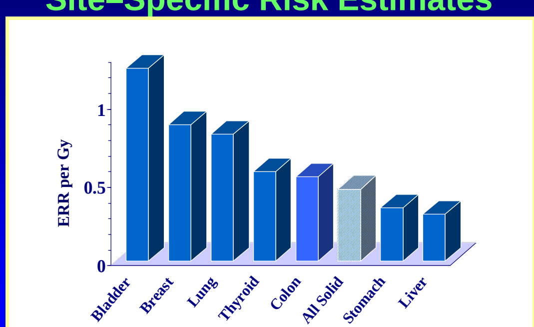
Sex ratio excluding sex-specific cancers;
breast, cervix, uterus, ovary, testes, prostate
ERR 1.8 EAR 0.9

For person age 70 exposed at age 30

Interpretation of Site-Specific Risks

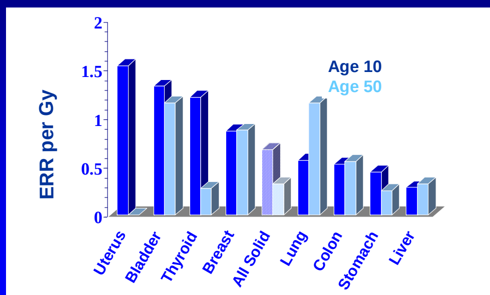
- Site-specific differences likely exist
- But much of observed variability is consistent with random variation
- Formal statistical tests generally lack power to detect real differences

Site–Specific Risk Estimates



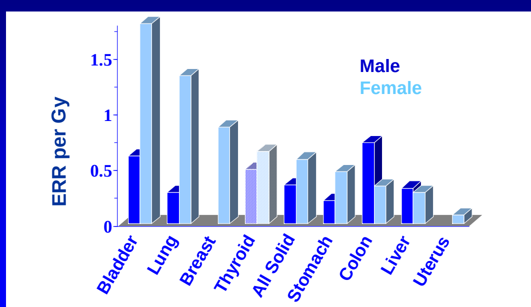
For person age 70 exposed at age 30

Age at Exposure Effects



ERR at age 70

Gender Effects



ERR at age 70 for exposure at age 30

Summary

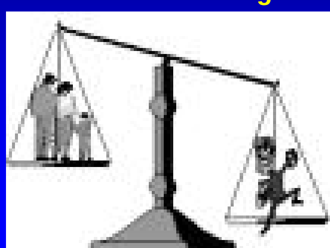
- Strong evidence for linear dose-response with no threshold
  - Increased risk 0 – 100 mSv
- Women have significantly higher risk
- Excess risk continues throughout life
- ERR decreases with increasing age at exposure and attained age
- EAR increases with attained age

Summary

- Age-time patterns don’t differ substantially for most individual sites
- With more detailed analyses, age at exposure and attained age differences difficult to distinguish
- Overall patterns similar to those seen in previous analyses
- Continue to find new results

Medical Radiation Dilemma

- Necessary tool
- Potential carcinogen



Medical Radiation Studies

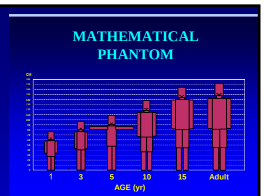
- Hundred’s of studies
- Different types of radiation
- Broad range of doses
- Various organs and tissues
- Diverse populations
- Impact on radiotherapy practice

Use of Medical Radiation in the United States

- U.S. has high medical exam rates
- Temporal trends 1980 to 1990
  - Diagnostic exams increased 20-25%
  - Radiation treatments increased 25-30%

UNSCEAR, 2000

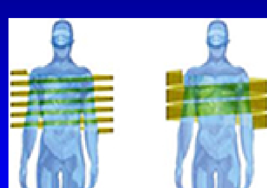
How We Estimate Doses



- Mathematical phantom with measurements in water
- Anthropomorphic phantoms
- Treatment-planning computer systems

Annual Diagnostic Exams in the United States, 1991-96

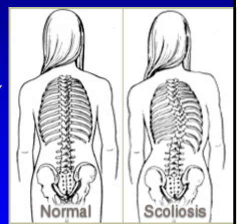
- 250,000,000 medical x-ray exams
- 8,202,000 nuclear medicine exams



UNSCEAR, 2000

Scoliosis and Breast Cancer

- 4,822 exposed
  644 unexposed
- Mean breast dose=0.11 Gy
- 77 deaths 45.6 expected
- ERR_{Gy} = 2.7 (-0.2-9.3)
- Results consistent with A-bomb survivors



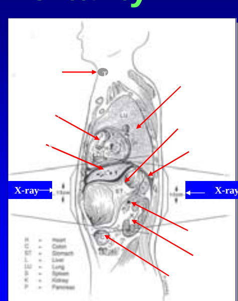
Doody et al, Spine 2001

Radiation Treatment for Benign Diseases

- Used frequently from 1930's to 1960's for various benign diseases
- Overall use has declined, but now treating some new diseases
- ^{131}I still treatment of choice for hyperthyroidism

Peptic Ulcer Mortality

- 1859 irradiated and 1860 non-irradiated peptic ulcer patients followed >30 years
- Doses to stomach and pancreas ~15 Gy, but lower to other organs
- Risks significantly elevated for stomach, pancreas and lung cancer deaths



Carr et al, Rad Res 2002

Non-Cancer Mortality After Peptic Ulcer Radiotherapy

Cause of death	RR	95%CI
Coronary heart disease	1.28	1.06 1.54
Myocardial infarction	1.44	1.11 1.86

Coronary heart disease increased with heart dose:

Dose, Gy	RR	95%CI
0.1-1.6	1.05	0.78-1.40
1.7-2.0	1.22	0.93-1.69
2+	1.52	1.10-2.10

(10 year survivors)

Second Cancers Following Radiotherapy

- New advances in cancer therapy have increased patient survival
- Growing concern about radiation induced second cancers
- Accurate dosimetry

Childhood Cancer Survivor Study

- 14,000 five-year U.S. survivors of childhood cancer, diagnosed 1970-86
- Detailed treatment information
- Periodic resurvey to update risk factor and outcome information
- Buccal cell DNA; tumor DNA
- Current mean age, 30 years

Thyroid Cancer after Radiotherapy for Childhood Cancer

- 69 cases; 265 matched controls
- Identified from 14,054 5-year survivors diagnosed 1970-86
- Thyroid cancer risk increased with dose up to 20-29Gy (OR=9.8, 3.2,35)
- Risk higher among survivors
  - <10 yr at 1st primary
  - With Hodgkins lymphoma

Sigurdson et al, 2005

Radiation Epidemiology Studies

Occupational Exposures

- Nuclear workers
- Uranium miners
- Radium dial painters
- X-ray technologists
- Radiologists
- Airline crew

Occupational Exposures

- Radiation workers can provide direct estimates of low-level exposure
- Medical workers are majority of radiation workers
  - Some early workers had substantial doses
- Nuclear workers carefully monitored
  - High exposure in FSU in early years
  - High exposure in special conditions

International Nuclear Worker Study

407,391 workers
5.2 million PYR
Mean cumulative dose 20 mSv

Cause	Deaths	ERR/Sv (90% CI)
Cancer*	6,519	0.97 (0.14, 1.97)
Leukemia**	196	1.93 (<0, 8.47

**Excluding leukemia*
*** Excluding CLL*

Cardis et al, 2005

Medical Radiation Workers

- Medical radiation workers represent largest exposed occupational group
  - about 2.3 million worldwide
  - half of radiation work force
  - large number are women
- Number of medical workers increasing

US Radiologic Technologist Study

- 146,022 technologists certified 1926 82
- Mostly female (73%)
- Age certified = 21, Current age = 53
- Two postal surveys
  ~70% response rate
- Cancer mortality, cardiovascular & musculoskeletal diseases, early menopause, cataracts, pregnancy outcomes

Doody et al 2002

Incident Cancer Risk: USRT

	Year began working			
	<1940	1940s	1950s	1960s
Breast	2.1*	0.9	1.1	0.9
Melanoma	8.4*	1.6	1.1	0.8
Acute leukemia		1.9	0.5	1.2
Basal cell skin		2.0*	1.2	1.1

* $p < 0.05$
Referent is 1970's, adjusted for age, work in other years

USRT Summary

- Early workers often had high exposures
- Suggestive evidence of an increased risk of leukemia (non CLL), cancers of the skin (melanoma, BCC), and breast among early workers
  - Risk elevated decades after initial exposures
- No excess cancer risk among recent workers
  - Marked improvements in radiation protection standards led to reduction in exposure
- Continued follow up necessary because recent workers exposed to new procedures

Environmental Exposures

- Excluding radon, is very small component of population exposure
- Exposures typically low
- Dosimetry extremely uncertain
- Causes great deal of public concern
- Try to study populations with unique exposures

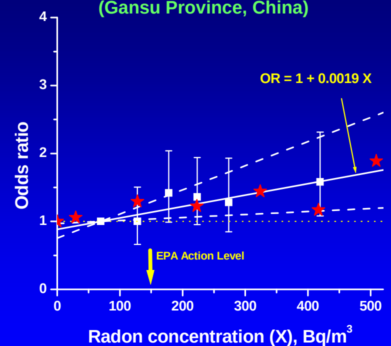
Lung Cancer And Residential Radon

- Large lung cancer case-control study in China
- Low mobility and high radon levels
- Lung cancer risks equal or exceed extrapolations from miner data

China Cave Dwellings

Wang et al AJE, 2002

Odds Ratios of Lung Cancer For Indoor Radon (Gansu Province, China)

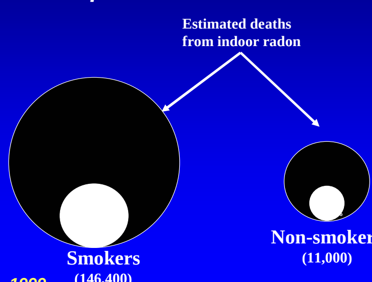


Wang et al, AJE, 2002

★ = Low-exposed miners

Annual U.S. Lung Cancer Deaths for Smokers and Non-smokers:

Contribution from indoor radon in white circles



Lubin, 1999

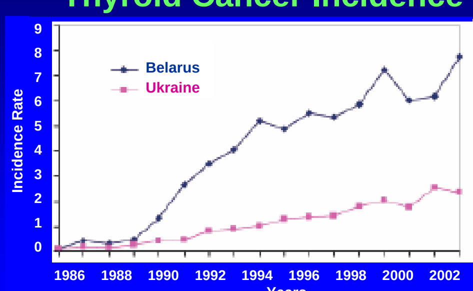
The Chernobyl Accident Ukraine, 26 April 1986

- Worst accident in nuclear history
- 10 days of releases into the atmosphere under varying meteorological conditions
- ^{131}I principal radionuclide
  - About 90% of dose
  - Inhaled and ingested

Pathway of Radioiodine Exposure from the Chernobyl Accident

- Concentrates in the thyroid; thyroid dose 15-20 fold higher than overall body dose
- Dose inversely proportional to thyroid mass, so higher dose to children
- Dose larger in iodine deficient areas

Thyroid Cancer Incidence



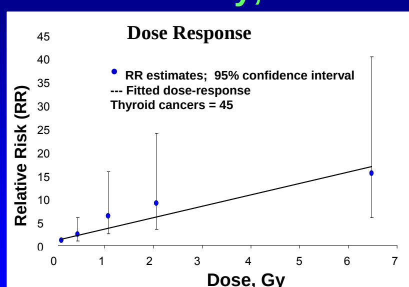
Chernobyl Forum, 2005

Belarus-Ukraine-NCI Collaborative Thyroid Cancer Screening Study

- Cohort study of 25,161 persons exposed <18 yr
- 2 arms:
  - Ukraine (n=13,243) Belarus (n=11,918)
- Direct thyroid activity measurements
- Wide range of thyroid doses
  - 44% <0.3 Gy;   28% >1 Gy
- >100 histologically verified thyroid cancers from first screening

Stezhko et al. Radiat Res 2004

Thyroid Cancer Prevalence Ukraine-NCI Study; 1998-2000



Tronko et al, JNCI 2006

Thyroid Cancer Prevalence Ukraine-NCI Study; 1998-2000

	ERR/Gy	*P*
Total	5.25	*<0.0001*
Gender		
male	2.21	*0.14*
female	16.6	
Age at exposure		
0 4	9.1	*0.58*
5 9	7.0	
10 18	3.4	

Tronko et al, JNCI 2006

Thyroid Cancer Risk Estimates from External Radiation and ^{131}I

	Study (reference)	EAR/10^4PYGy	ERR/Gy
External	Int'l pooled analysis (Ron et al. 1995)	4.4 (1.9-10)	7.7 (2.1-29)
Chernobyl	Case-control study in Belarus & Russia (Cardis et al. 2005)	N.A.	4.5 (1.2-7.8)
	Cohort study in Ukraine (Tronko et al. 2006	N.A.	5.2 (1.7-27)
	Ecological study in Ukraine (Likhtarov et al. 2006)	1.5 (1.2-1.9)	8.0 (4.6-15)
	Ecological study in Belarus & Ukraine (Jacob et al. 2006)	2.7 (2.2-3.1)	19 (11-27)

Ron E. Health Phys In press

Chernobyl Summary

- Excess thyroid cancers still occurring
- Risk appears to decrease with increasing age at exposure, little effect for adult exposure
- The number of excess cancers larger among women, but role of gender not clear in terms of relative risk
- Iodine deficiency may enhance the risk
- Deaths have been been relatively low (<1%)
- Risks are compatible with estimates from external irradiation

New Cohorts

- Kazakhstan test site residents
- Mayak Nuclear Facility
  - Mayak nuclear workers
  - Techa River residents
  - Ozyorsk population
- Airline crew
- Patients treated with new technologies?

Conclusions (1)

- Most cancers can be induced by radiation
  - Clear evidence for leukemia, breast, thyroid, salivary glands, stomach, colon, lung, liver, non-melanoma skin, ovary, bladder, brain, bone
- Young age at exposure appears to increase risk
- Risk persists throughout life

Conclusions (2)

- Little evidence to suggest a threshold
- For solid cancer, data suggest a linear dose response
- At extremely high doses the dose-response appears to flatten out, probably due to cell-killing

Questions Needing More Research

- How much cancer is caused by radiation?
- How long does risk last after exposure?
- How does radiation cause cancer?
- Why do organs & tissues vary in sensitivity?
- Is there individual susceptibility to radiation?
- How does radiation interact with other exposures?