

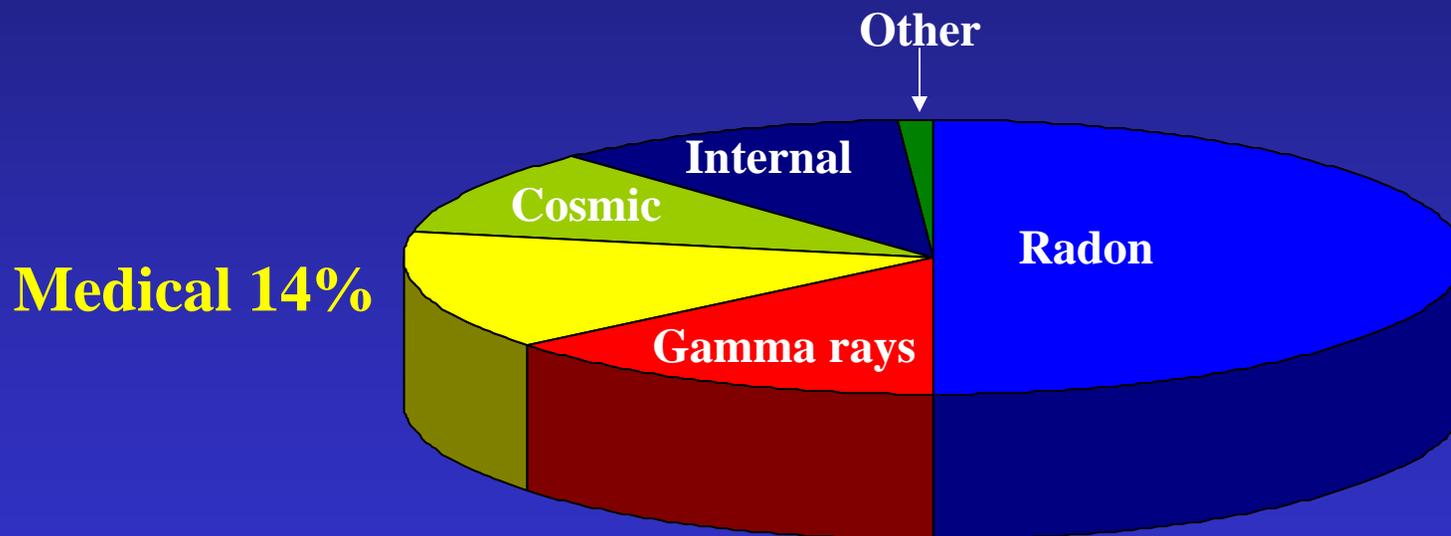
Cancer Risks Following Medical Exposure to Radioactive Iodine (I-131)

Elaine Ron

**Radiation Epidemiology Branch
National Cancer Institute, NIH**



Sources of Ionizing Radiation



Contributions to Average Annual Dose in UK

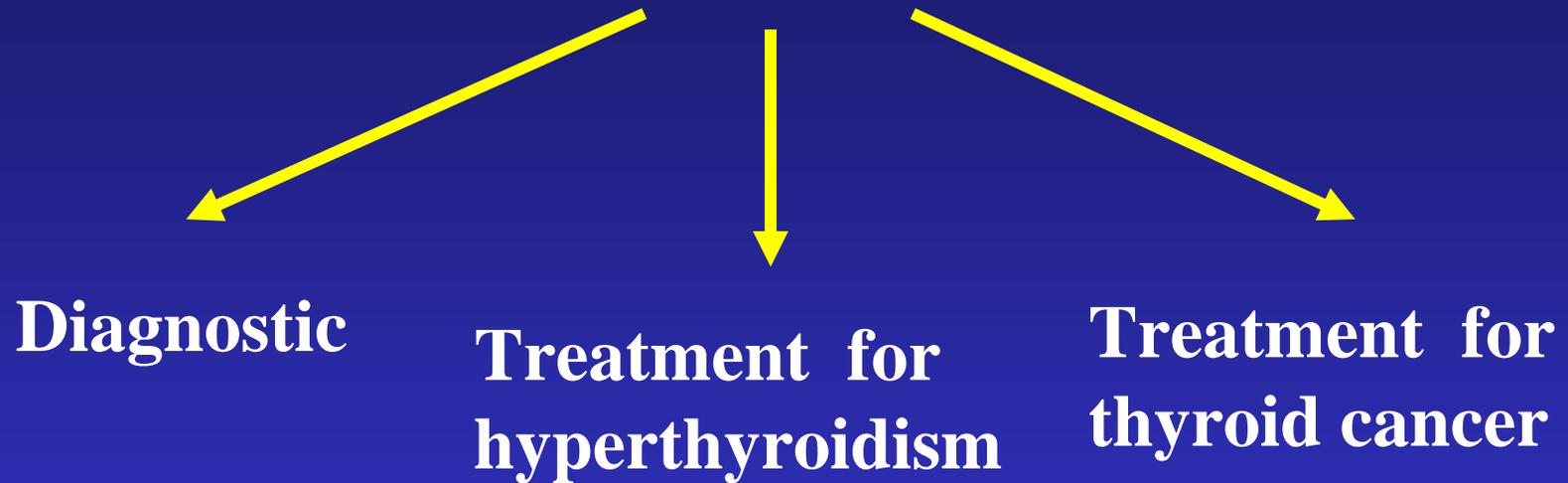
Concerns

- **Exposure to external radiation during childhood can cause thyroid cancer**
- **Children exposed to I-131 from Chernobyl have increased risk of thyroid cancer**
- **Data scarce regarding childhood I-131 medical exposure and thyroid cancer**
- **Other late effects of I-131 not well known**

Background

- I-131 is a beta emitter with a half-life of about 8 days
- I-131 is readily absorbed by the thyroid
 - inhaled
 - ingested
- I-131 also absorbed by the salivary glands, stomach, small intestine, and bladder

I-131 Uses in Medicine



Annual Use of Medical I-131*

Procedure	No./1000 People (mean)	% of Nuclear Medicine
Scans	4.1	22
Uptake	0.9	5
Hyperthyroidism	0.11	68
Thyroid cancer	0.04	21

**UNSCEAR 2000; 1991-96*

Exposure and Dose*

Procedure	Mean Activity (MBq)
Scan	17
Uptake	3.1
Hyperthyroidism	415
Thyroid cancer	4,760

* *UNSCEAR 2000; 1991-96*

Medical Radiation Dilemma

- **Necessary tool**
- **A potential carcinogen**

Issues Related to I-131 Carcinogenesis

- **Shape of the dose-response**
- **Effect of gender**
- **Influence of age at irradiation**
- **Temporal patterns of risk**

Cancers of Interest

Thyroid
Leukemia
Salivary Gland
Bladder
Stomach

Problems in Evaluating Cancer Risk from I-131 Exposure

- **Large uncertainties in dose estimates**
- **Limited childhood medical exposure**
- **Inconsistent experimental data**

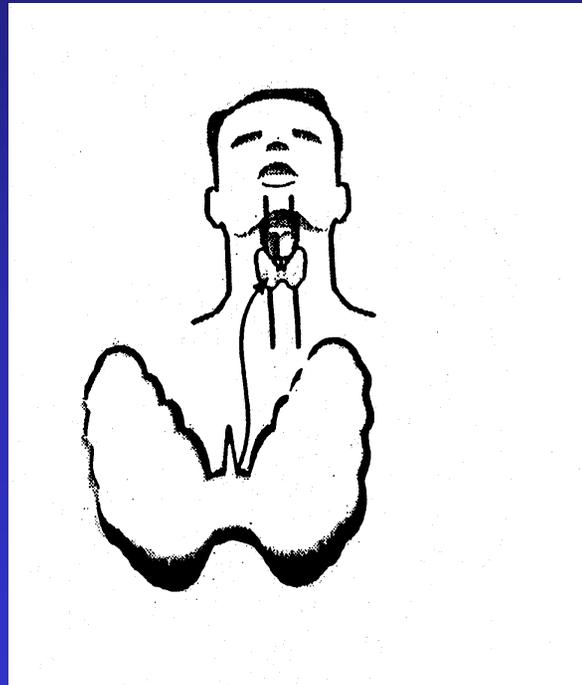
I-131 Dose Uncertainties: Medical

- **Administered activity little correlation with dose**
- **Thyroid size often not known**
- **Non-uniform distribution of I-131 in gland**

I-131 Epidemiologic Studies

Use	Country	Patients	Activity
Diagnostic	Sweden	35,000	52 μ Ci
Hyperthyroid	Sweden	10,000	13.7 mCi
	U.S.	35,000	10.4 mCi
	U.K.	7,500	8.5 mCi
Thyroid cancer	Sweden	834	123 mCi
	England	258	>100 mCi
	Denmark	194	N.A.
	Italy	730	145 mCi
	Switzerland	298	>100 mCi

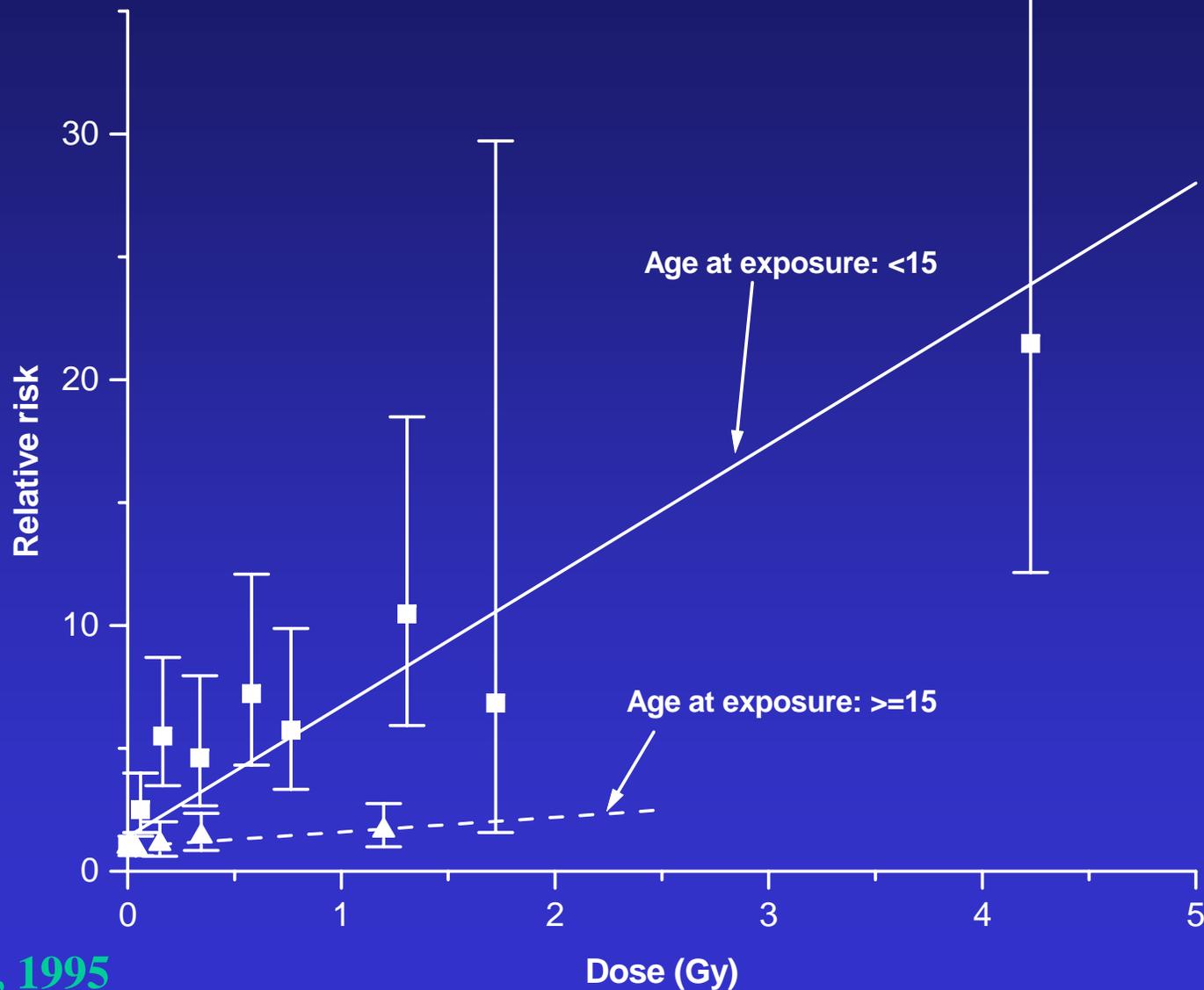
Thyroid



What Is Known About External Radiation

- Thyroid is uniquely sensitive to radiation
- Benign and malignant tumors occur at relatively low doses
- Dose-response consistent with linearity
- Relative risk increases with decreasing age at exposure
- Risk elevated >40 years after exposure

Relative Risk for Thyroid Cancer



Ron et al, 1995

What Is Not Known About I-131

- Is I-131 as tumorigenic as external radiation?
- Are patterns of risk the same?
- Are other thyroid diseases related to I-131?

Swedish Diagnostic I-131 Study

Study population	36,792
Prior external radiotherapy (%)	5
With suspected thyroid tumor (%)	32
Without suspicion of thyroid tumor	24,010
Women (%)	77
Mean age at first exam (y)	43
Patients <20 y at exposure (%)	7
Mean follow-up (y)	27
Mean I-131 administered activity (MBq)	1.6
Mean thyroid dose (Gy)	0.9
Mean dose to other organs (Gy)	<.01

Holm et al 1988, 1989, Hall et al, 1996; Dickman et al, 2003

Risk (SIR) Of Thyroid Cancer Incidence by Reason for Referral*

Swedish Diagnostic I-131

Reason for Referral	Cancers	SIR	95% CI
Prior x-ray	24	9.83	6.30-14.6
Suspicion of thyroid cancer	69	3.48	2.71-4.41
Other reasons	36	0.91	0.64-1.26

Dickman et al, 2003

Risk (SIR) Of Thyroid Cancer Incidence by Dose*

Swedish Diagnostic I-131

Time since exposure (y)	<u>Thyroid Dose, Gy</u>			
	≤ 0.25	0.25-0.5	0.5-1.0	>1
5-9	1.1	0	0.72	3.2 (1.2-6.9)
10-19	0.26	0.89	0.66	0.73 (0.15-2.1)
20+	0.23	1.13	1.19	1.05 (0.39-2.3)
ALL	0.45	1.07	0.86	1.27 (0.7-2.1)

**Persons without prior exposure and no suspicion of thyroid tumor
(n=24,010)*

Risk Of Thyroid Cancer Incidence By Age at Exposure*

Swedish Diagnostic I-131

Age (y)	Obs	SIR	95% CI
<20	2	0.96	0.12 – 3.5
21-50	23	0.89	0.57-1.3
51-75	11	0.94	0.47-1.7

* >5 years after exposure; Pts. without prior XRT and no suspicion of thyroid tumor (n=24,010)

Dickman et al, 2003

Thyroid Nodule Prevalence Following Diagnostic I-131

Nodule	Dose (Gy)		
	<0.25	0.25-1.0	>1.0
Single			
No. women	26	19	23
RR	1.0	1.6	3.3
ERR/Gy		1.2 (0.4-3.2)	
Multiple			
No. Women	14	16	9
RR	1.0	2.4	2.1
ERR/Gy		0.1 (0.4-1.5)	

Hall et al, 1996

**I-131 still treatment of choice for
hyperthyroidism**

Hyperthyroidism Studies

	Sweden	U.S.	U.K.
Study population	10,552	35,593	7,417
I-131 treated (%)	100	65	100
Women (%)	82	79	83
Mean age at 1 st treatment	57	46	57
Mean activity (mCi)	13.7	10.4	8.5

Holm et al, 1991; Hall et al, 1992; Ron et al, 1998; Franklyn et al, 1998, 1999

RISK OF THYROID CANCER INCIDENCE

Swedish I-131 Hyperthyroidism Study

	OBS*	SIR
TOTAL	18	1.3 (0.8 - 2.0)
Type of hyperthyroidism+		
Graves' disease	6	0.8 (0.3 - 1.8)
Toxic nodular goiter	10	1.7 (0.8 - 3.2)
Years since treatment		
1-4	4	1.3 (0.4 - 3.4)
5-9	5	1.2 (0.4 - 2.8)
10+	9	1.3 (0.6 - 2.5)

** ≥ 1 year after therapy; + type unknown for 2 patients*

Holm et al, 1991

RISK OF THYROID CANCER MORTALITY

U.S. Thyrotoxicosis Study

	OBS*	SIR
TOTAL	28	2.8 (1.8 - 4.0)
Treatment		
I-131	24	4.0 (2.5 - 5.9)
Graves' disease	16	2.8 (1.6 - 4.5)
Toxic nodular goiter	7	17.7 (7.1 - 36.5)
Surgery	4	1.1 (0.3 - 2.7)
Drugs	0	---
Years since I-131 treatment		
1-4	12	12.5 (6.4 - 21.8)
5-9	1	0.8 (0 - 4.7)
10+	11	2.8 (1.4 - 5.0)

** ≥ 1 year after therapy*

Ron et al, 1998

Risk Of Thyroid Cancer

U.K. I-131 Hyperthyroidism Study

	Thyroid Cancers	Thyroid Deaths
Observed	9	5
Expected	2.8	1.8
Obs./Exp.	3.2	2.8
95% CI	1.7-6.2	1.2-6.7

Franklyn et al, 1998, 1999

Reasons For Possible Differences Between I-131 And External Radiation

- **Low dose rate of I-131**
- **Non-uniform distribution of I-131**
- **Cell killing at high exposures**
- **Underlying thyroid disease**
- **Uncertainties in dose**
- **Little information on childhood exposure**

Suggested RBE Values

Walinder, 1972	0.1 (Dose 2,200-11,000)
Lee et al, 1982	~1 (Dose 80 - 850 cGy)
NCRP, 1985	0.1-1.0 (0.3 recommended)
Laird, 1987	0.66 (95% CI 0.14 - 3.1)
IOM/NAS, 1998	0.66-1.0
Brenner, 1999	0.6

LEUKEMIA

RISK OF LEUKEMIA MORTALITY

U.S. Thyrotoxicosis Study

Years since I-131 exposure	Non-CLL		CLL		
	Obs	SIR	Obs	SIR	
<1	2	1.6 (0.2 - 6.0)	0	0	---
1 - 4	8	1.6 (0.7 - 3.2)	2	0.9 (0.1 - 3.2)	
5 - 9	14	2.1 (1.1 - 3.5)	5	2.0 (0.6 - 4.6)	
10+	31	1.0 (0.7 - 1.4)	12	1.1 (0.6 - 2.0)	

RISK OF LEUKEMIA MORTALITY

U.S. Thyrotoxicosis Study

Treatment	Non-CLL		CLL	
	Obs	SIR	Obs	SIR
I - 131	55	1.2 (0.9 - 1.6)	19	1.2 (0.7 - 1.9)
Graves' disease	52	1.2 (0.9 - 1.6)	19	1.3 (0.8 - 2.0)
Toxic nodular goiter	2	0.9 (0.1 - 3.3)	0	----
Surgery	31	1.2 (0.8 - 1.6)	12	1.3 (0.7 - 2.2)
Drugs	1	0.5 (0 - 2.9)	0	----

RISK OF LEUKEMIA MORTALITY BY DOSE

U.S. Thyrotoxicosis Study

Bone Marrow Dose (mGy)	Non-CLL		CLL	
	Obs	SIR	Obs	SIR
0	31	1.0	12	1.0
1 - 49	38	0.9	8	0.5
50+	13	1.1	3	0.6
p value for trend	>0.5		>0.5	

Ron et al, 1998

RISK OF LEUKEMIA INCIDENCE

Swedish I-131 Studies

	Diagnostic I-131	Hyperthyroidism Therapy	Cancer Therapy
No. patients	36,326	9,860	802
Mean bone marrow dose (mGy)	0.19	48	251
All leukemias			
No. cases	152	37	6
SIR	1.2 (0.98 - 1.4)	0.8 (0.6 - 1.1)	2.4 (0.9 - 5.2)
Non-CLL			
No. cases	103	25	2
SIR	1.2 (0.95 - 1.4)	0.8 (0.6 - 1.2)	1.2 (0.2 - 4.4)

RISK OF LEUKEMIA INCIDENCE BY DOSE

Swedish I-131 Studies

Bone Marrow Dose (mGy)	No. Leukemias	RR	95% CI
0 - 0.01	12	1.0	
0.02 - 0.10	48	1.0	0.5 - 1.8
0.11 - 10	92	1.3	0.7 - 2.3
11 - 100	32	0.8	0.4 - 1.5
>100	11	1.8	0.8 - 4.2

RISK OF LEUKEMIA INCIDENCE

Swedish I-131 Studies

Years since exposure	All Leukemias		Non-CLL	
	Obs	SIR	Obs	SIR
2 - 9	51	0.9 (0.6 - 1.1)	38	1.0 (0.7 - 1.3)
10 - 19	93	1.3 (1.0 - 1.6)	63	1.3 (1.0 - 1.6)
>20	51	1.1 (0.8 - 1.4)	29	1.0 (0.6 - 1.4)

Hall et al, 1992

RISK OF LEUKEMIA FOLLOWING I-131 TREATMENT FOR THYROID CANCER

Study	No. Patients	Obs	SIR	95% CI
Dottorini et al, 1995	626	0	0	---
Hall et al, 1991	834	4	2.4	0.7 - 6.2
Edmonds & Smith, 1986	258	3	12	2.4 - 35
Brincker et al, 1973	194	2	20	2.5 - 74
Glanzmann, 1992	298	3	6.2	1.3 - 2.5

OTHER CANCERS

Cancer Risk After ^{131}I Therapy for Hyperthyroidism

Cohort	Subjects	Elevated Risks
Sweden	10,522	stomach, kidney, brain
U.S.	35,573	lung, breast, kidney, thyroid
England	7,417	Small bowel, thyroid

RISK (SIR) OF OTHER CANCERS FOLLOWING I-131 TREATMENT FOR THYROID CANCER

Cancer Site	Dottorini et al 1995 n = 730	Glanzmann 1992 n = 298	Hall et al 1991 n = 834	Edmund & Smith 1986 n = 258
All Sites	---	1.9 (33)	1.9 (99)	1.5 (20)
Salivary	60 (3)	---	15 (3)	0 (0)
Stomach	0.5 (1)	1.7 (1)	1.8 (7)	0.9 (1)
Breast	2.1 (7)	1.9 (5)	0.7 (9)	2.4 (6)
Bladder	2.6 (2)	8.8 (7)	1.6 (4)	6.5 (3)

() observed cases

Conclusions

- **Little evidence that either I-131 or external radiation induces thyroid cancer in adults**
- **Insufficient data to adequately compare I-131 and external radiation in children**
- **I-131 appears to be less effective in inducing leukemia and solid tumors other than thyroid**

I-131 in Medicine

- **I-131 plays an important role in medicine, particularly as treatment for hyperthyroidism and thyroid cancer.**
- **Potential cancer risks appear to be taken into account when recommending therapy.**
- **I-131 is rarely used to treat hyperthyroidism in children which seems appropriate since not enough is known about risks.**