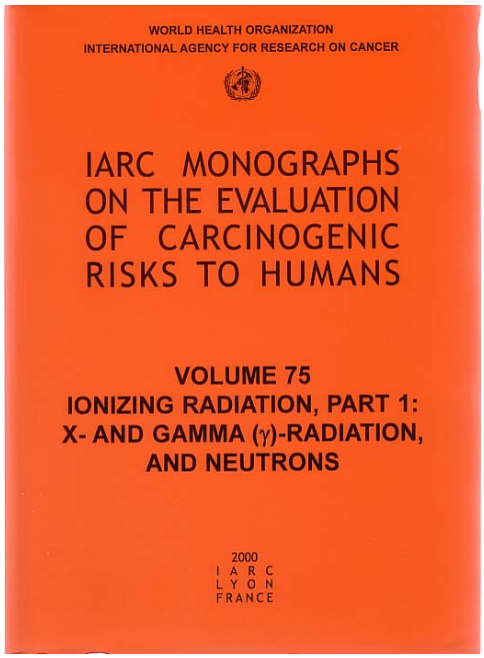
NATIONAL CANCER INSTITUTE
RADIATION EPIDEMIOLOGY BRANCH
Rockville, Maryland

Radiation Epidemiology Course
10 May 2004

"Cancer Risk Following Therapeutic Irradiation"

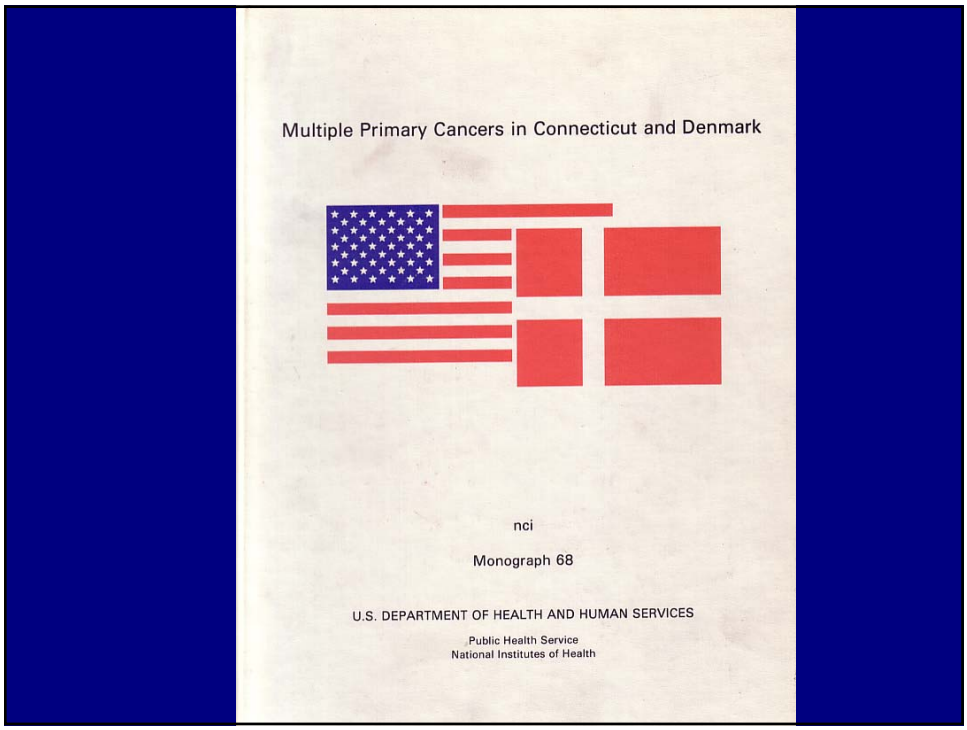
John D. Boice, Jr (IEI, Vanderbilt)



"Evidence for causal associations comes primarily from epidemiologic studies of the atomic bomb survivors and patient populations."

"There are well over 100 studies of patient populations linking radiation to cancer."

IARC 75, 2000



Secondary Cancers

- **INTRODUCTION**
- **STUDIES OF ADULTS**
  - Hodgkin's disease
    - Breast
    - Lung
    - Leukemia
  - Breast cancer
  - Cervical cancer
- **STUDIES OF CHILDREN**
  - Childhood Cancer
  - Retinoblastoma
- **Comparisons with A-bomb Survivors**
- **CONCLUSIONS**

SECOND CANCERS: DEFINITION

- **Bilroth, 1889**
- **Warren and Gates, 1932**
  - **Criteria for multiple primary cancers:**
    - **Definite picture of malignancy**
    - **Distinct**
    - **Not metastatic**

SECOND CANCERS: IMPORTANCE

- Clinical
  - Effect on patient
  - Morbidity and mortality
- Epidemiologic
  - Cancer etiology
  - Quantification of risk
  - Dose-response relationships
- Carcinogenesis
  - Insight into mechanisms
  - Applicable to all cancer
  - Ultimate goal: prevention of first cancer

NCI SEER 1973 - 1993

Population-Based Cancer Registries (9 Areas)

14% of U.S. Population

120,000 New Cancers / Yr

1.4 Million Cancer Diagnoses (1973-93)

95,000 2nd Cancers (6.6%)
87,000 2nd Cancers Expected (6.2%)

161 / 10,000 / Year (2nd Cancer Incidence)
148 / 10,000 / Year Expected

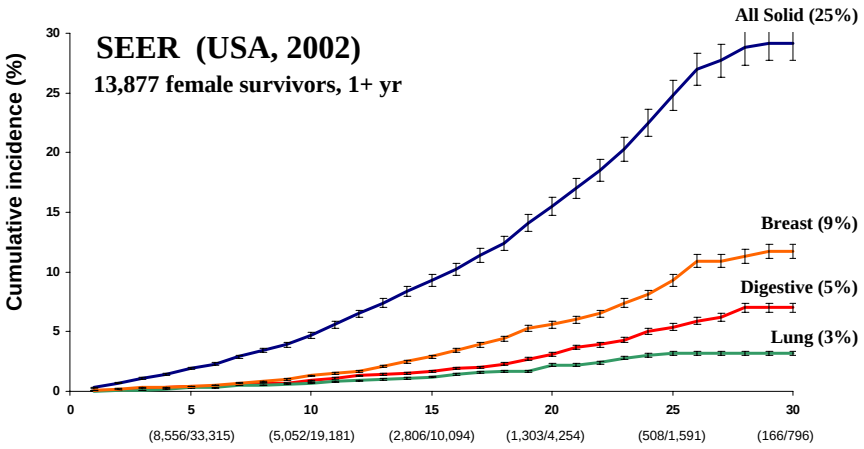
Second Cancers are common

Second Cancer Studies - Adults

Primary	Secondary	Reference
Hodgkin's Disease	Breast	Travis, JAMA 2003;290:465
	Breast	van Leeuwen, JNCI 2003;95:971
	Lung	Travis, 2002;94:182
	Lung	Gilbert, Rad Res 2003;159:161
	All	Swerdlow, JCO 2000;18:498
Female Breast	Leukemia	Smith, JCO 2003;21:1195
	Leukemia	Crump, JCO 2003; 21:3066
	Leukemia	Curtis, N Engl J Med 1992;326:1745
	Breast	Boice, N Engl J Med 1992;326:781
	Lung	Inskip, JNCI 1994;86:983
Uterine Cervix	All	Boice, Radiat Res 1988;116:3
Non-Hodgkin's Lymphoma	Bladder	Travis, JNCI 1995;87:524
Ovary	Bladder	Travis, Cancer Res 1996;56:1564
	Leukemia	Travis, N Engl J Med 1999;340:351
Lung	Lung	Tucker, JNCI 1997;89:1782
Testis	Leukemia	Travis, JNCI 2000; 92:1165

Substantial area of research

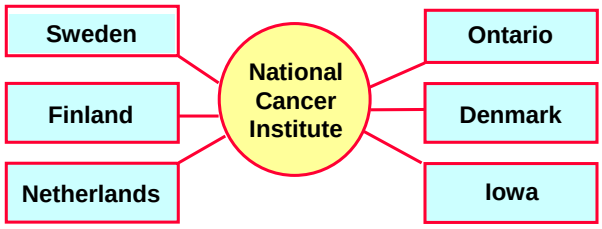
Second Cancer After Hodgkin's Disease



Dores, JCO 20:3484, 2002

25% incidence @ 30 y

Breast Cancer Following Hodgkin's Disease International Case - Control Study (2003)



Travis et al. JAMA 290:465, 2003

Definition of Cohort:

- Diagnosis of Hodgkin's Disease: 1965 –1994, <31 yr
- Survival of 1 or more years

Final Cohort: 3,817 (105 cases, 266 controls)

Large series provide insights

Breast Cancer After Hodgkin's Disease

	Dose to Breast (Gy)						
	0-4	4-7	7-23	23-28	28-37	37-40	40+
Cases	15	13	16	9	20	12	17
Controls	76	30	30	30	31	31	29
Relative Risk	1.0	1.8	4.1*	2.0	6.8*	4.0*	8.0*

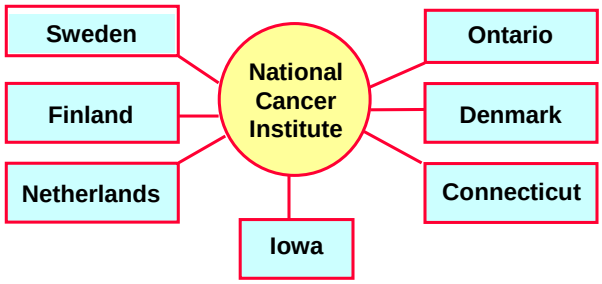
	Alkylating Agents (No. Cycles)			
	0	1-4	5-8	9+
Cases	68	10	17	4
Controls	132	20	55	29
Relative Risk	1.0	0.7	0.6	0.2*

Travis et al. JAMA 290:465, 2003

Dose computed to tumor site. High dose risk.
Early onset. Chemotherapy can protect.

Lung Cancer Following Hodgkin's Disease

International Case - Control Study (2002)



Definition of Cohort:

Travis et al. JNCI 94:182, 2002

- Diagnosis of Hodgkin's Disease: 1965 -1994
- Survival of 1 or more years

Final Cohort: 22,977 (222 cases, 444 controls)

Lung Cancer After Hodgkin's Disease

	Radiation Dose to Lung (Gy)					
	0	>0-5	5-14	15-29	30-39	40+
Cases	72	22	14	14	51	26
Controls	158	75	18	22	87	33
Relative Risk	1.0	1.25	7.5*	9.3	9.6*	10.0*

	Cigarettes (pks/d)				
	Never	Former	<1	1-2	2+
Cases	8	29	48	74	23
Controls	108	74	74	58	11
Relative Risk	1.0	7.2*	13.3*	33.7*	84.9*

Travis et al. JNCI 94:182, 2002

Gilbert et al. Radiat Res 159:161, 2003

Lung Cancer After Hodgkin's Disease Radiotherapy and Smoking

		Lung Dose (Gy) <5 Gy	Lung Dose (Gy) 5+ Gy
Smoking	-	1.0 (11 / 76)	7.6 (28 / 60)
	+	6.0 (10 / 22)	49.1 (24 / 10)

"-" denotes light or no (no. cases / no. controls)

Travis et al, *J Natl Cancer Inst* 94:182, 2002

Gilbert et al. Radiat Res 159:161, 2003

High dose interaction Another reason to stop smoking.

Lung Cancer After Hodgkin's Disease Radiotherapy and Alkylating Agents

		Lung Dose (Gy) <5 Gy	Lung Dose (Gy) 5+ Gy
Alkylating agents	-	1.0 (21 / 98)	5.9 (53 / 90)
	+	4.2 (73 / 135)	8.0 (52/ 70)

"-" < 1mo or no treatment (no. cases / no. controls)

Travis et al, *J Natl Cancer Inst* 94:182, 2002

Evidence for AA effect. Interaction additive.

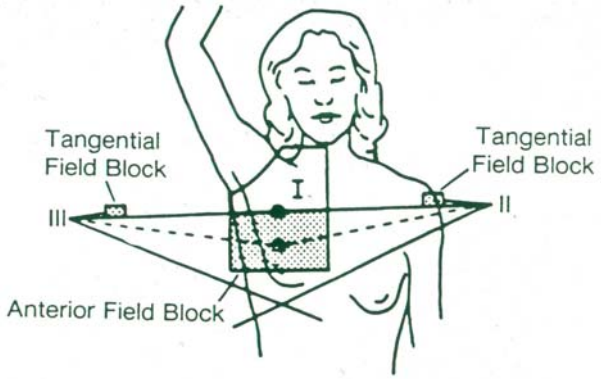
Acute Leukemia After Hodgkin's Disease

Study	No. of Patients	No. of Observed Leukemias	Relative Risk
SEER (2002)	32,591	249	9.9
IARC (1990)	9,552	163	9.0
IDHD (1992)	2,411	158	27.5
Canada/US (1995)	9,280	122	23.9
BNLI (2000)	5,519	45	14.6
Netherlands (1994)	1,939	31	34.7
UICC (1988)	1,681	18	64.0
Nordic (1996)	1,641	7	17.0
Stanford (1988)	1,507	28	66.0
Oslo (1993)	1,152	9	24.3
LESG (1987)	1,036	12	89.0
Gustave Roussy (1994)	892	8	27.6
CALGB (1982)	798	10	133.0
NCI (1987)	192	7	95.7

Actuarial risks generally 1-5% at 20 years

Boice, Chemotherapy Source Book, 2001

Earliest effect from intense chemo.



RADIOTHERAPY DOSE TO CONTRALATERAL BREAST

Dose to contralateral breast can be high

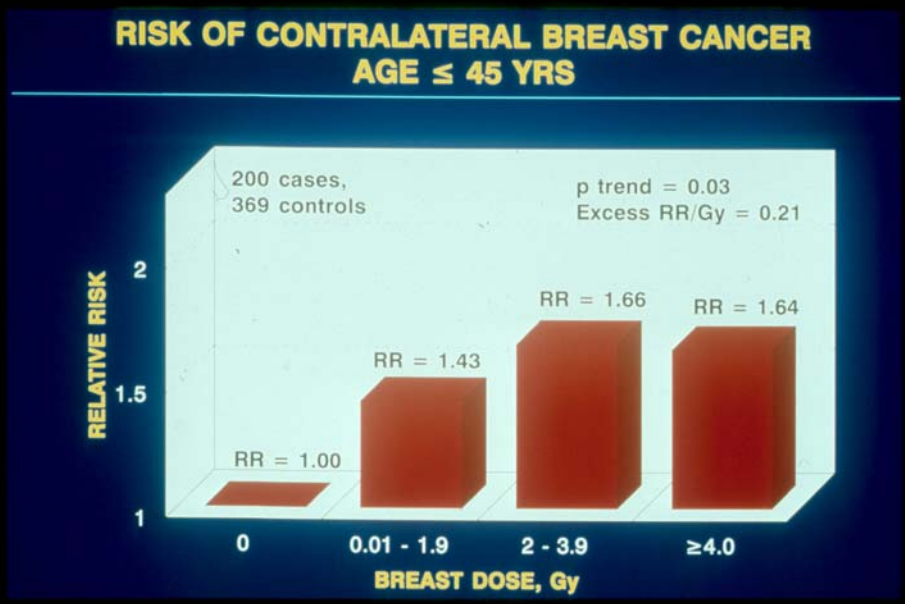
Secondary Breast Radiotherapy for Breast Cancer

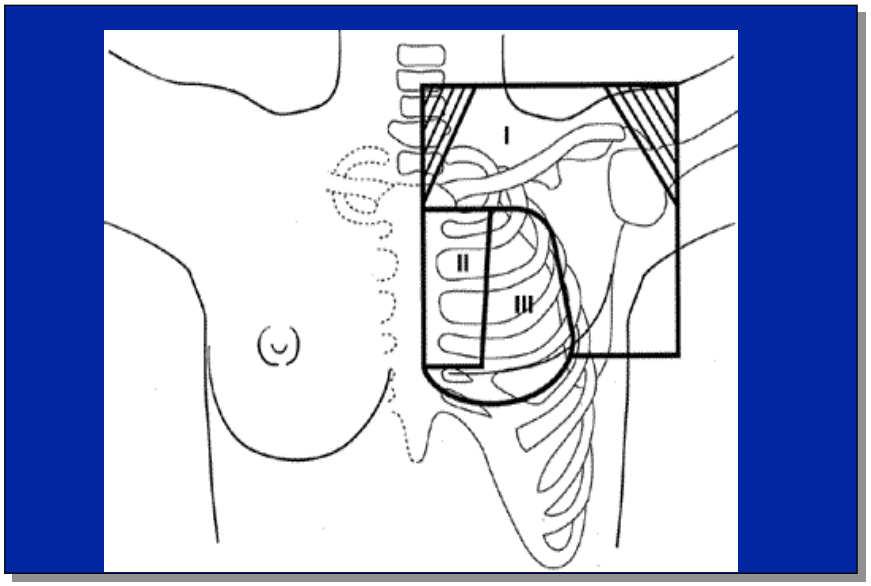
	RR	95% CI
All Subjects*	1.19	0.9-1.5
Time After Exposure (Yr)		
5-9	0.99	0.7-1.4
≥10	1.33	1.0-1.8
Age at Exposure (Yr)		
<35	2.26	0.9-5.7
35 -	1.46	0.9-2.3
≥45	1.01	0.8-1.4

*655 Cases, 1189 Controls

Boice et al, *NEJM* 326:781, 1992

Risk after 10 years among young. Example of age modification.





Adjuvant Postmastectomy Radiation Fields

LEUKEMIA AFTER BREAST CANCER

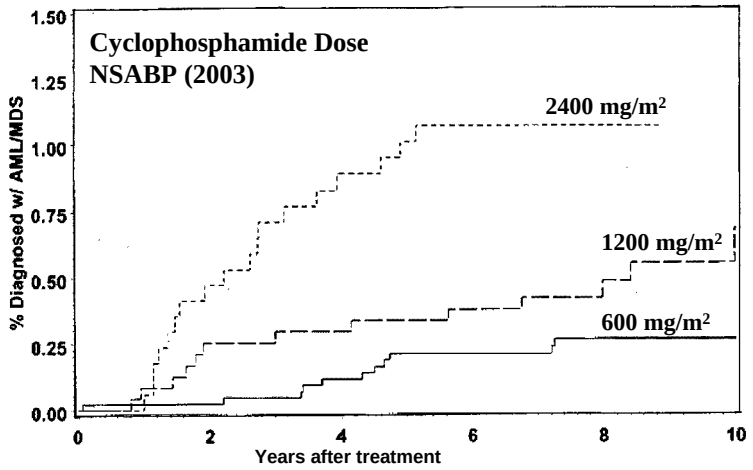
CHEMOTHERAPY	RADIOTHERAPY: NO	RADIOTHERAPY: YES
NO	1.0 (20/138)	2.4 * (12/51)
YES	10.0 * (25/32)	17.4 * (23/14)

Relative Risks (Cases/Controls)

Curtis, NEJM 326:1745, 1992

Chemotherapy and radiotherapy interaction.

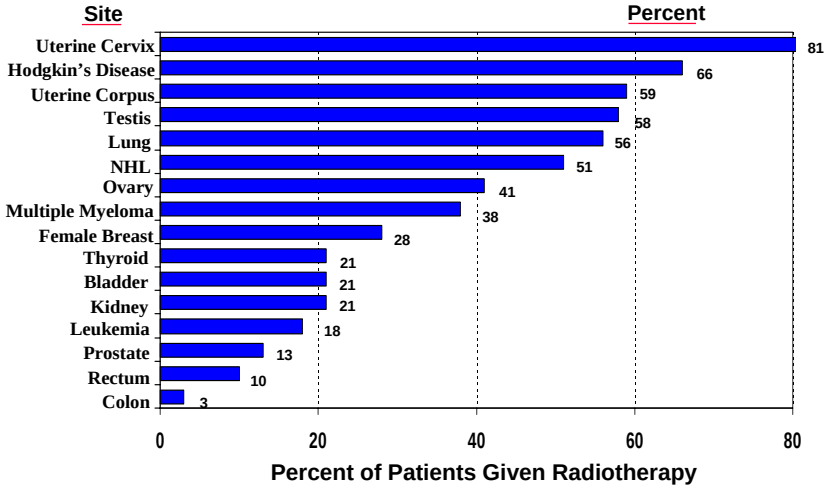
Leukemia After Breast Cancer



Smith, JCO 21:1195, 2003

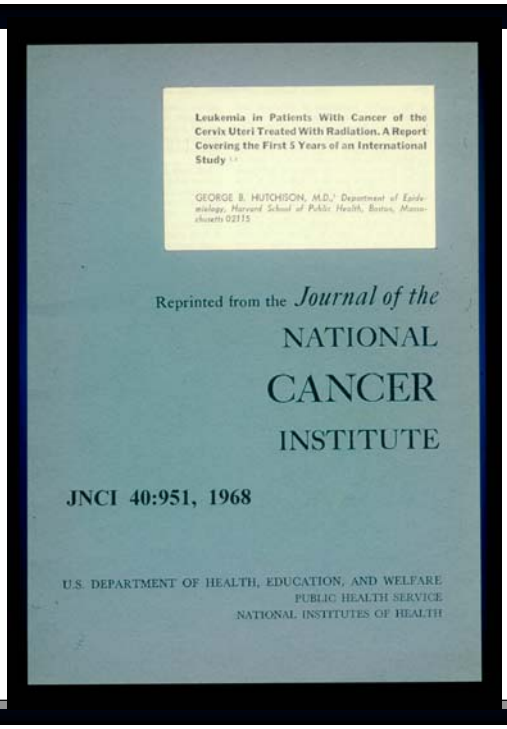
Dose matters.

Radiotherapy as First Course of Therapy



Inskip, Multiple Primaries, 1999

Connecticut 1935-82; SEER, 1972-90



Leukemia in Patients With Cancer of the Cervix Uteri Treated With Radiation. A Report Covering the First 5 Years of an International Study

GEORGE B. HUTCHISON, M.D.,[1] Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115

Reprinted from the *Journal of the* NATIONAL CANCER INSTITUTE

JNCI 40:951, 1968

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

Cervical Cancer

Number: 30,000 women

Dose: 500-1500 rad (Marrow)

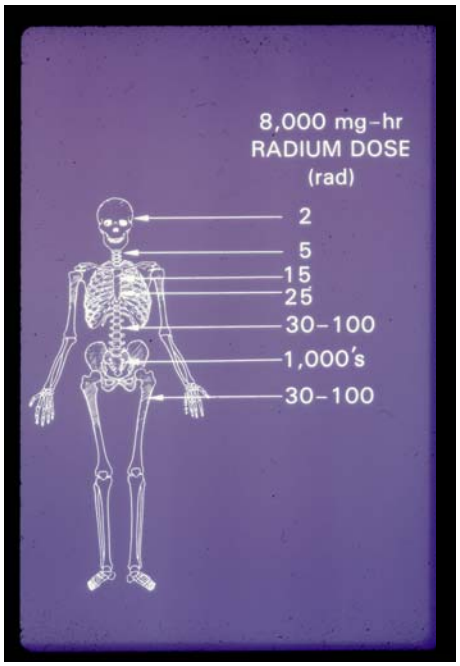
Leukemia
- **Observed:** 13
- **Expected:** 15.5

Risk: 0

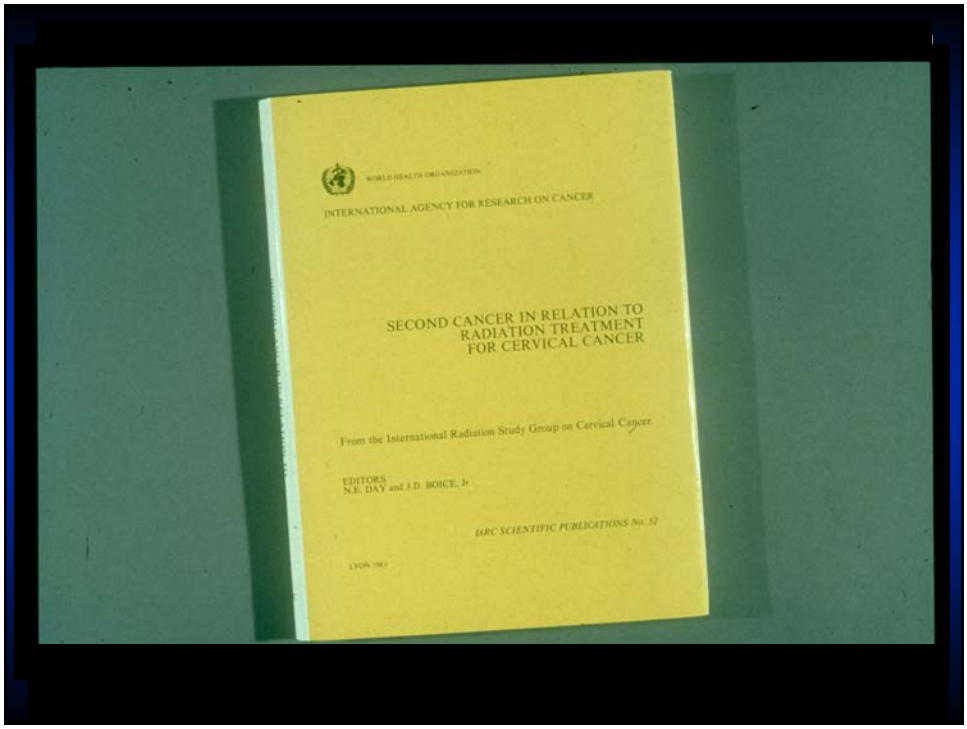
Boice & Hutchison, *J Natl Cancer Inst* 65:115, 1980

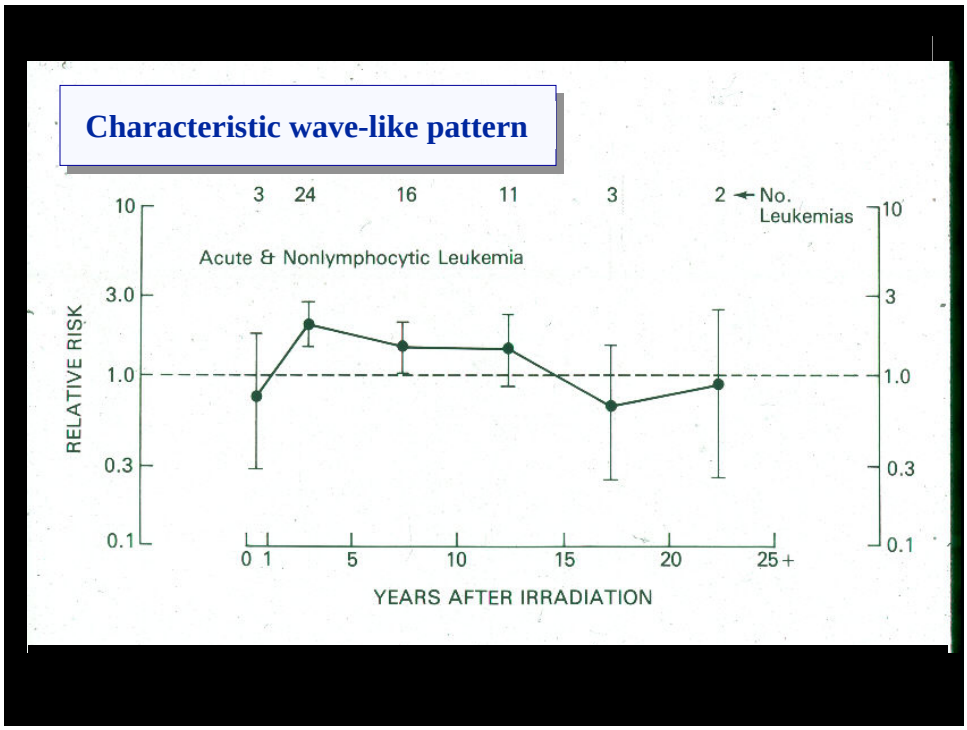
Why no risk? Cellular killing? Reason why no epidemic of secondary leukemias?

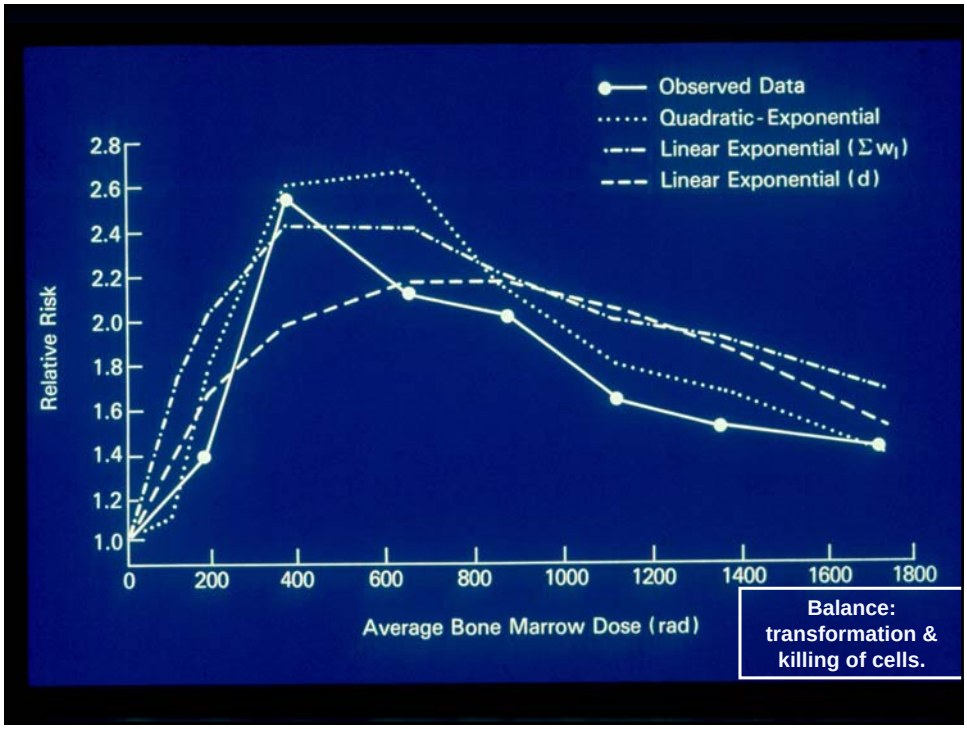
Large doses to small volumes result in cell killing



But essentially whole body exposure at low doses


WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
SECOND CANCER IN RELATION TO RADIATION TREATMENT FOR CERVICAL CANCER
From the International Radiation Study Group on Cervical Cancer
EDITORS
N.E. DAY and J.D. BOICE, Jr
IARC SCIENTIFIC PUBLICATIONS No. 32
LYON 1983


Characteristic wave-like pattern
3 24 16 11 3 2 ← No. Leukemias
Acute & Nonlymphocytic Leukemia
RELATIVE RISK
10
3.0
1.0
0.3
0.1
0 1 5 10 15 20 25+
YEARS AFTER IRRADIATION



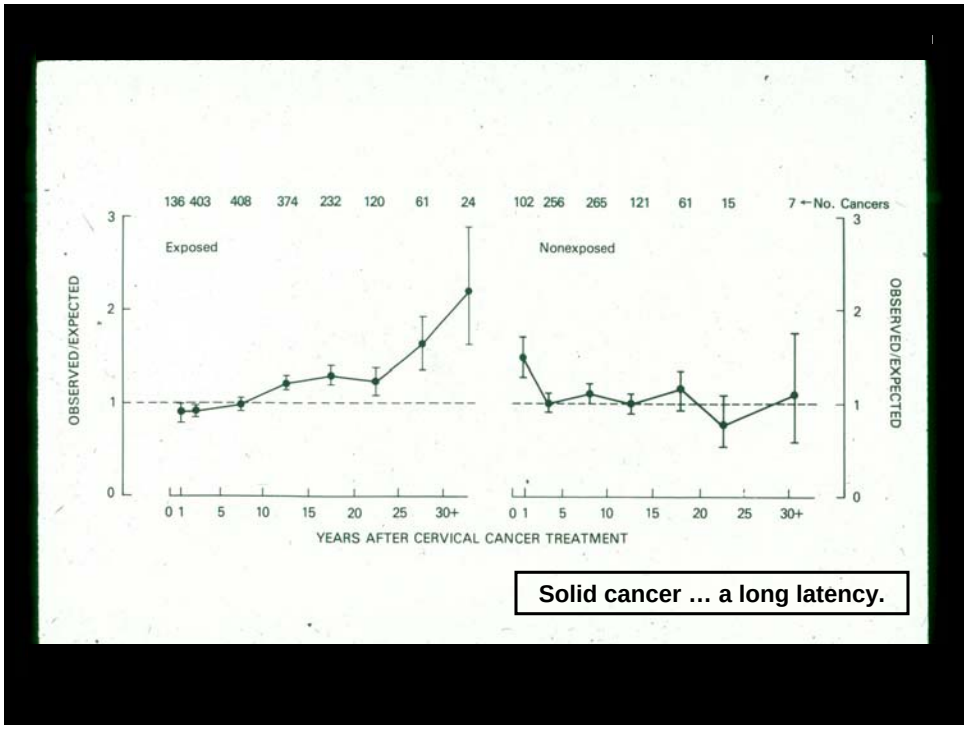
Comparing Treatment-Related Leukemia Risks

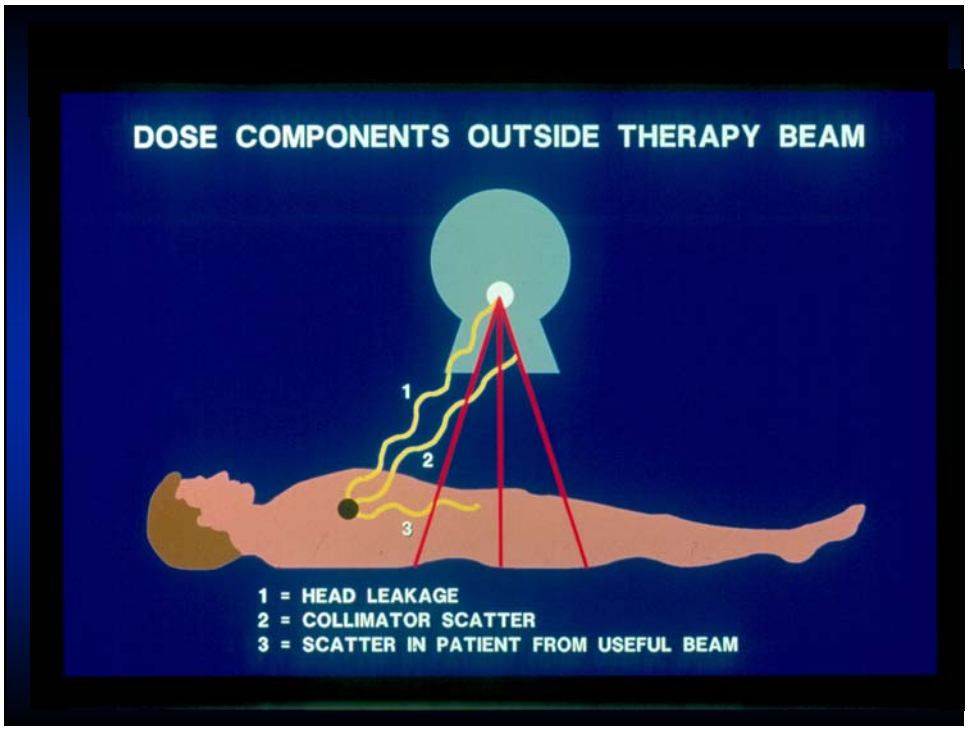
	Radiotherapy Cervical Cancer	Chemotherapy Ovarian Cancer
Number Women	82,616	998
PY of Followup	547,222	2,028
Leukemia (ANLL)		
Observed	52	12*
Expected	39	0.11
O/E (95% CI)	1.3 (1.0-1.7)	110 (56-191)
Excess Risk	2.4 / 100,000 / yr	5.8 / 1,000 / yr

Boice, JNCI, 1985;74:955

Greene, NEJM, 1982;307:1416

* Melphalan (10), Chlorabucil (2)


136 403 408 374 232 120 61 24
102 256 265 121 61 15
7 ← No. Cancers
Exposed
Nonexposed
OBSERVED/EXPECTED
0 1 2 3
0 1 5 10 15 20 25 30+
YEARS AFTER CERVICAL CANCER TREATMENT
Solid cancer … a long latency.


DOSE COMPONENTS OUTSIDE THERAPY BEAM
1
2
3
1 = HEAD LEAKAGE
2 = COLLIMATOR SCATTER
3 = SCATTER IN PATIENT FROM USEFUL BEAM

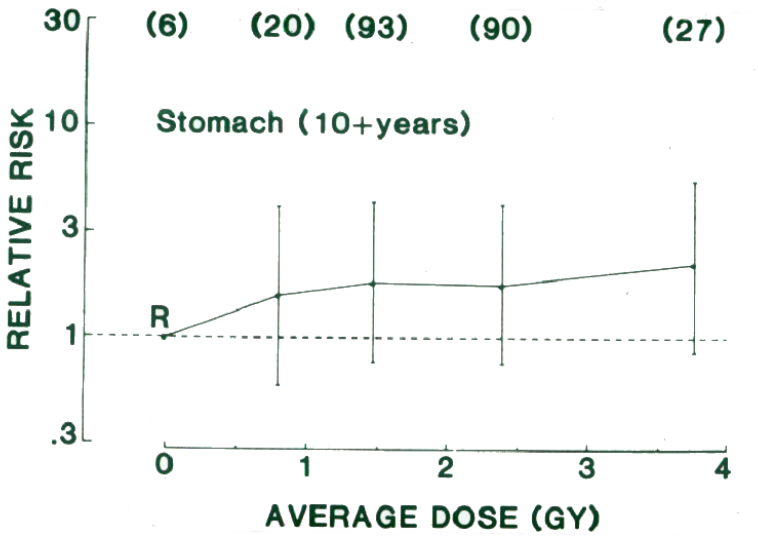
Lightly Irradiation Sites - Cervical Cancer

Second Cancer	Number Cases	Organ Dose (ave. GY)	RR at 1 Gy (90% CI)
Stomach	338	2.0	1.69 (1.0 - 3.3)
Pancreas	211	1.9	1.00 (0.7 - 1.6)
Liver	19	1.5	1.00 (0.7 - 1.3)
Kidney	134	2.0	1.71 (1.0 - 3.2)
Breast	838	0.3	1.03 (0.1 - 2.3)

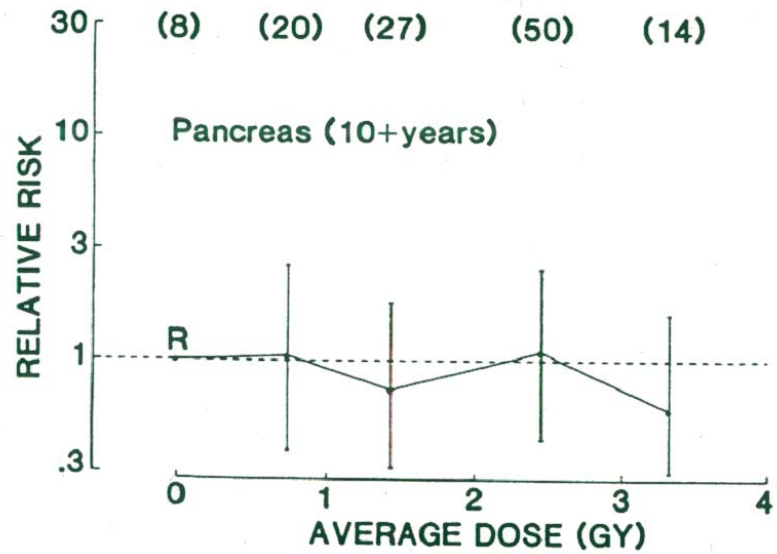
Boice, JNCI, 1985;74:955

Boice, Radiat Res, 1988;116:3

Kleinerman, Cancer, 1995;76:442



Boice, *Rad Res* 116:3, 1988



Boice, *Rad Res* 116:3, 1988

Cancers Induced Only at High Radiation Doses

Second Ca	Mean Dose, Gy	Dose - Response	First Site
Rectum	30 - 60	p = 0.002	Cervix
	≥ 30	---	Ovary, Endom.
Bone	22	p = 0.16	Cervix
	27	p = < 0.05	Childhood Ca
	20 - 33	p = < 0.05	Retinoblastoma
Conn. Tissue	11 - 20	p = 0.05	Retinoblastoma
Uterine corpus	165	P = 0.14	Cervix
Vagina	66	P = 0.02	Cervix

Curtis, NCRP Proc 18, 1998

Poteniating Factors (Effect Modifiers)

Radiotherapy and Chemotherapy

Breast	→ Leukemia	Curtis, NEJM 1992;86:1315
Hodgkin's Disease	→ Lung	Travis, JNCI 2002:94:182
Ovary	→ Leukemia	Travis, NEJM 1999;340:351
Acute Leukemia	→ Brain	Reilling, Lancet 1999;354:34
Childhood Cancer	→ Bone	Tucker, NEJM 1987;317:588

Radiotherapy and Cigarette Smoking

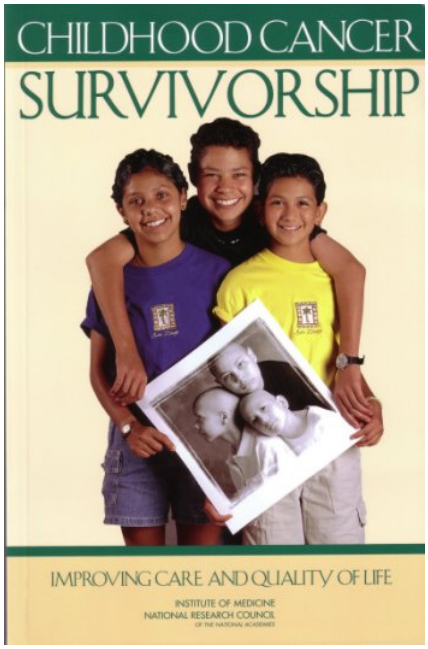
Hodgkin's Disease	→ Lung	van Leeuwen, JNCI 1995;87:1530
Breast Cancer	→ Lung	Neugut, Cancer 1994;73:1615
Lung Cancer	→ Lung	Tucker, JNCI 1997;89:1782

Radiotherapy and Genetic Predisposition

Retinoblastoma	→ Sarcoma	Wong, JAMA 1997;278:1262 Tucker, NEJM 1987;317:588

Radiotherapy and Age at Exposure

Breast	→ Breast	Boice, NEJM 1991;326:781
Hodgkin's Disease	→ Breast	Hancock, JNCI 1993;85:25
All	→ Thyroid	Tucker, Cancer Res 1991;51:2885
All	→ Bone	Inskip, Multiple Primaries, 1999



www.nap.edu
2003

With increased survival, late effects take on more importance.

Second Cancer Studies - Children

Primary	Secondary	Reference
All Cancers	All	Garwicz, IJ Cancer 2000;88:672
	All	Neglia, JNCI 2001;93:618
	All	Mertens, JCO 2001;19:3163
	Leukemia	Tucker, JNCI 1987;78:459
	Bone	Tucker, NEJM 1987;317:548
	Bone	Hawkins, JNCI 1996;88:270
	Bone	Le Vu, Int J Cancer 1998;77:370
	Thyroid	Tucker, Cancer Res 1991;51:2885
Hodgkin's Disease	All	Bhatia, NEJM 1996;334:745
	All	Sankila, J Clin Oncol 1996;14:1442
	All	Wolden, J Clin Oncol 1998;16:1536
Wilms Tumor	All	Breslow, J Clin Oncol 1995;13:1851
Retinoblastoma	All	Wong, JAMA 1997;278:1262
Leukemia	All	Pui, NEJM 2003;349:640
	Brain	Relling, Lancet 1999;354:34
Bone Marrow Transplant	All	Curtis, NEJM 1997;336:897

Substantial area of research

2nd Cancers After Childhood Cancer (LESG)

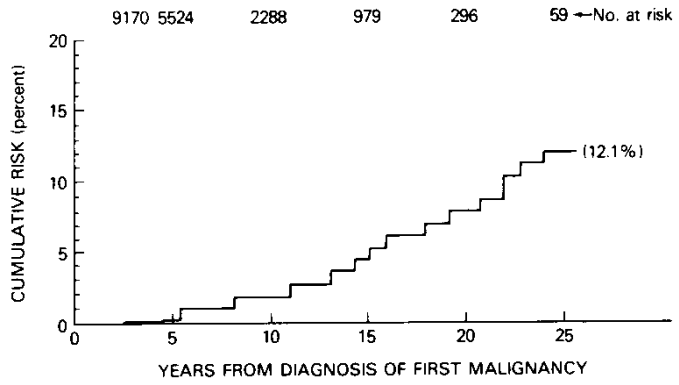
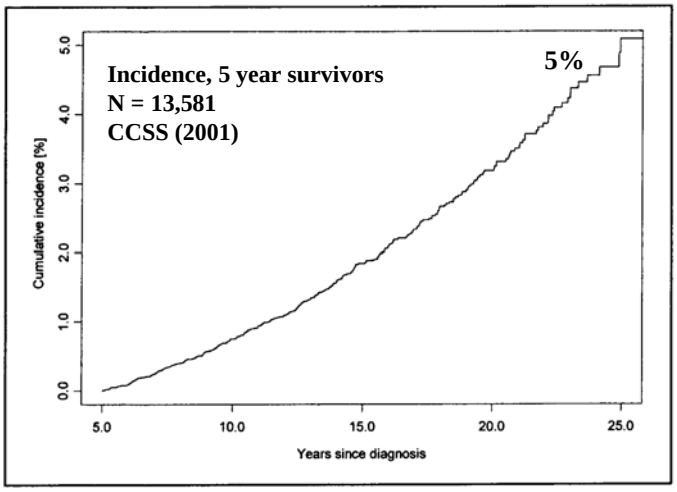


FIG. 1. Cumulative risk of developing a second malignancy among 9,170 persons who survived 2 or more years after the diagnosis of a childhood cancer.

Tucker, In: Boice & Fraumeni, 1984

Early figure. Influenced by type of childhood cancers studied.

2nd Cancers After Childhood Cancer (CCSS)



Neglia, JNCI 93:618, 2001

More recent, but excludes certain tumors (e.g. RB)

Second Cancer After Childhood Cancer (N = 13,581; 5 yr Survivors, CCSS)

	Obs	Obs/Exp	95% CI
All Second Cancers	314	6.4	5.7-7.1
Brain and CNS	36	9.9	6.9-13.6
Bone	28	19.1	12.8-27.7
Soft Tissue Sarcoma	32	6.3	4.3-8.9
Breast (female)	60	16.2	12.4-20.8
Thyroid	43	11.3	8.2-15.27
Leukemia	24	6.9	4.4-10.2

Neglia, JNCI 93:618, 2001

Very high risks, in part because background low but also Rx

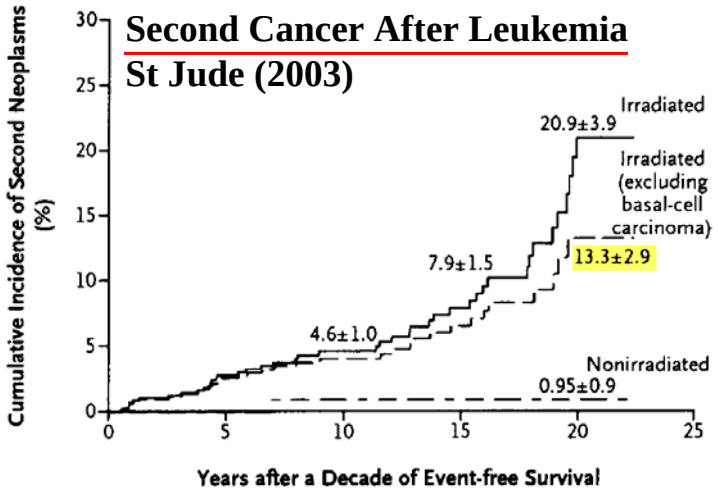
Second Cancer After Childhood Cancer (N=25,120) Radiotherapy Risk (Nordic Countries)

Site	Cases	Controls	RR	95% CI
All sites	234	678	4.3	3.0-6.2
Bone & Conn Tissue	31	89	19.8	4.5-87
Breast	24	71	11.5	3.2-41
Brain & CNS	48	143	2.8	1.4-5.5
Leukemia	20	57	2.6	0.8-8.5

Garwicz, Int J Cancer 88:672, 2000

Role of Radiotherapy

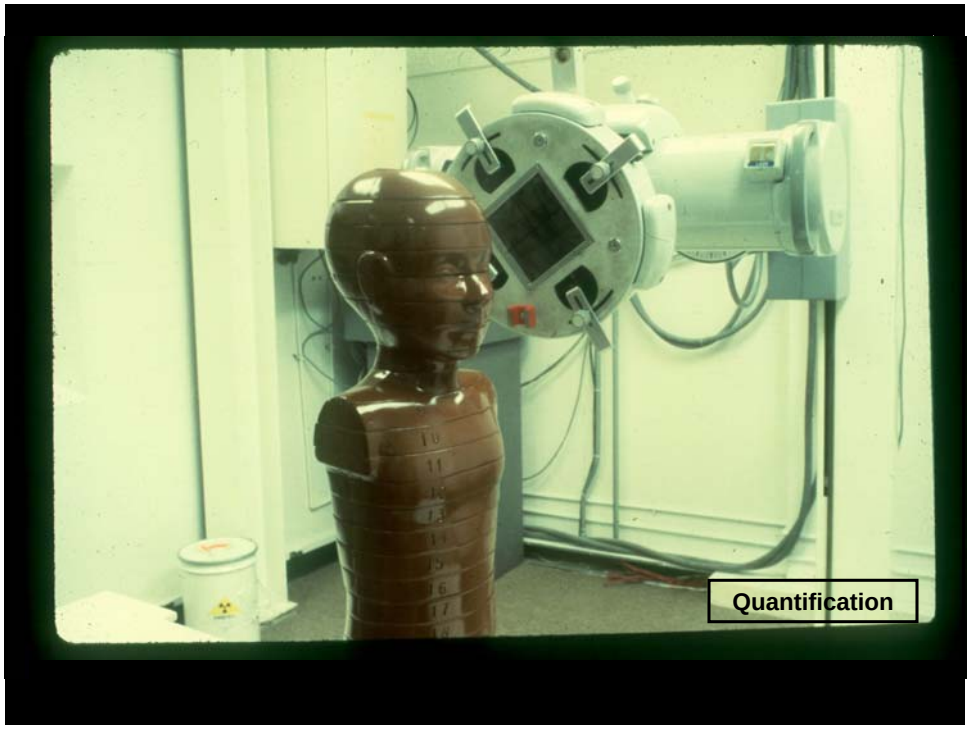
Second Cancer After Leukemia St Jude (2003)



No. at Risk					
Irradiated	597	508	317	200	72
Nonirradiated	259	167	51	2	2

Pui, NEJM 349:640, 2003

Almost all the risk associated with radiotherapy



Thyroid After Childhood Cancer (LESG)

Table 2 *Estimated matched relative risk of thyroid cancer by radiation dose to the thyroid*

	Radiation dose (cGy)			
	<200	200–999	1000–2999	>3000
No. of cases[a]	3	7	7	5
No. of controls	40	17	14	11
Relative risk	1.0[b]	14.2	13.5	17.4
95% confidence interval		1.7–122	1.4–127	1.4–217

Tucker, Cancer Res 51:2885, 1991

High dose effect. Flat response.
Induction vs killing.

Leukemia After Childhood Cancer (LESG)

RR by Radiation Dose

Specification	RR by radiation dose, rad					
	0	<250	250-	1,000-	1,500-	≥2,000
No. of cases	5	5	3	4	5	3
No. of controls	12	11	31	11	13	12
RR	1.0[a]	1.2	0.1	0.8	0.7	0.4

RR by Chemotherapy Dose

Specification	RR for alkylator score:				
	0	1-2	3-4	5-6	≥7
No. of cases	9	1	3	7	5
No. of controls	61	12	7	7	3
RR	1.0[a]	0.7	8.4	16.0	24.2[b]

Tucker, JNCI 78:459, 1987

Little effect of XRT. AA effect strong.

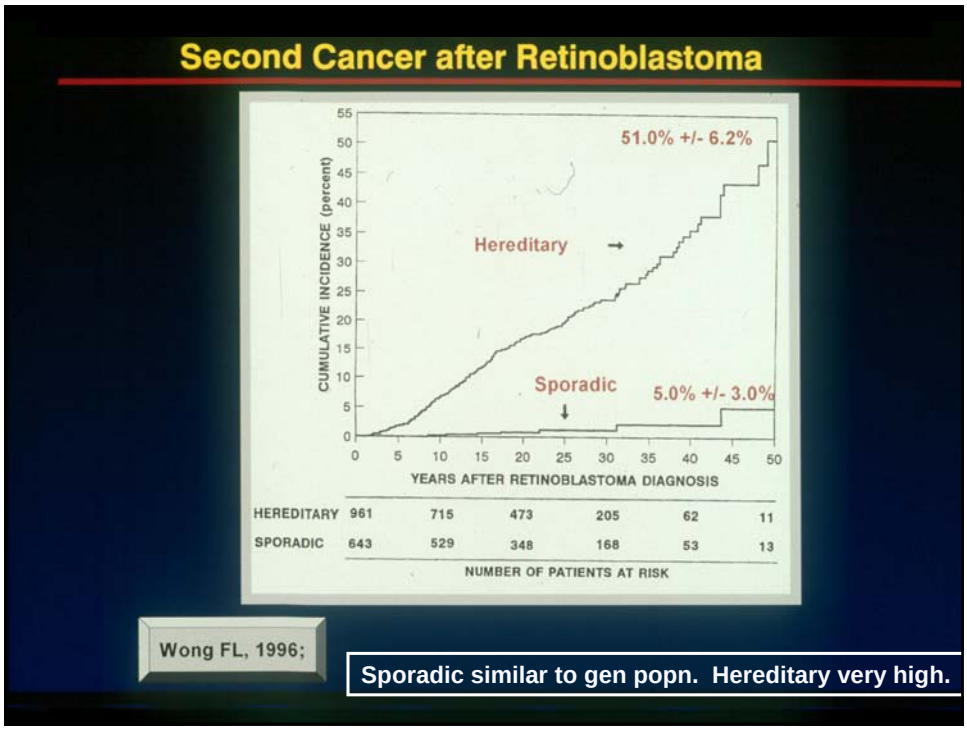
Bone After Childhood Cancer

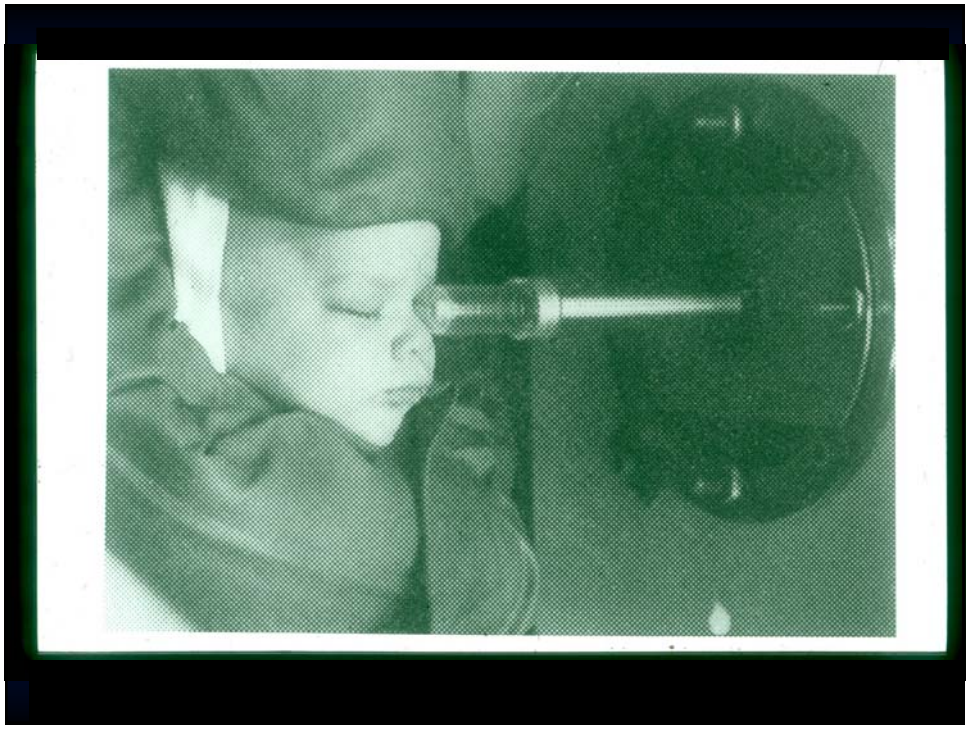
Table 3. Matched Relative Risk of Bone Sarcoma, According to Radiation Dose and Alkylator Score (LESG , 1987)

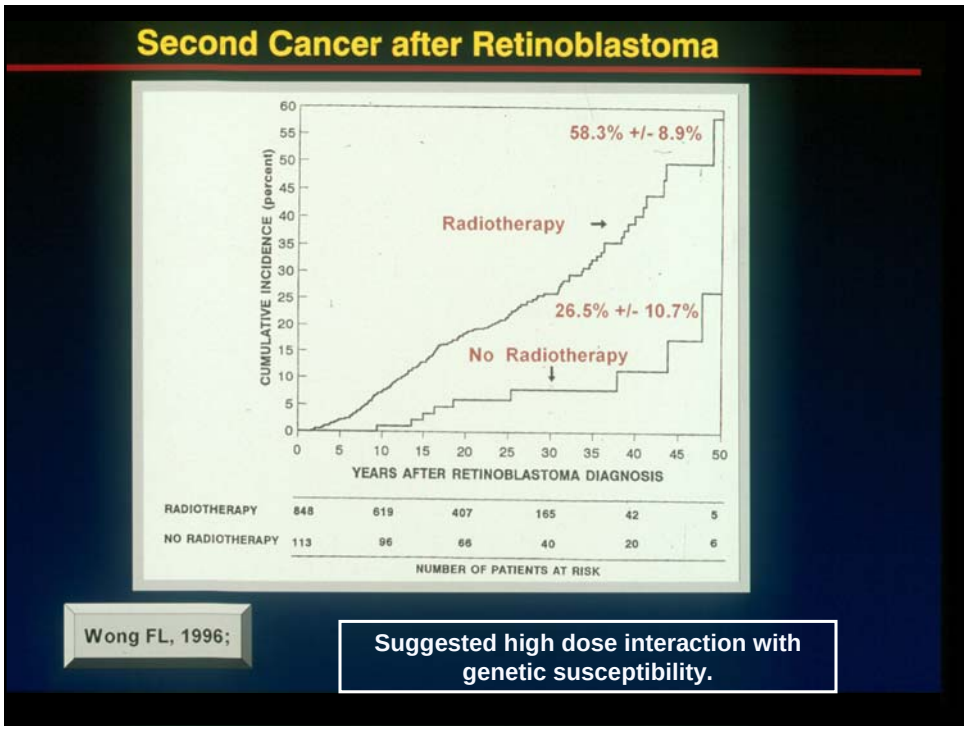
RADIATION DOSE	ALKYLATOR SCORE		
	0	1 or 2	≥3
None			
Relative risk	1.0	4.8	8.5
No. cases:controls	6:44	1:4	3:3
<1000 rad			
Relative risk	1.3	0.4	1.3
No. cases:controls	5:43	1:13	3:14
≥1000 rad			
Relative risk	37.4	14.2	59.2
No. cases:controls	21:45	11;26	13:12

Tucker, NEJM 317:588, 1987

Radiation effect and Alkylating Agent effect.


Second Cancer after Retinoblastoma
51.0% +/- 6.2%
Hereditary
Sporadic
5.0% +/- 3.0%
CUMULATIVE INCIDENCE (percent)
0 5 10 15 20 25 30 35 40 45 50 55
0 5 10 15 20 25 30 35 40 45 50
YEARS AFTER RETINOBLASTOMA DIAGNOSIS
HEREDITARY 961 715 473 205 62 11
SPORADIC 643 529 348 168 53 13
NUMBER OF PATIENTS AT RISK
Wong FL, 1996;
Sporadic similar to gen popn. Hereditary very high.




Second Cancer after Retinoblastoma
58.3% +/- 8.9%
Radiotherapy
26.5% +/- 10.7%
No Radiotherapy
CUMULATIVE INCIDENCE (percent)
0 5 10 15 20 25 30 35 40 45 50 55 60
0 5 10 15 20 25 30 35 40 45 50
YEARS AFTER RETINOBLASTOMA DIAGNOSIS
RADIOTHERAPY 848 619 407 165 42 5
NO RADIOTHERAPY 113 96 66 40 20 6
NUMBER OF PATIENTS AT RISK
Wong FL, 1996;
Suggested high dose interaction with genetic susceptibility.

Sarcoma Dose Response - Retinoblastoma

Sarcoma Type	Radiation Dose, Gy 0 - 4.9	5.0-	10-	30-	60+
Soft-Tissue					
Observed	9	4	10	5	3
RR	1.0	1.6	4.6 *	6.4 *	11.7
All Sarcomas					
Observed	12	8	20	13	14
RR	1.0	1.9 *	3.7 *	4.5 *	10.7 *

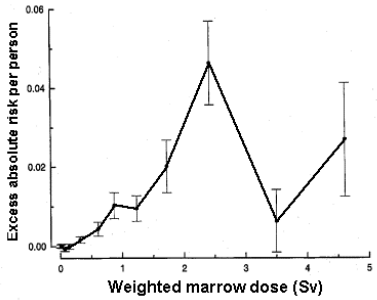
Wong et al, *JAMA*, 278:1262, 1997

* P<0.05

High dose effect, > 5 Gy.

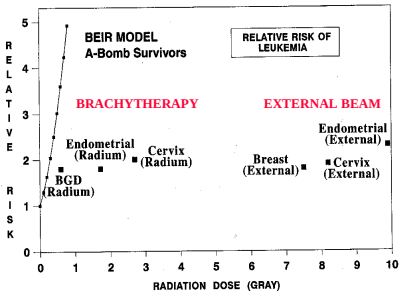
Leukemia Excluding CLL

Atomic Bomb Survivors



Pierce, *Radiat Res* 146:1, 1996

Medical Studies



Boice, *Leukemia* (Henderson, ed), 2002

Lung Cancer - Comparisons with LSS

	No. Cases		ERR / SV	
Medical Study	Study	LSS	Study	LSS
Kaldor (1992)	40	135	0.27	1.23
Inskip (1994)	59	178	0.20	1.96**
van Leeuwen (1995)	30	135	0.37	1.23
Mattsson (1997)	19	364	0.38	1.85**
Davis (1989)	69	936	- 0.16	0.59**
Griem (1994)	162	750	0.60	0.69
Weiss (1994)	1126	855	0.05	0.65**
Howe (1995)	1178	936	0.00	0.59**

**LSS inconsistent with medical study
LSS = Life Span Study (A-bomb survivors)

Little, *IJRB* 77:431, 2001

"Relative risks tend to be lower in the medical series than in the Japanese A-bomb survivors. The most marked discrepancies…are for leukemia, where 12 of the 17 medical studies have significantly lower relative risks…"

Little, *IJRB* 77:431, 2001

Second Cancer - Summary

- Numbers substantial -- especially important after childhood
- Exceptional dose assessment opportunities
- Unique opportunities to study:
  - Interactions
  - High doses
  - Low doses
  - Understudied cancers
- These opportunities will <u>not</u> soon go away

Overviews

International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 75. Ionizing Radiation, Part 1: X- and Gamma (γ)-Radiation, and Neutrons. Lyon, France: IARC, 2000.

Little MP. Cancer after exposure to radiation in the course of treatment for benign and malignant disease. Lancet Oncol 2001;2:212-20.

Little MP. Comparison of the risks of cancer incidence and mortality following radiation therapy for benign and malignant disease with the cancer risks observed in the Japanese A-bomb survivors. Int J Radiat Biol 2001;77:431-64.

Neugut AI, Meadows AT, Robinson E. Multiple Primary Cancer. Lippincott, Philadelphia, 1999.

Van Leeuwen FE, Travis LB. Adverse effects of treatment: second cancers. In: Cancer--Principles & Practices of Oncology, 6th Edition (DeVita, Hellman, Rosenberg, eds). Lippincott, Williams & Wilkins, 2001.