Radiation Carcinogenesis

Eric J. Hall, D.Phil., D.Sc., FACR, FRCR
Columbia University Medical Center, N.Y.

Marie Curie and Her Daughter Irene –

Thought to have Died of Leukemia

Knowledge of Radiation-Induced Cancer Comes from:

- A-bomb survivors
- Accidents
- Individuals medically exposed
  - Includes second cancer in RT patients

Radiation Carcinogenesis – The Human Experience

Leukemia & Solid Tumors	Japanese survivors
Leukemia	Patients irradiated for alkylosing spondylitis
Thyroid	Children irradiated for enlarged thymus Children epilated for ***tinea capitis***
Breast	Patients treated with x-rays for postpartum mastitis Patients fluoroscoped repeatedly during management of tuberculosis
Lung	Uranium miners
Bone	Dial painters who ingested radium Injections of radium for tuberculosis or ankylosing spondylitis

Absolute Risk Model

- Leukemia follows an **absolute risk model**, i.e., a discrete dose-related "crop" of radiation-induced cancer over and above the spontaneous level.

Relative Risk Model

- Some cancers may follow a **relative risk model**, i.e., the natural incidence increased by a constant factor
- Since natural cancer incidence increases with age, this model would predict a large number of **excess cancers** late in life following irradiation

Latency

- **Leukemia** has the shortest latency of about **5 years**
- **Solid tumors** have a latency of **20 or more years**

Favored Time-Related Relative Risk Model

Factors considered:

- Dose ($Dose^2$)
- Gender
- Age at exposure
- Time since exposure

Radiation Epidemiology

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

Types of Epidemiologic Studies

- Cohort
- Case-Control
- Ecologic

Excess Cancer Mortality
Lifetime Risk/100,000/0.1 Sv

	BEIR V (U.S. Population) Males	BEIR V (U.S. Population) Females	UNSCEAR 88 (Japanese Population)	
Breast	--	70	Breast	60
Respiratory	190	150	Lung	151
Digestive system	170	290	Stomach	126
			Colon	79
Other solid	300	220	Other solid	194
Leukemia	110	80	Leukemia	100
Total	**770**	**810**	**Total**	**710**

Dose Rate Effectiveness Factor (DREF)

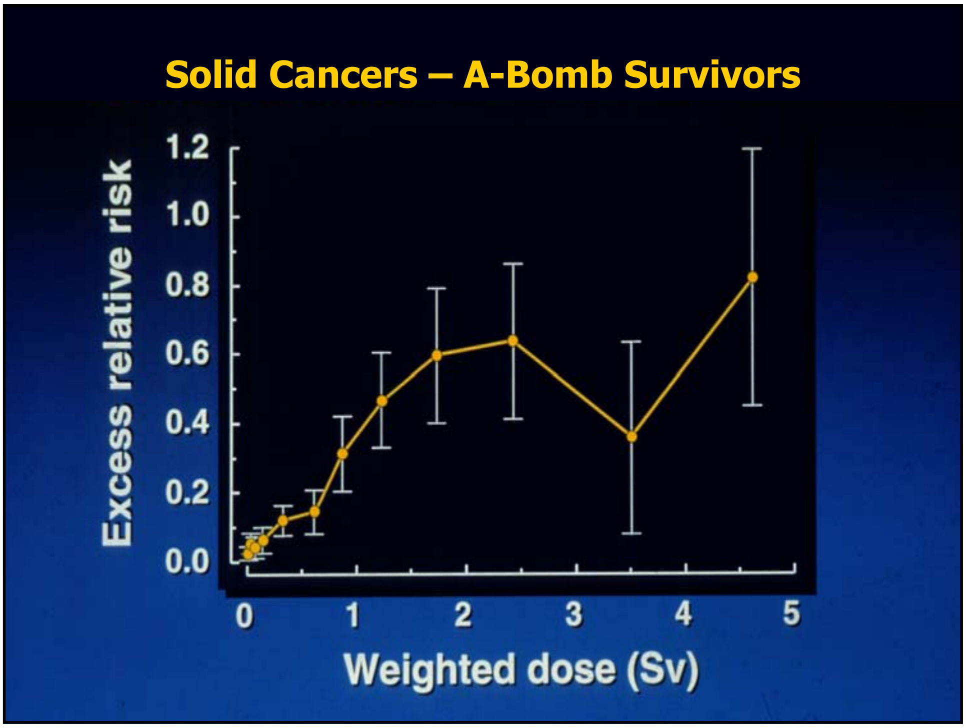
- The factor by which cancer risks should be reduced when radiation is delivered at low doses and low dose-rates, compared with a single high dose rate acute exposure.

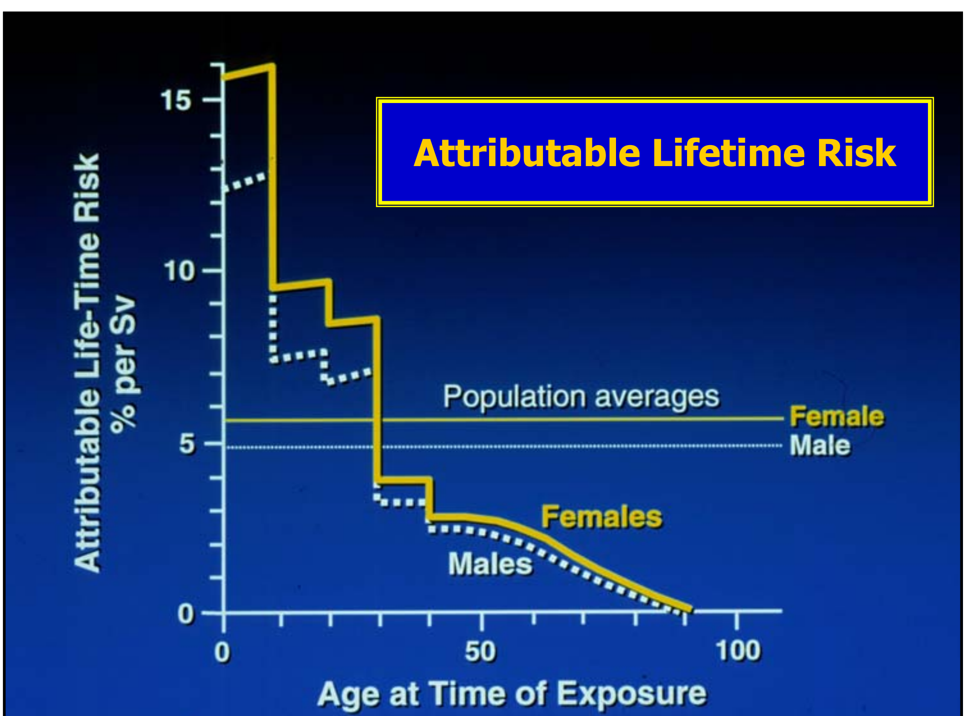
DREF

- NCRP (1978) 2 to 10 (animal studies)
- BEIR III (1980) 2.25 (α/β ratio)
- BEIR V (1990) 2 to 10 (best estimate 4)
- UNSCEAR (1977) 2.5 (leukemia at high & low doses)
- UNSCEAR (1986) 2 to 10
- BEIR VII (2005) 1.5 (Cf Linear/Quadratic)

Total Excess Fatal Cancer (ICRP) %/Sv

	High dose High d/r	Low dose Low d/r
General population:	**10%**	**5%**
Working population:	**8%**	**4%**


Solid Cancers – A-Bomb Survivors
Excess relative risk
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Weighted dose (Sv)


Attributable Lifetime Risk
Attributable Life-Time Risk
% per Sv
15
10
5
0
Population averages
Female
Male
Females
Males
0
50
100
Age at Time of Exposure

Atomic Bomb Survivors Life Span Study (LSS)

Second Solid Cancer Incidence Report 1958-1998

Preston et al. submitted

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

Second Cancer Incidence Report

- 1958-1998
- 105,427 people
- ~50% alive in 1998
  ~85% of those <20 ATB
- First primary tumors
- DS02 organ dose estimates

Preston et al, submitted

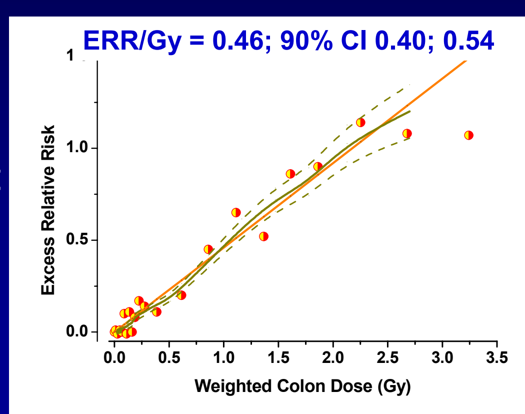
LSS Incidence Cohort*

Dose, Gy	Subjects	(%)
<0.005	35,545	44.3
0.005 - 0.1	27,789	34.6
0.1 - 0.2	5,527	6.9
0.2 - 0.5	5,935	7.4
0.5 - 1	3,173	3.9
1 - 2	1,647	2.1
2+	564	0.7

** Excludes 25,247 NIC*

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

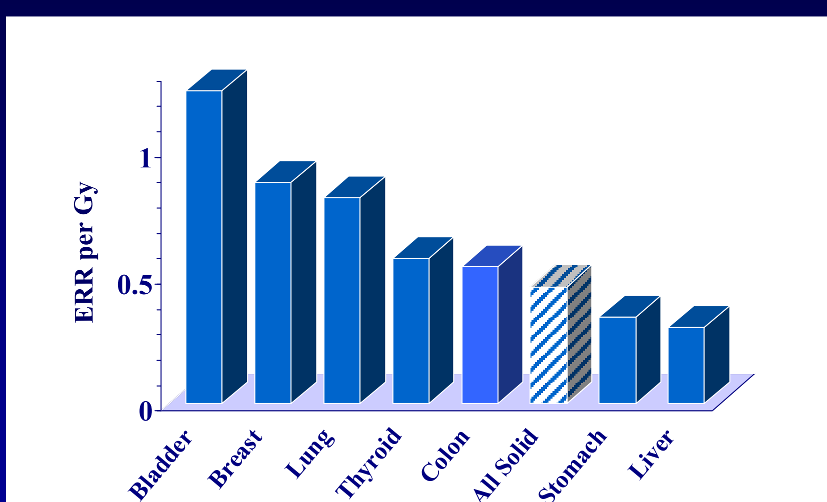


Sex-averaged at age 70 for exposure at age 30

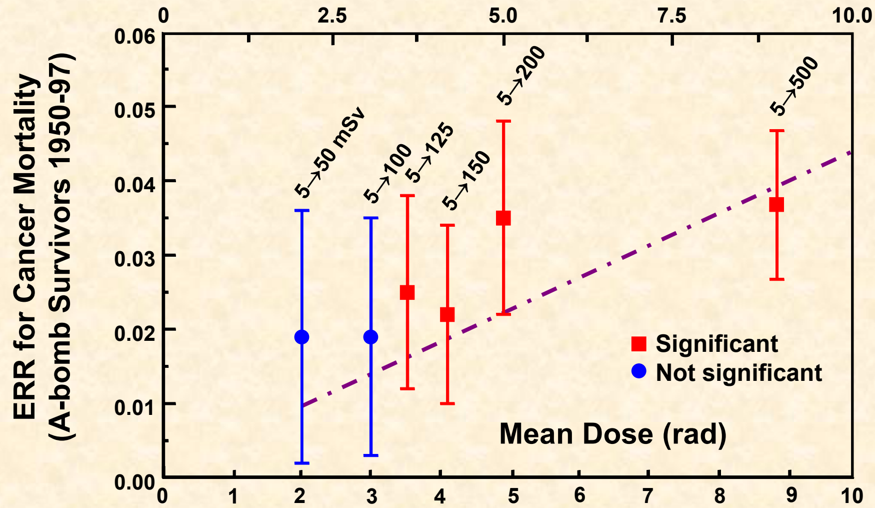
Distribution of Solid Cancers

Site	1958-1998
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
Oral cavity	277
Nervous system	281

Site–Specific Risk Estimates



For person age 70 exposed at age 30



Lowest dose category in which a significant increase in cancer risk is seen in A-bomb survivors

- Cancer incidence: 5-100 mSv. Mean: 29 mSv

  (Pierce et al 2000)

- Cancer mortality: 5-125 mSv. Mean: 34 mSv

  (Preston et al. 2003)

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

Pooled Thyroid Cancer Studies

Cohort Studies

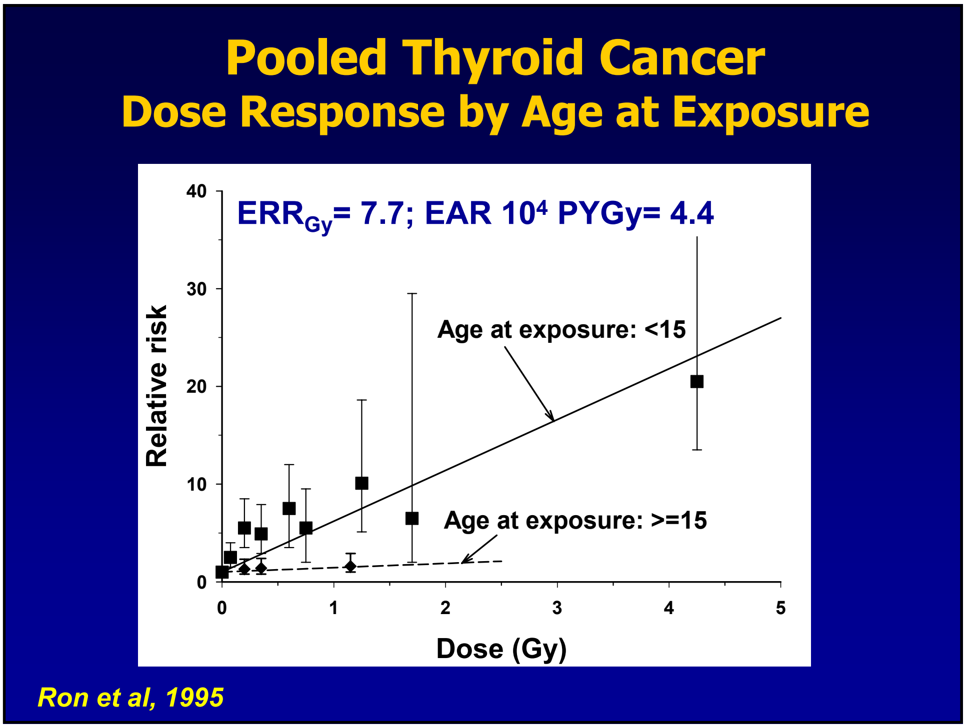
A-Bomb Survivors
Thymus, Rochester
Tinea Capitis, Israel
Tonsils, Chicago
Tonsils, Boston

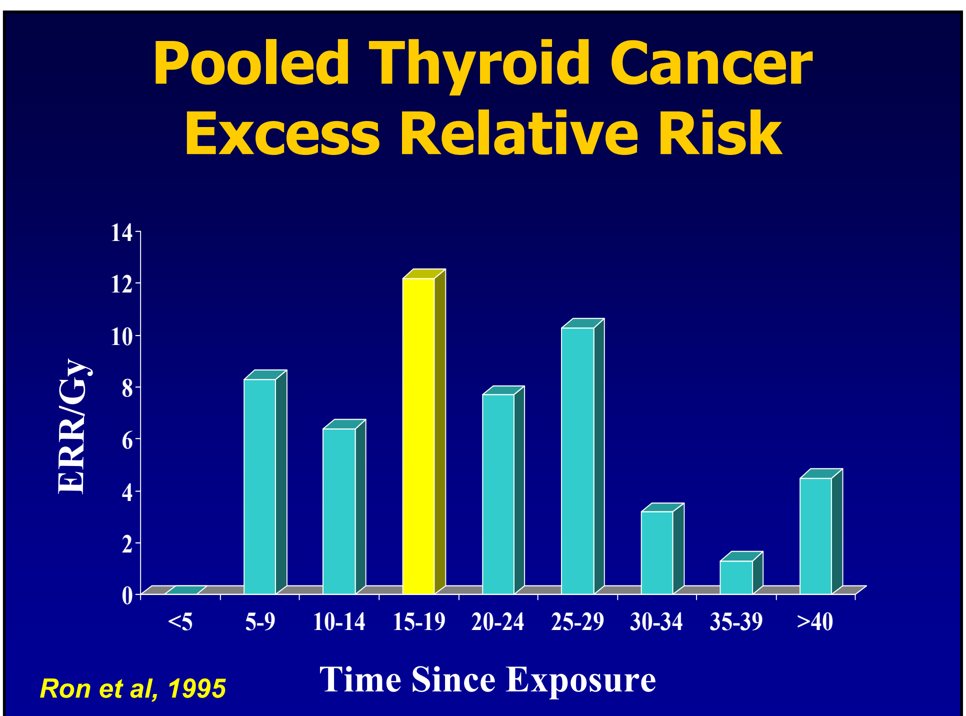
Case-Control Studies

Cervical Cancer, Intl
Childhood Cancer, Intl

120,000 people
3,000,000 person years
700 thyroid cancers
Exposure age $\leq$15

Ron et al, 1995


Pooled Thyroid Cancer
Dose Response by Age at Exposure
ERR$_{Gy}$= 7.7; EAR 10^4 PYGy= 4.4
Relative risk
40
30
20
10
0
Age at exposure: <15
Age at exposure: >=15
0
1
2
3
4
5
Dose (Gy)
Ron et al, 1995


Pooled Thyroid Cancer
Excess Relative Risk
ERR/Gy
14
12
10
8
6
4
2
0
<5
5-9
10-14
15-19
20-24
25-29
30-34
35-39
>40
Time Since Exposure
Ron et al, 1995

The Chernobyl Accident Ukraine, 26 April 1986

- Worst accident in nuclear history
- 10 days of releases into the atmosphere under varying meteorological conditions
- Widespread and spotty fallout due to rain and changing wind directions

Chernobyl-Related Thyroid Cancer

- 40 million Ci of Iodine-131 released
- Worst radiation accident
- Large increases in childhood thyroid cancer in contaminated areas beginning about 4 years after the accident
- Initial reports questioned because of possible bias due to intensive screening
- Evidence of real excess now, but still cannot be quantified precisely

Thyroid Cancer Associated with ^{131}I Exposure from Chernobyl, Belarus & 4 regions in Russia

- 276 cases, 1300 controls; <15 y at accident
- Majority had thyroid doses of 16-399 mGy
- Doses higher in Belarus than Russia
- At 1 Gy, risk 3-fold higher in iodine deficient area than elsewhere
- KI dietary supplement decreased risk by 1/3

Cardis et al, 2005

Thyroid Cancer Associated with ^{131}I Exposure from Chernobyl, Belarus & 4 Regions in Russia

Radiation type	OR_{Gy} (95% CI)
Total dose	5.5 (2.2-8.8)
^{131}I	5.2 (2.2-8.2)
All iodine isotopes	5.2 (2.2-8.3)
Adjusted all iodine isotopes*	5.9 (1.6-10.2)

***Adjusted for external and long-lived nuclides**
Cardis et al, 2005

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

IARC 15 Country Study (Cardis et al. 2005)

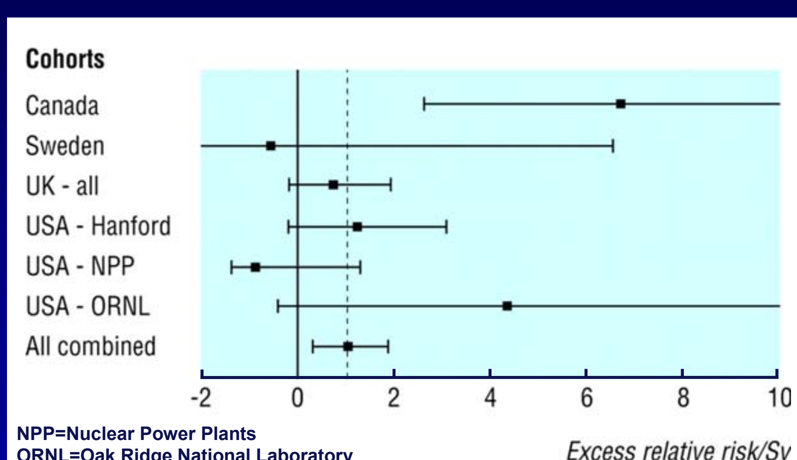
- 600,000 nuclear workers
- Average cumulative dose = 19.4 mSv
- All cancers (except leukemia) ERR
  = 0.97 (0.14 to 1.97)/Sv
- Leukemia ERR = 1.93/Sv (NS)

International Analysis
407,391 Nuclear Workers

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

Cardis et al, 2005

IARC 15 Country Study
(Cardis et al. 2005)



Cardis, E et al. BMJ 2005;331:77

Mortality in Radiologists

100 years of Observation on British Radiologists: Mortality from Cancer and Other Causes 1897-1997

A. Berrington, S.C. Darby, H.A. Weiss & R. Doll

The British Journal of Radiology 74:507-519, 2001.

All Cancers British Radiologists

Years	SMR
1897-1920	1.75
1921-1935	1.24
1936-1954	1.12
1955-1979	0.71
all post 1920	1.04

SMR's compared with other medical professionals.

British Radiologists

All years post 1920

SMR for cancer	1.04 n.s.
SMR non-cancer	0.86 s.s.
SMR all mortality	0.91 s.s.

Radiation: The Elixir of Life

- Cameron J.R.
  Radiation Increases the Longevity of British Radiologists
  Br J Radiol 75:637, 2002
- Cameron J.R.
  Longevity is the Most Appropriate Measure of Health Effects of Radiation
  Radiology 229:13, 2003

Mortality of US Radiologists (6,500) Compared with Other Specialists: 1900-69

Cause of Death	Ratio of SMR RSNA ACP*	Ratio of SMR RSNA AAOO†
All Causes	1.22	1.31
Cancers	1.34	1.56
Diseases Nervous System	1.32	1.34
Diseases Circulatory System	1.20	1.29
External Causes	1.05	0.96
All Other	1.22	1.39

** ACP - American College of Physicians*
† AAOO - Amer. Acad. Of Ophthalmology & Otolaryngology

The Bottom Line

- There was a clear excess of cancer in the early Radiologists before radiation protection standards were introduced. (1928)
- No excess cancer incidence observed in radiologists now (but the numbers are small).
- On the other hand, there is no evidence that radiologists live longer than other physicians - i.e., radiation is not good for you!

Use of Medical Radiation in the United States

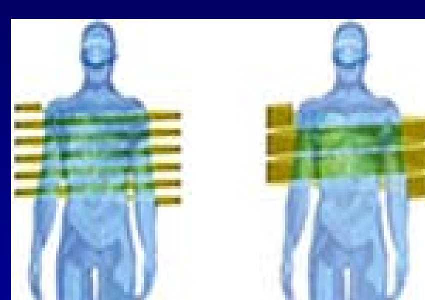
- U.S. has high medical exam rates
- Temporal trends

  1980 to 1990
  - Diagnostic exams increased 20-25%
  - Radiation treatments increased 25-30%

UNSCEAR, 2000

Annual Diagnostic Exams in the United States, 1991-96

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



UNSCEAR, 2000

Adjusted ORs and CIs for the Association of Child's Postnatal Diagnostic X-rays – and ALL by Gender

X-rays	Girls		Boys	
(n)	No.	OR (CI)	No.	OR (CI)
None	275	1.00	295	1.00
1	73	1.14 (0.66-1.96)	109	0.94 (0.56-1.55)
≥2	68	2.26 (1.20-4.23)	133	1.39 (0.91-2.14)

Claire Infante-Rivard, Géraldine Mathonnet, and Daniel Sinnett
Environmental Health Perspectives – Vol. 108, No. 6, June 2000

Childhood Cancer and Irradiation *in Utero*

- Number of children with Leukemia or cancer before 10 years **7649**
- Number x-rayed in utero **1141**
- Number of matched controls **7649**
- Number of controls irradiated in utero **774**
- Number of films **1 to 5**
- Fetal doses per film **0.46 to 0.2 rad (4.6 to 2 mGy)**
- Relative cancer risk estimate assuming radiation to be the causative agent **1.52**

Childhood Cancer from Fetal X-Rays

- Low dose irradiation of the fetus in utero, particularly in last trimester, causes an increased risk of childhood cancer
- 40% increase in risk from an obstetric x-ray examination
- Radiation doses of ~10 mGy (1 rad) increases the risk
- Excess absolute risk is about 6% per Gy

- Doll & Wakeford 1997

Irradiation in Utero (Wakeford & Little, 2005)

- Risk of childhood cancer from ~10mSv is not zero – exact risk uncertain.

Second Cancers Following Radiotherapy

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

Radiotherapy Patients

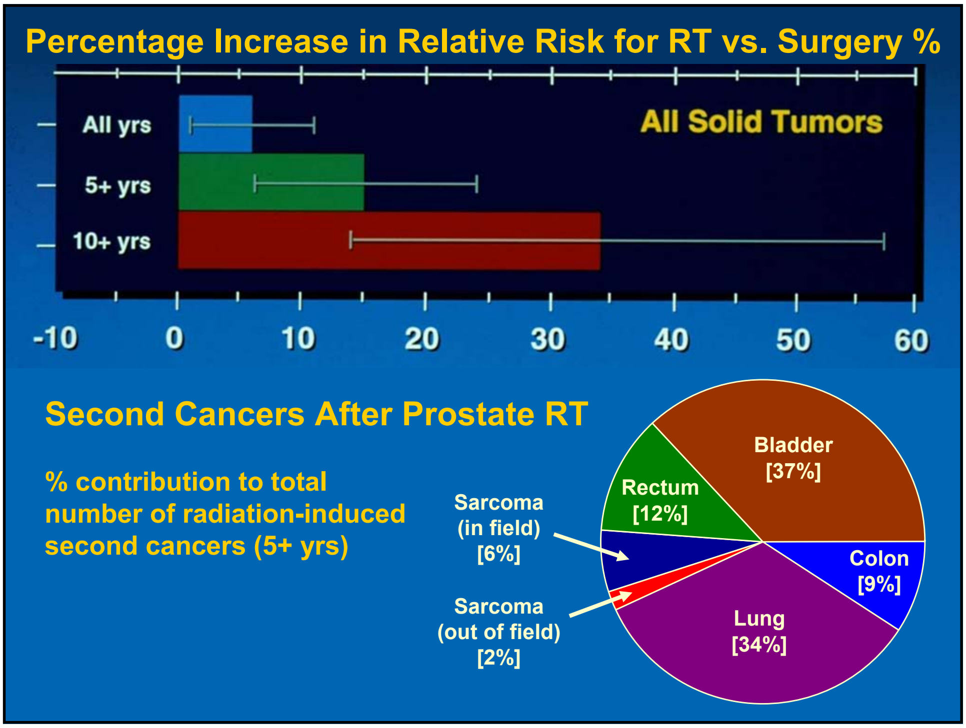
- In most cases, difficult to assess risk of second cancers because no good control available.
- Exceptions:
  - Ca Prostate & Cervix where surgery is an option.
  - Hodgkin's disease where risk of breast cancer in young women is obvious.

Radiotherapy Patients

- **Carcinomas:** Site adjacent to and remote from treated area. Large number, small RR.
- **Sarcomas:** In heavily irradiated tissues. Small number, large RR.
- More important as younger patients are treated and/or better cure rates.

Prostate Cancer, Treated with Radiotherapy or Surgery (SEER Program) 1973-93

	RT	Surgery
Persons at risk	**51,584**	**70,539**
Person-years at risk	**218,341**	**312,499**
Ave. follow-up after diagnosis (y)	**4.2**	**4.4**
Ave age at diagnosis (y)	**70.3**	**71.4**
Ave. age at second CA diagnosis (y)	**75.3**	**77.0**
% of person-years at risk:		
0-1 years after primary diagnosis	**18.2**	**17.4**
1-5 years after primary diagnosis	**52.1**	**51.5**
5-10 years after primary diagnosis	**22.7**	**23.4**
10+ years after primary diagnosis	**6.9**	**7.7**

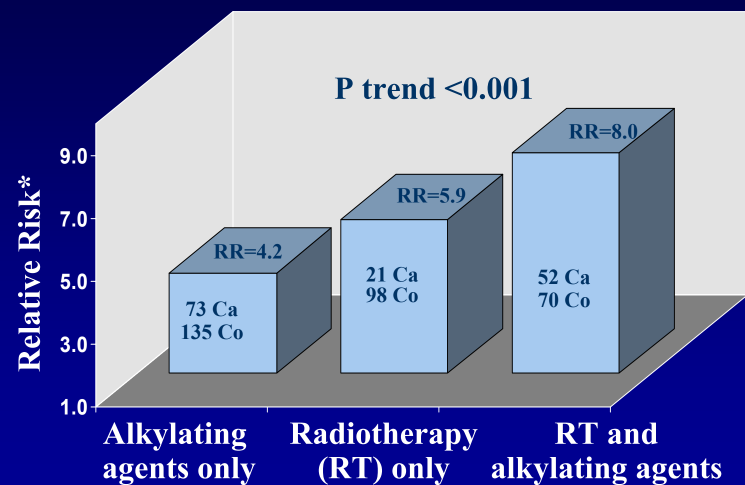


Risk of *Radiation-Associated* Second Malignancy After Prostate-Cancer Radiotherapy

All survivors	1 in 290
5+ yrs survivors	1 in 125
10+ yrs survivors	1 in 70

Brenner et al 1999

Lung Cancer after Hodgkin's Disease by Type of Treatment *



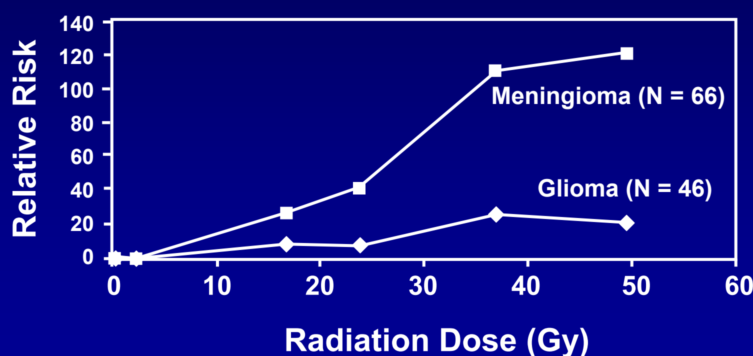
Travis LB, et al. JNCI, 2002

*Adjusted for tobacco use

Second Cancers After Hodgkin's Lymphoma

- 55 cases of Breast CA in 3869 patients treated (obs/exp 2.24)
- Risk of 60% in women treated before 16 years old
- Risk decreases with age at therapy
- Risk only slightly elevated at age >30 years

Brain Tumors Following Cranial Irradiation of Children with Leukemia



Neglia and Inskip, in press

End