Studies of Medically-Irradiated Populations External Radiation

NATIONAL CANCER INSTITUTE
RADIATION EPIDEMIOLOGY BRANCH
Rockville, Maryland
Radiation Epidemiology Course

15 May 2007
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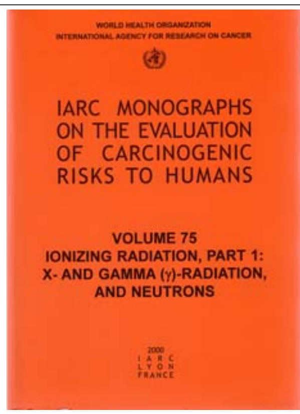
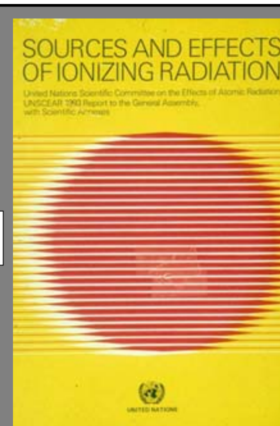
Outline – Medical Irradiation Studies

- Introduction - Importance
- Cancer Treatment
- Non-Cancer Treatment
- Diagnostic Exposure

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

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



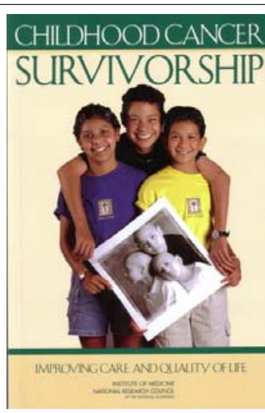


UNSCEAR 2000
2007 Soon

Radiation risks.

Tables on epidemiologic study strengths and limitations.

With increased survival, late effects take on more importance.

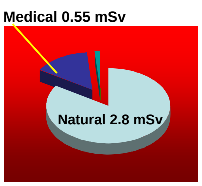


www.nap.edu
2003

Charles Schultz, Peanuts

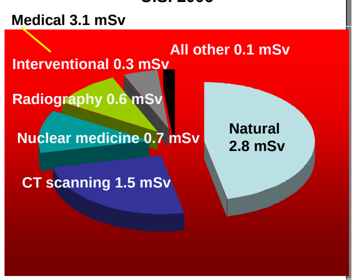
Estimate of changes in U. S. radiation exposure

U.S. 1980



Total ~ 3.6 mSv per caput

U.S. 2006



Total ~ 6.0 mSv per caput

Radiation Epidemiology Studies in Medicine

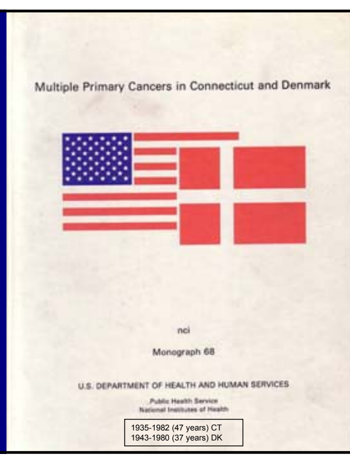
Cancer Treatment	Non-Malignant Treatment	Diagnostic Exams
Cervix	Thymus	TB-Fluoroscopy
Hodgkin	Spondylitis	Scoliosis
Endometrial	Tonsils	Dental
Ovary	Tinea capitis	Head & Neck
Breast	Peptic ulcer	Mixed diagnostic X-rays
Testis	Hemangioma	In utero
Childhood	Gynecolgic	Nuclear imaging
	Breast	
	Hyperthyroidism	

Cancer Treatment

- **STUDIES OF ADULTS**
  - Hodgkin lymphoma
    - Breast
    - Lung
  - Breast cancer
  - Cervical cancer
- **STUDIES OF CHILDREN**
  - Childhood Cancer
  - Retinoblastoma
- **COMPARISONS WITH A-BOMB SURVIVORS**

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**


Multiple Primary Cancers in Connecticut and Denmark

nci

Monograph 68

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

1935-1982 (47 years) CT
1943-1980 (37 years) DK

Secondary Carcinogenesis in Patients Treated with Radiation: A Review of Data on Radiation-Induced Cancers in Human, Non-human Primate, Canine and Rodent Subjects

Herman Suit,[a,1] Saveli Goldberg,[a] Andrzej Niemierko,[a] Marek Ancukiewicz,[a] Eric Hall,[b] Michael Goitein,[a] Winifred Wong[a] and Harald Paganetti[a]

[a] Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and [b] Center for Radiological Research, Columbia University, New York, New York

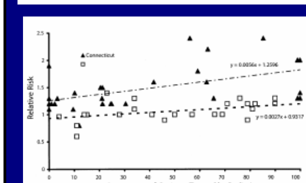
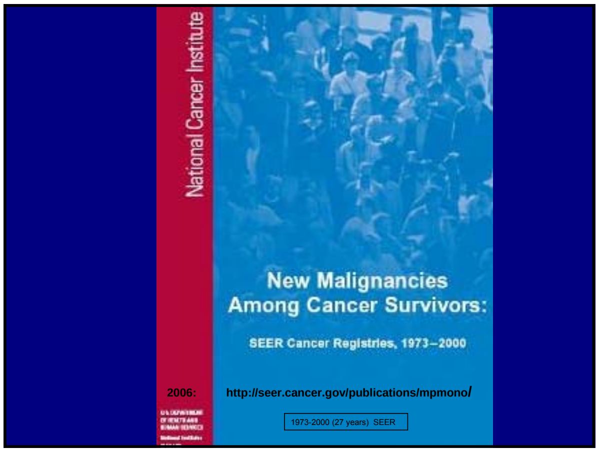


FIG. 3. RR as a function of proportion of patients of irradiated in the Connecticut and Danish Cancer Registries (6).

Radiation Research 167, 12-42, 2007

Treatment planning to reduce dose to uninvolved normal tissue

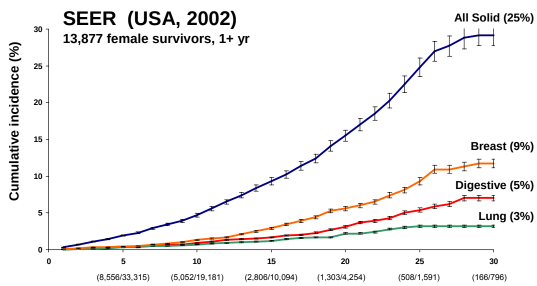


Second Cancer Studies - Adults

Primary	Secondary	Reference
Hodgkin Lymphoma	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 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

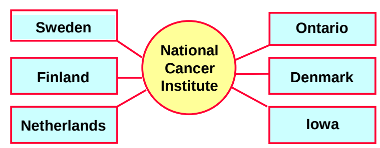
Second Cancer After Hodgkin Lymphoma



Dores et al *JCO* 20:3484, 2002

25% incidence @ 30 y

Breast Cancer Following Hodgkin Lymphoma 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

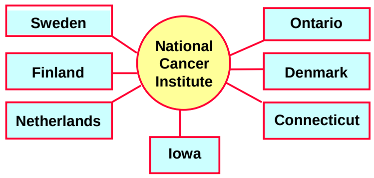
Dose computed to tumor site. High dose risk. Early onset. Chemotherapy can protect.

Absolute Risks (%) Breast After Hodgkin Lymphoma -- Counseling

Age at HL diagnosis		15 yr			25 yr		
Age at counseling (yr)		25	25	35	35	35	45
Age at end of risk projection (yr)		35	45	45	45	55	55
Treatment for HL							
Mediastinal RT	AA		(%)			(%)	
None	Yes	0.1	0.8	0.8	0.8	2.5	2.0
<40 Gy	Yes	0.7	4.2	3.8	4.0	12.3	9.6
≥40 Gy	Yes	0.8	5.1	4.7	4.8	14.9	11.6
None	No	0.3	1.8	1.6	1.7	5.4	4.1
<40 Gy	No	1.4	8.7	8.1	8.3	24.5	19.4
≥40 Gy	No	1.7	10.5	9.8	10.1	29.0	23.2

Travis ... Gail, *JNCI* 97:1428, 2005

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

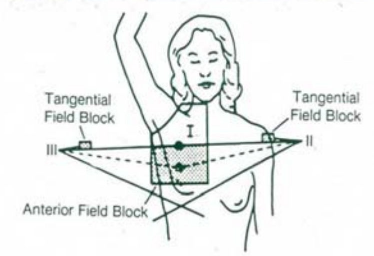
Lung Cancer After Hodgkin's Disease
Radiotherapy and Smoking

		Lung Dose (Gy)	
		<5 Gy	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)

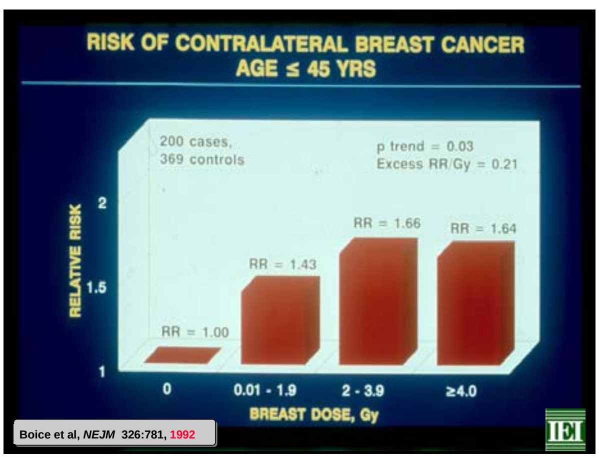
Travis et al, *J Natl Cancer Inst* 94:182, 2002 Gilbert et al. Radiat Res 159:161, 2003

High dose interaction Another reason to stop smoking.



RADIOTHERAPY DOSE TO CONTRALATERAL BREAST

Dose to contralateral breast can be high



Secondary Breast
Radiotherapy for Breast Cancer

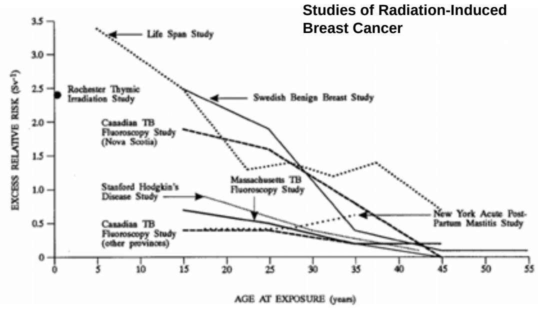
	RR	95% CI
All Subjects*	1.19	0.9-1.5
Time After Exposure (Yr)		
5-9	0.99	0.7-1.4
≥10	1.33	1.0-1.8
Age at Exposure (Yr)		
<35	2.26	0.9-5.7
35 -	1.46	0.9-2.3
≥45	1.01	0.8-1.4

*655 Cases, 1189 Controls

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

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

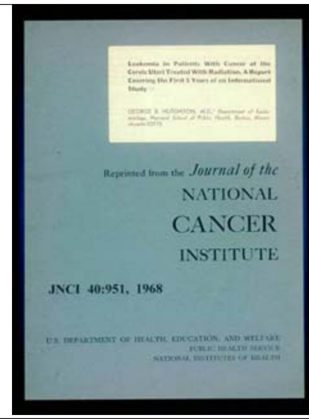
BREAST CANCER RISK BY AGE AT EXPOSURE



Studies of Radiation-Induced Breast Cancer

UNSCEAR 1994, p. 155
Strong effect of age at exposure

Preston et al. Rad Res 2002



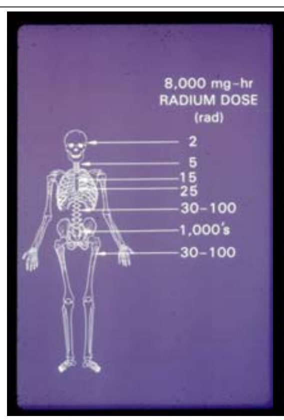
Cervical Cancer

Number:	30,000 women
Dose:	500-1500 rad (Marrow)
Leukemia	
Observed:	13
Expected:	15.5
Risk:	0

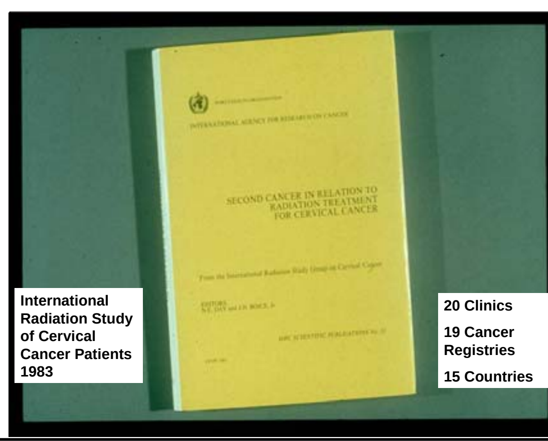
Boice & Hutchison, *J Natl Cancer Inst* 65:115, 1980

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

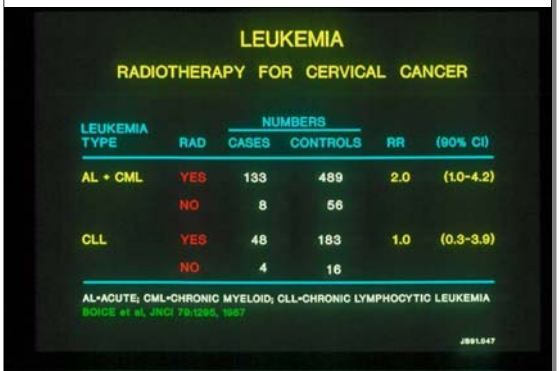


International Radiation Study of Cervical Cancer Patients 1983

20 Clinics

19 Cancer Registries

15 Countries



LEUKEMIA

RADIOTHERAPY FOR CERVICAL CANCER

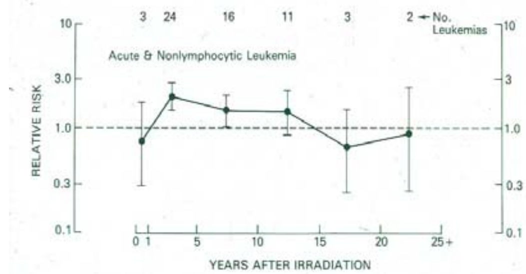
LEUKEMIA TYPE	RAD	NUMBERS CASES	NUMBERS CONTROLS	RR	(90% CI)
AL + CML	YES	133	489	2.0	(1.0-4.2)
	NO	8	56		
CLL	YES	48	183	1.0	(0.3-3.9)
	NO	4	16		

AL=ACUTE; CML=CHRONIC MYELOID; CLL=CHRONIC LYMPHOCYTIC LEUKEMIA

BOICE et al, JNCI 79:1295, 1987

J891.047

Characteristic wave-like pattern



Boice et al *JNCI*, 1985;74:955

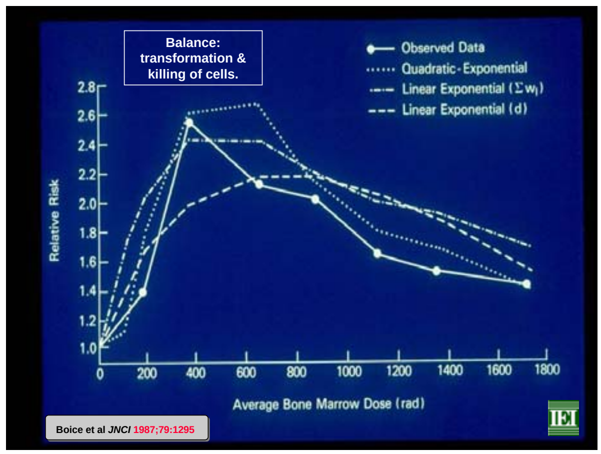
Leukemia by Years after Radiotherapy Cervical Cancer

Second Cancer (ICD-7)	Years after radiotherapy 1-4	5-9	10-14	15-19	20-24	25-29	30+	Total
Chronic lymphatic leukemia (204.0)								
Obs	3	4	4	4	5	2	3	25
Exp	6.00	6.17	5.53	4.81	4.00	2.90	2.91	32.33
O/E	0.50	0.65	0.72	0.83	1.25	0.69	1.03	0.77
Acute and nonlymphocytic leukemia (204.2, 204.3)								
Obs	24	21	8	9	11	3	6	82
Exp	12.68	12.43	10.54	8.48	6.58	4.50	2.04	59.28
O/E	1.89 *	1.69 *	0.76	1.06	1.67	0.67	1.48	1.38 *

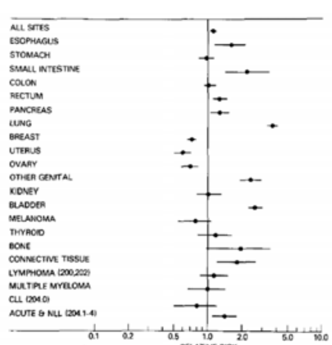
ANLL increased <10y

CLL is not increased at any interval

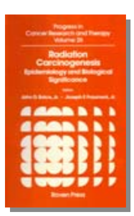
Kleinerman, Cancer, 1995;76:442



Cervical Cancer

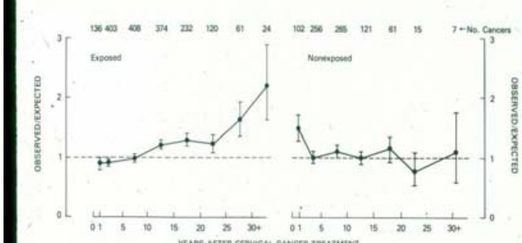


Tissues differ in their relative sensitivity to the carcinogenic effects of radiotherapy

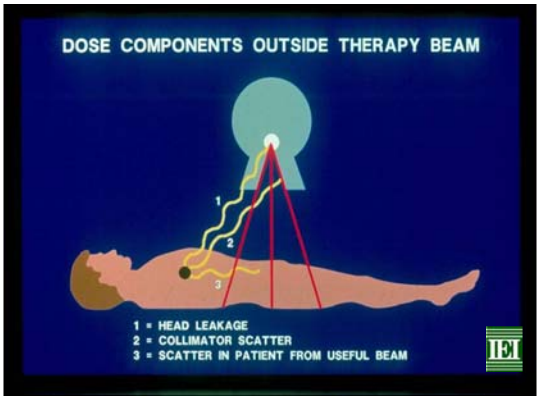


Boice et al *B&F* p165, 1984

Solid cancer … a long latency.



Boice et al *JNCI*, 1985;74:955



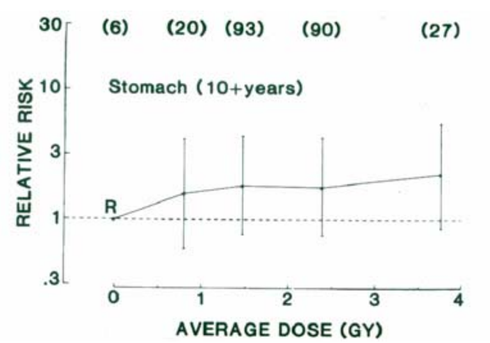
Lightly Irradiation Sites - Cervical Cancer

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)

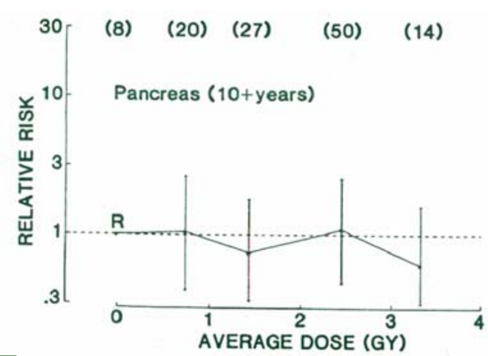
Boice, JNCI, 1985;74:955

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

Lung Cancer – Medical Studies Compared 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 = Atomic bomb survivor Life Span Study
* Diagnostic irradiation

Little, *IJRB* 77:431, 2001

Medical Studies – Lower Risk

"Relative risks tend to be lower in the medical series than in the Japanese A-bomb survivors.

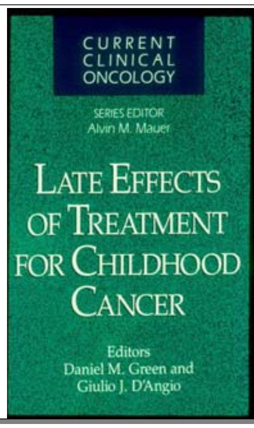
The most marked discrepancies … are for leukemia, where 12 of the 17 medical studies have significantly lower relative risks…"

Cell killing, fractionation, protraction

Little, *IJRB* 77:431, 2001

Cancer Therapy

- Low-dose scatter not well studied
- Large numbers
- Excellent dosimetry
- Risks lower than atomic bomb survivors
- More could be done to quantify risks < 1 Gy



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
	Brain	Neglia, JNCI 2006; 98:1528
	Thyroid	Tucker, Cancer Res 1991;51:2885
	Thyroid	Sigurdson, Lancet 2005; 365:2014
Hodgkin Lymphoma	All	Bhatia, NEJM 1996;334:745
	Breast	Travis, JAMA 2003; 290:465
Wilms Tumor	All	Breslow, J Clin Oncol 1995;13:1851
Retinoblastoma	All	Wong, JAMA 1997;278:1262
	STS	Kleinerman, JNCI 2007; 99:24
Leukemia	All	Pui, NEJM 2003;349:640
	Brain	Relling, Lancet 1999;354:34
Bone Marrow Transplant	All	Curtis, NEJM 1997;336:897

2nd Cancers After Childhood Cancer (LESG)

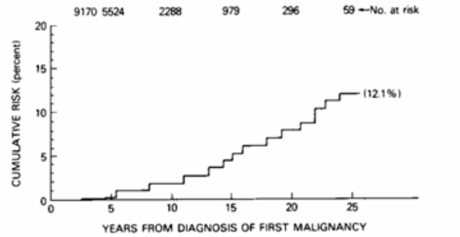
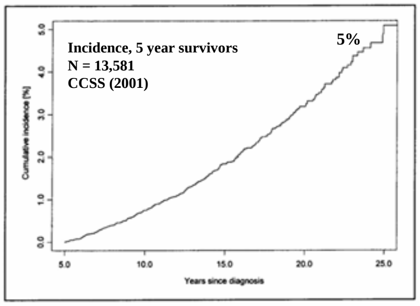


FIG. 1. Cumulative risk of developing a second malignancy among 9,170 persons who survived 2 or more years after the diagnosis of a childhood cancer.

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 et al, *JNCI* 93:618, 2001

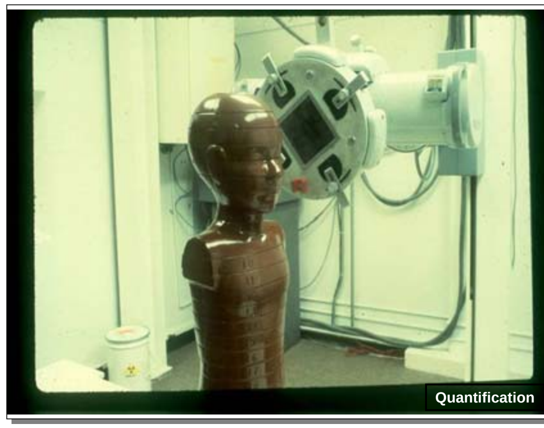
Very high risks, in part because background low but also Rx

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



Thyroid After Childhood Cancer (LESG)

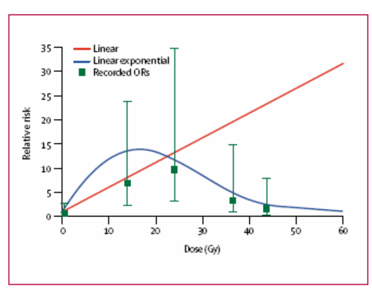
Table 2. ***Estimated matched relative risk of thyroid cancer by radiation dose to the thyroid***

	Radiation dose (cGy)			
	<200	200-	1000-	>3000
No. of cases	3	7	7	5
No. of controls	40	17	14	11
Relative risk	1.0	14.2	13.5	17.4
95% confidence interval		3.7-122	1.4-127	1.4-217

Tucker, Cancer Res 51:2885, 1991

High dose effect. Flat response. Induction vs killing.

Thyroid Cancers After Childhood Cancer (CCSS)



Sigurdson, Lancet 365:2014, 2005

See also Tucker, Cancer Res 51:2885, 1991

Leukemia After Childhood Cancer (LESG)

RR by Radiation Dose

Specification	RR by radiation dose, rad: 0	<250	250-	1000-	1500-	≥ 2000
No. of cases	5	5	3	4	5	3
No. of controls	12	11	31	11	13	12
RR	1.0	1.3	0.1	0.8	0.7	0.4

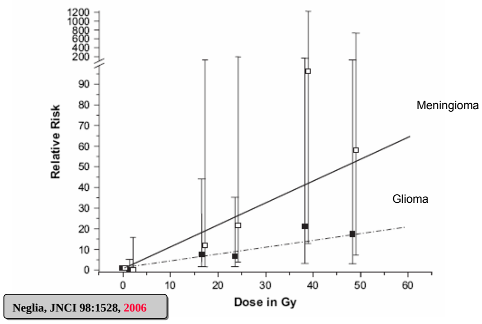
RR by Chemotherapy

Specification	RR for alkylator score: 0	1-	3-	5-	≥ 7
No. of cases	9	1	3	7	5
No. of controls	61	12	7	7	3
RR	1.0	0.7	8.4	16.0	24.2

Tucker, JNCI 78:459, 1987

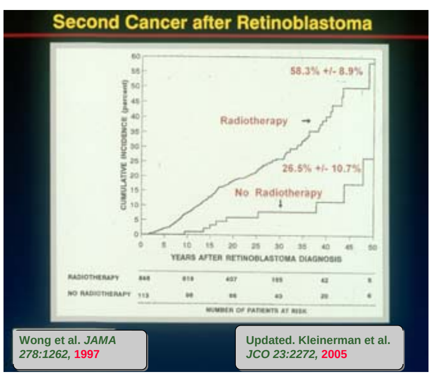
Little radiation effect. AA effect strong.

Brain Cancers After Childhood Cancer (CCSS)



Neglia, JNCI 98:1528, 2006

Retinoblastoma



Possible 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*

* P<0.05

Wong et al, JAMA, 278:1262, 1997

See recent Kleinerman et al. JNCI 99:24-31, 2007

High dose effect, > 5 Gy.

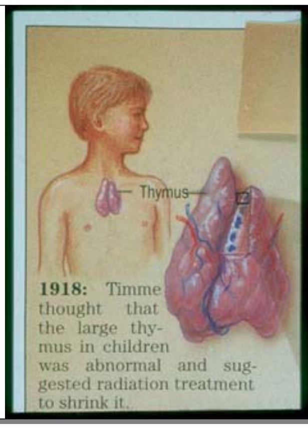
Second Cancers

- Numbers Substantial -- Especially Important After Childhood
- Chemotherapy → Leukemia, bone, bladder, other
- Radiotherapy → most solid cancers, little leukemia
- New Treatments → continued need to evaluate
- Tremendous amount of research ongoing
- Future studies will also focus on genetic predisposition and interaction
- Lifetime surveillance and programs of patient awareness.

Radiation Epidemiology Studies in Medicine

Cancer Treatment	Non-Malignant Treatment	Diagnostic Exams
Cervix	Thymus	TB-Fluoroscopy
Hodgkin	Spondylitis	Scoliosis
Endometrial	Tonsils	Dental
Ovary	Tinea capitis	Head & Neck
Breast	Peptic ulcer	Mixed diagnostic X-rays
Testis	Hemangioma	In utero
Childhood	Gynecolgic	Nuclear imaging
	Breast	
	Hyperthyroidism	

Newborns were treated at 6 mo.

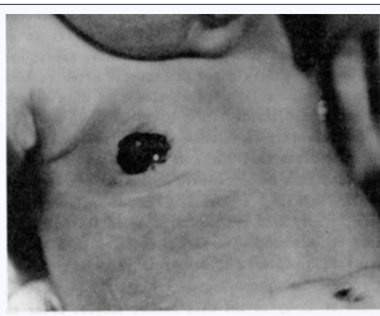


Breast Cancer Thymus Irradiation

Breast Dose (cGy)	0	1 -	50 -	200+
No. of breast cancers	12	8	6	8
Relative Risk	1.0	2.7	6.7	4.7
95% CI	--	1.1-6.7	2.4-18.7	1.9-12.1

Hildreth et al, *NEJM* 321:1281, 1989

Immature breast tissue at risk but risk manifests many years later



Cavernous hemangioma in girl, 6 months old
1936, Ra-226, 6.6 Gy to breast

Breast Cancer After Infant Exposure Dose Rate Reduction (DDREF = 7)

Study Exposure	Breast Dose (Gy)*	Number Treated	Breast Ca	Excess Risk (10^4 WY- Gy)
Thymus				
High-dose-rate x-ray	0.7	3,312	34	34.0
Hemangioma				
Low-dose-rate gamma	0.4	17,082	226	5.1

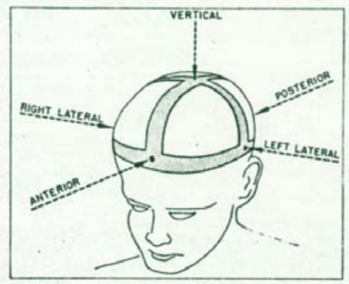
*Ranges (0.02-7.5 Gy) & (0.02-35 Gy)

Preston et al, *Radiat Res*, 158:220, 2002

Consistent with a *low dose rate* having a smaller effect

Radiotherapy for Ringworm
5 treatments, 3-12 minutes each

Fig 1.—Five Treatment fields used in the Adamson-Kienbock treatment were positioned with the aid of a "cap" made from steel bands.



Thyroid
Tinea Capitis - Israel

Number Exposed:	10,834
Number Nonexposed:	16,226
Thyroid Dose (mean):	9 cGy
Observed Thyroid Cancers:	43
Expected:	10.7
RR (95% CI):	4.0 (2.3 - 7.9)

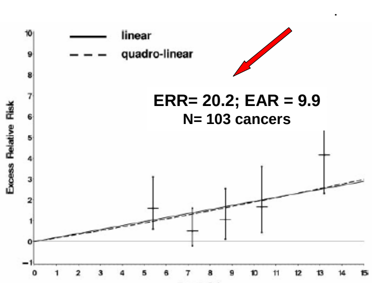
Ron et al, *Radiat Res* 120:516, 1989

Discussion …

- **Effect primarily among immigrants, mainly from Morocco, not Israeli born (Ron, Rad Res 1989)**
- **"Irradiation for tinea capitis was given to many Jews in Morocco prior to immigration…"(Modan, JNCI 1980)**
- **Genetic susceptibility & family clustering (4 sisters thyroid disease)**
- **Wiggle could increase dose x 3**
- **Immigrants from Morocco came from Atlas Mt region, and diets deficient in stable iodine**

Thyroid Cancer Dose Response
Israeli Tinea Capitis 2007

Conclusions: Our findings agree with patterns of risk modification seen in most studies of radiation-induced thyroid cancer, although risk per unit dose seems higher. Our data show that 40 yr after irradiation, ERR decreases dramatically, although remaining significantly elevated. The hypothesis of different genetic susceptibility of the Jewish population deserves further exploration.

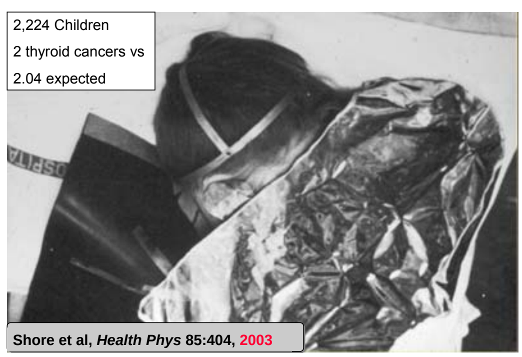


Sadetzki et al. *J Clin Endocrinol Metab* 91: 4798–4804, 2006

Authors discuss: Genetics, Surveillance, Screening, Compensation

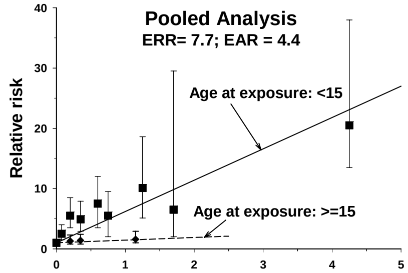
NY Tinea Capitis

2,224 Children
2 thyroid cancers vs
2.04 expected



Shore et al, *Health Phys* 85:404, 2003

Thyroid Cancer & External Radiation Risk Dose Response by Age at Exposure



Ron et al, *Radiat Res* 141:259, 1995

Genetic Predisposition to Radiation-induced Meningioma -- Israeli Tinea Capitis 2007

Interpretation **Our results support the idea that genetic susceptibility increases the risk of developing meningioma after exposure to radiation.**

Further studies are needed to identify the specific genes involved in this familial sensitivity to ionising radiation. DNA repair and cell-cycle control genes, such as the ataxia-telangiectasia gene, could be plausible candidates for investigation.

Flint-Richter P, Sadetzki S. *Lancet Oncol* 8: 403–10, 2007

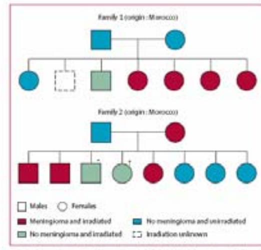


Figure 2: Family tree of two families with four RAM in first-degree relatives Family 1 includes seven siblings of whom four sisters and one brother were irradiated for tinea capitis and all four sisters developed meningiomas. Family 2 includes an irradiated mother and eight siblings of whom five were irradiated. The mother and three of the irradiated siblings (two brothers, one sister) developed meningiomas. Also, two irradiated siblings were diagnosed with leukaemia (*) or breast cancer (†).

Non-Cancer Therapy

- **Opportunity to study effects of low dose scatter**
- **Opportunity to study protraction and DDREF**
- **Cell-killing not as big a problem**
- **Confounding and bias are important for low dose evaluations. The bias may be greater than effect to be detected**

Radiation Epidemiology Studies in Medicine

Cancer Treatment	**Non-Malignant Treatment**	**Diagnostic Exams**
Cervix	Thymus	TB-Fluoroscopy
Hodgkin	Spondylitis	Scoliosis
Endometrial	Tonsils	Dental
Ovary	Tinea capitis	Head & Neck
Breast	Peptic ulcer	Mixed diagnostic X-rays
Testis	Hemangioma	In utero
Childhood	Gynecolgic	Nuclear imaging
	Breast	
	Hyperthyroidism	

Risk of Cancer from Diagnostic X-rays: Estimates for the UK and 14 Other Countries

"**Findings**: Our results indicate that in the UK about 0.6% of the cumulative risk of cancer to age 75 years could be attributable to diagnostic X-rays. This percentage is equivalent to about 700 cases of cancer per year."

Berrington de Gonzalez, *Lancet 363:345,* 2004

Lung collapse therapy for tuberculosis and associated multiple chest fluoroscopic x-rays

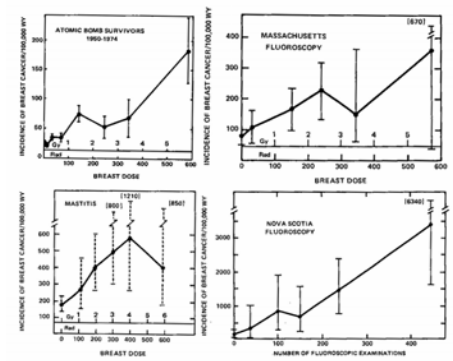
Studies of low-dose fractions accumulating to high dose.

Breast
TB - Fluoroscopy, Massachusetts

Number Exposed:	2,573
Number Unexposed:	2,367
No. Chest Fluoroscopies (mean):	88
Breast Dose (mean):	79 cGy
Observed Breast Cancer:	147
Expected:	114
RR (95% CI):	1.29 (1.1 - 1.5)

Boice et al, *Radiat Res* 126:214, 1991

Boice & Monson, *J Natl Cancer Inst* 59:823 1977



Boice et al, *Radiology* 131:589, 1979

Severe Scoliosis

Breast Cancer
Scoliosis

No. Female Patients	**5,573**
Years Treated	**1912 - 1965**
Age, Mean (yr)	**10.6**
No. X-rays	
Range	**0 - 618**
Mean	**24.7**
Breast Dose (cGy)	
Range	**0 - 170**
Mean	**11**
Breast Cancer Deaths	
Observed	**77**
Expected	**45.6**
O/E (95% CI)	**1.69 (1.3-2.1)**

Doody et al. Spine 25:2052, 2000

Sensitivity of immature breast

Lung
TB - Fluoroscopy, Massachusetts

Number Exposed:	6,285
Number Unexposed:	7,100
No. Chest Fluoroscopies (ave):	77
Lung Dose (mean):	84 cGy
Observed Lung Cancer:	69
Expected:	86
RR (95% CI):	0.8 (0.6 - 1.0)

Davis et al, *Cancer Res* 49:6130, 1989

Lung
TB - Fluoroscopy, Canada
Compared to Japanese LSS

	Multiple Fluoroscopy		Atomic Bomb	
Lung Dose (cGy)	**# Lung Ca**	**RR (95% CI:)**	**# Lung Ca**	**RR (95% CI:)**
< 1	723	1.0	248	1.0
1 -	180	0.87 (0.7-1.0)	290	1.26 (1.1-1.5)
50 -	92	0.82 (0.7-1.0)	38	1.45 (1.0-2.1)
100 -	114	0.94 (0.8-1.2)	30	1.93 (1.3-2.9)
200 -	41	1.09 (0.8-1.5)	10	2.65 (1.5-4.7)
300+	28	1.04 (0.7-1.5)	3	--

Howe G, *Radiat. Res.* 1995; 142:295

Leukemia
TB - Fluoroscopy, Massachusetts

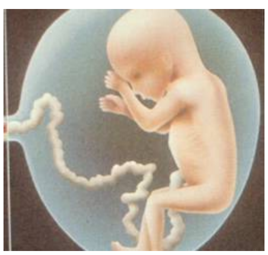
Number Exposed:	6,285
Number Unexposed:	7,100
No. Chest Fluoroscopies (ave):	77
Bone Marrow Dose (mean):	9 cGy
Observed Leukemia:	17
Expected:	18.9
RR (95% CI):	0.9 (0.5 - 1.8)

Davis et al, *Cancer Res* 49:6130, 1989

Conclusion - Fractionation

- Tissues differ with respect to response to fractionated exposures
- Studies of low dose fractions that cumulate to high doses provide opportunity to study “low dose effects”
- Even for low dose effects (breast and thyroid) age modification can be more important. Generalizations don’t necessarily hold.

Pregnancy and Medical Radiation



Oxford Prenatal X-ray Survey

Childhood Cancer	Cases No.	% X-ray	RR
Leukemia			
Lymphatic	2,007	14	1.5
Myeloid	866	14	1.5
Lymphoma	719	13	1.4
All Leuk/Lymphoma	4,771	14	1.47
Wilms	590	15	1.6
CNS	1,332	13	1.4
Neuroblastoma	720	14	1.5
Bone	244	11	1.1
Other Solid	856	15	1.6
All Solid	3,742	14	1.47

Bithell, Stewart, *Br J Cancer* 31:271, 1975

Biologically plausible to have same RR ?

The results were the same for leukemia, lymphosarcoma, cerebral tumors, neuroblastoma, Wilms' tumor and for all other cancer. Given the differences in the epidemiology of these neoplasms, which reflects etiology, it seems unlikely that each would have the same relative risk as the others after maternal diagnostic radiation exposure.

Miller. *NCRP Proc 6* (Apr), 1984

UNSCEAR, VIENNA, 1996

On the balance of evidence, we conclude that irradiation of the fetus *in utero* increases the risk of childhood cancer, that an increase in risk is produced by doses of the order of 10 mGy, and that in these circumstances the excess risk is approximately 6% per Gy.

Doll & Wakeford. ***Br J Radiol*** **(Feb) 1997**

GROUNDS FOR UNCERTAINTY

1. A-bomb *in utero* study of childhood cancer is negative
2. All cohort studies are negative — only case-control studies are positive and more susceptible to bias
3. Biological Implausibility; equality of relative risks for leukemia and solid tumors
4. Twins have lower risk than singletons despite more frequent x-rays
5. Supporting animal evidence is weak

Doll and Wakeford. Br J Radiol 70:130, 1997
Little and Wakeford, JRP 2002; Int J Radiat Biol 2003
Boice and Miller, Teratology 59, 227, 1999
UNSCEAR, 1994; MacMahon NEJM 1985.

Results of Obstetric - Radiation Cohort Studies

Study	**# Irrad. Cancers**	**Total Cancer: RR (95% CI)**	**Leukemia: RR (95% CI)**
Edinburgh/London [1]	9	---	0.86 (0.4-1.6)
UK National Cohort [2]	12	1.20 (0.6-2.5)	---
Chicago [3]	4	1.19 (0.4-4.0)	0.66 (0.1-5.0)
Baltimore [4]	13	1.05 (0.5-2.1)	1.62 (0.6-4.6)
US Perinatal Project [5]	7	1.09 (0.5-2.4)	---
Rochester, NY [6]	3	---	0.92 (0.3-3.1)
Combined Studies	48	1.12 (0.7-1.7)	0.98 (0.6-1.6)

(1) Court-Brown BMJ 1960; (2) Golding BJC 1990; (3) Griem 1967, Oppenheim 1974; (4) Diamond AJE 1973; (5) Shiono JNCI 1980; (6) Murray NEJM 1959

WM Court Brown, R Doll, A Bradford Hill

"Altogether information was obtained about **39,166 liveborn children whose mothers were known to have been subjected to abdominal or pelvic irradiation during their pregnancy.** Among their children, nine were discovered to have died of leukaemia before the end of 1958. The expected number was estimated to be 10.5…

It is concluded that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy is not established."

BMJ November 26, 1960

It seems likely that the question of the association between fetal irradiation and childhood cancer will fade into medical history unresolved and remain a source of more confusion than enlightenment.

MacMahon. *N Engl J Med* 312:576, 1985

Annals of the ICRP

ICRP Publication 90 (2003)
Biological Effects after Prenatal Irradiation (Embryo and Fetus)

" Although the arguments fall short of being definitive because of the combination of biological and statistical uncertainties involved, they raise a serious question of whether the great consistency in elevated RRs, including embryonal tumours and lymphomas, may be due to biases in the OSCC study rather than a causal association. "

Conclusion – Prenatal

- Leukemia excess plausible
- No individual dosimetry
- Causal association questioned
- Prudent to assume risk

Studies of Medical Exposure - 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

Relevant References - 1

Amundson S, et al. Low-dose radiation risk assessment. Report of an International Workshop on Low Dose Radiation Effects held at Columbia University Medical Center, New York, April 3-4, 2006. *Radiat Res* 166:561-565, 2006.

Boice JD Jr. Ionizing radiation. In: <u>Cancer Epidemiology and Prevention, 3rd Edition</u>. (Schottenfeld D, Fraumeni JF Jr, eds). New York, Oxford University Press (2006).

Boice JD Jr. Radiation-induced leukemia. In: <u>Leukemia, Seventh Edition</u> (Henderson ES, Lister TA, Greaves MF, eds). Philadelphia, W.B. Saunders, 2002, pp 152-169.

Fry RJM, Boice JD Jr. Radiation carcinogenesis. In: <u>Oxford Textbook of Oncology, Second Edition</u> (Souhami RL, Tannock I, Hohenberger P, Horiot J-C, eds). New York: Oxford Press, 2002, pp 167-184.

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Little MP. Cancer after exposure to radiation in the course of treatment for benign and malignant disease. <u>Lancet Oncol</u> 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. <u>Int J Radiat Biol</u> 2001;77:431-64.

National Council on Radiation Protection and Measurements. Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation. NCRP Report No. 136. Bethesda, MD: NCRP, 2001.

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Neugut AI, Meadows AT, Robinson E. <u>Multiple Primary Cancer</u>. Lippincott, Philadelphia, 1999.

Tubiana M, et al. Dose-effect relationships and the estimation of carcinogenic effects of low doses of ionizing radiation. Joint Report No. 2, Academie Nationale de Medecine, Institut de France-Academie des Sciences, Paris, 2005.

United Nations Scientific Committee on the Effects of Atomic Radiation. UNSCEAR 2000 Report to the General Assembly, with Scientific Annexes. Sources and Effects of Ionizing Radiation. Vol I: Sources, Vol II: Effects. E.00.IX.4. New York, United Nations, 2000.

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