Childhood and adult cancer following exposure in early life and *in utero*

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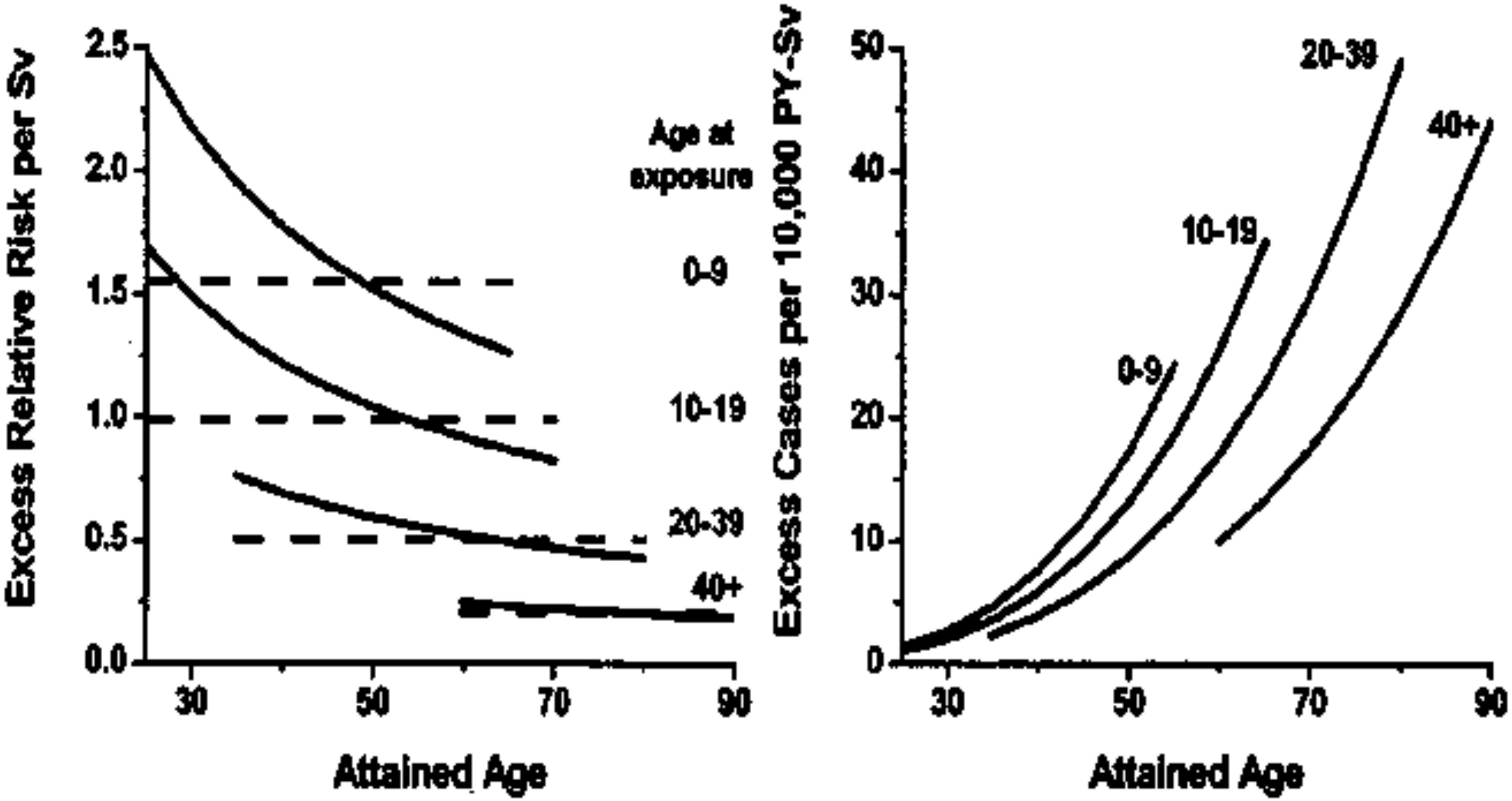
Childhood exposures

- Substantial epidemiological evidence showing higher risk of cancers for exposure in childhood compared to later in life
  - Atomic bomb survivors
  - Patients with medical exposures
  - Subjects with environmental exposures

- Risk is seen overall and particularly for
  - Childhood and adult leukaemia
  - Childhood and adult thyroid cancer
  - Breast cancer

A–bomb survivors – solid cancer mortality *(Preston et al, 2003)*



The left panel presents fitted sex-averaged ERR estimates using both attained-age-declining (solid black line) and attained-age-constant (dashed lines) forms

A–bomb survivors – mortality from specific cancers

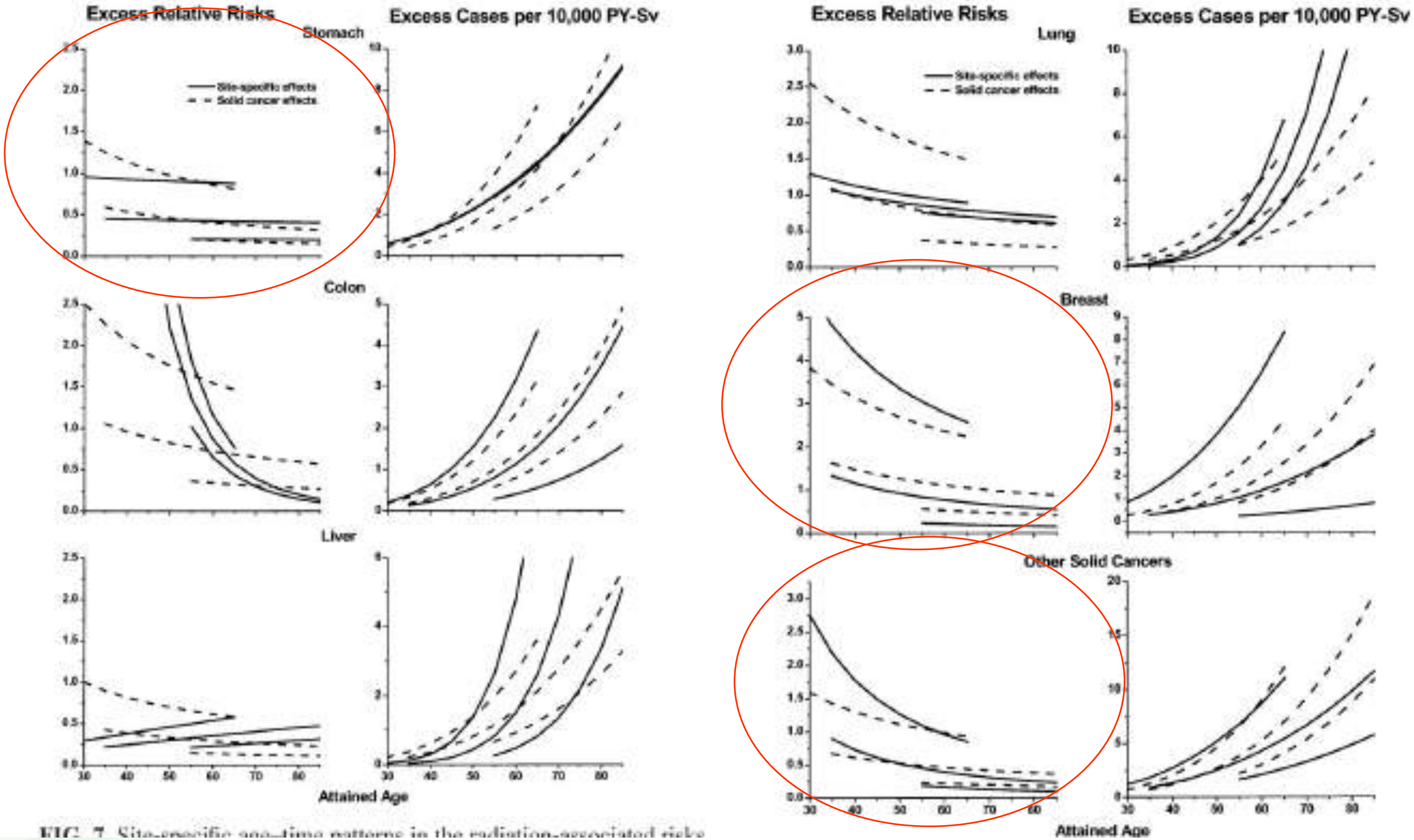


FIG. 7. Site-specific age–time patterns in the radiation-associated risks

Israeli tinea capitis study - influence of age at irradiation on cancer risk

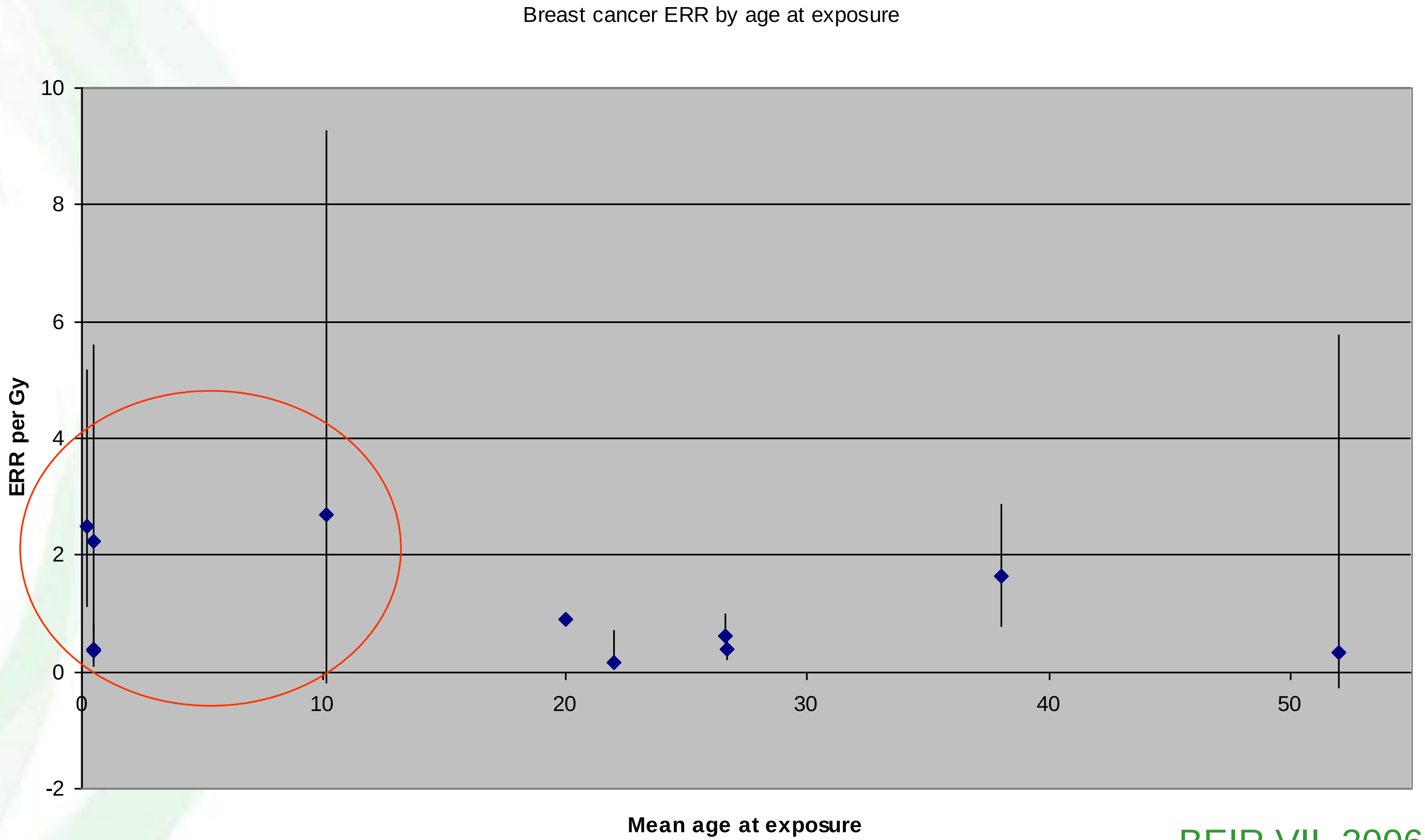
Slide courtesy S. Sadetzki

The Tinea Capitis study: ERR/Gy & 95% CI of selected tumors by age at irradiation

Age at irradiation		Benign meningioma*	Malignant brain*	Thyroid**
<5	ERR/Gy	**4.48**	**3.56**	**33.9**
	95% CI	*1.60-11.01*	*0.96-9.91*	*18.6-57.2*
5-9	ERR/Gy	**5.03**	**2.24**	**12.9**
	95% CI	*2.49-10.26*	*0.75-5.54*	*5.2-24.4*
10+	ERR/Gy	**4.11**	**0.47**	**21.1**
	95% CI	*1.71-9.16*	*-2.74*	*6.5-43.2*
			P=0.03	P=0.02

** Sadetzki S et al, Radiation Research; 2005 / ** Sadetzki S et al, J Clin Endocrinol Metab; 2006*

Distribution of study-specific estimates of ERR/Gy for breast cancer according to average age at exposure



BEIR VII, 2006

Pooled Analysis of Cohort Studies of Persons Exposed before Age 15 Years: Modifiers of Excess Relative Risk per Gy (ERR/Gy)

Variable	Categories	Number of cases	Modifying effect[a]	P value[b]
Gender	Male	202	0.5	0.07
	Female	271	**1.0**	
Attained age (years)	<20	62	**1.0**	0.15
	20–29	146	0.5	
	30–39	192	0.1	
	40+	73	0.0	
Time since exposure (years)	<5	2	<0	<0.001
	5–9	21	1.3	
	10–14	26	**1.0**	
	15–19	68	2.2	
	20–24	78	1.5	
	25–29	143	2.1	
	30–34	71	0.7	
	35–39	41	0.3	
	40+	23	1.0	
Age at first exposure (years)	<1	64	**1.0**	0.004
	1–4	251	1.0	
	5–9	111	0.5	
	10–14	47	0.2	
Number of treatments	1	373	**1.0**	0.18
	2+	63	0.7	

Ron et al, 1995

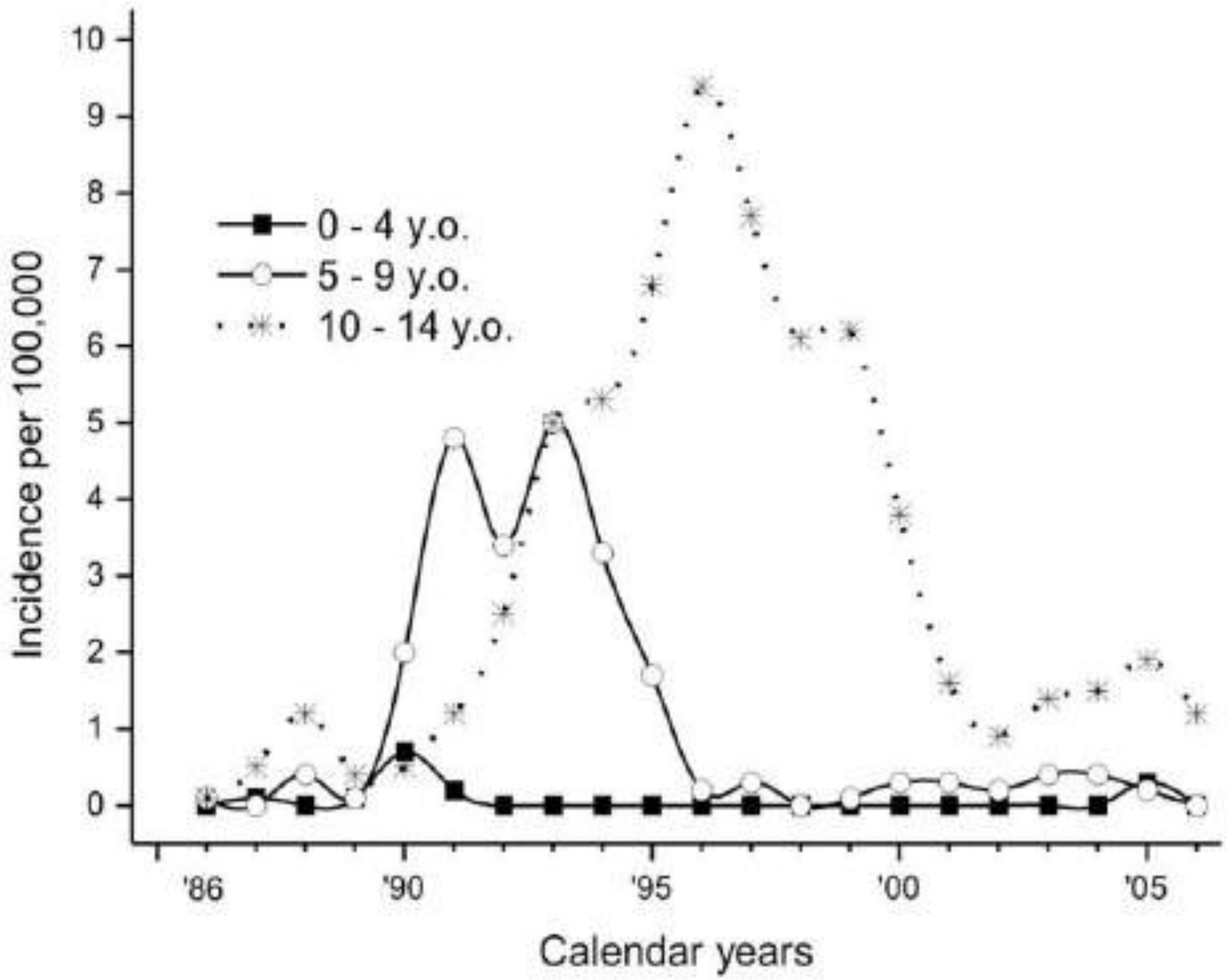
real.cat

Thyroid cancer risk following exposure in childhood

Reference	Country	Number of cases	Years of diagnosis	ERR at 1 Gy (95% CI)
External exposures				
Ron *et al*, 1995	International	436		**7.7** (2.1-28.7)
Radio-iodines				
Astakhova *et al*, 98	Belarus	107	(1988-92)	*OR ≥1 Gy vs. <0.3Gy*: **5.04** (1.5-16.7) to **5.84** (1.96-17.3)
Davis *et al*, 2004	Russia	26	(1991-97)	N.A
Cardis *et al*, 2005	Belarus, Russia	276	(1992-98)	**4.5** (2.1-8.5) to **7.4** (3.1-16.3)
Jacob *et al*, 2006	Belarus and Ukraine	1 089	(1990-01)	**18.9** (11.1-26.7)
Tronko *et al*, 2006	Ukraine	45	(1998-00)	**5.25** (1.7-27.5)
Zablotska et al 2010	Belarus	85	(1996-04)	**2.15** (0.81–5.47)
Brenner et al 2011	Urkaine	65	(1998-07)	**1.91 (**0.43-6.34)

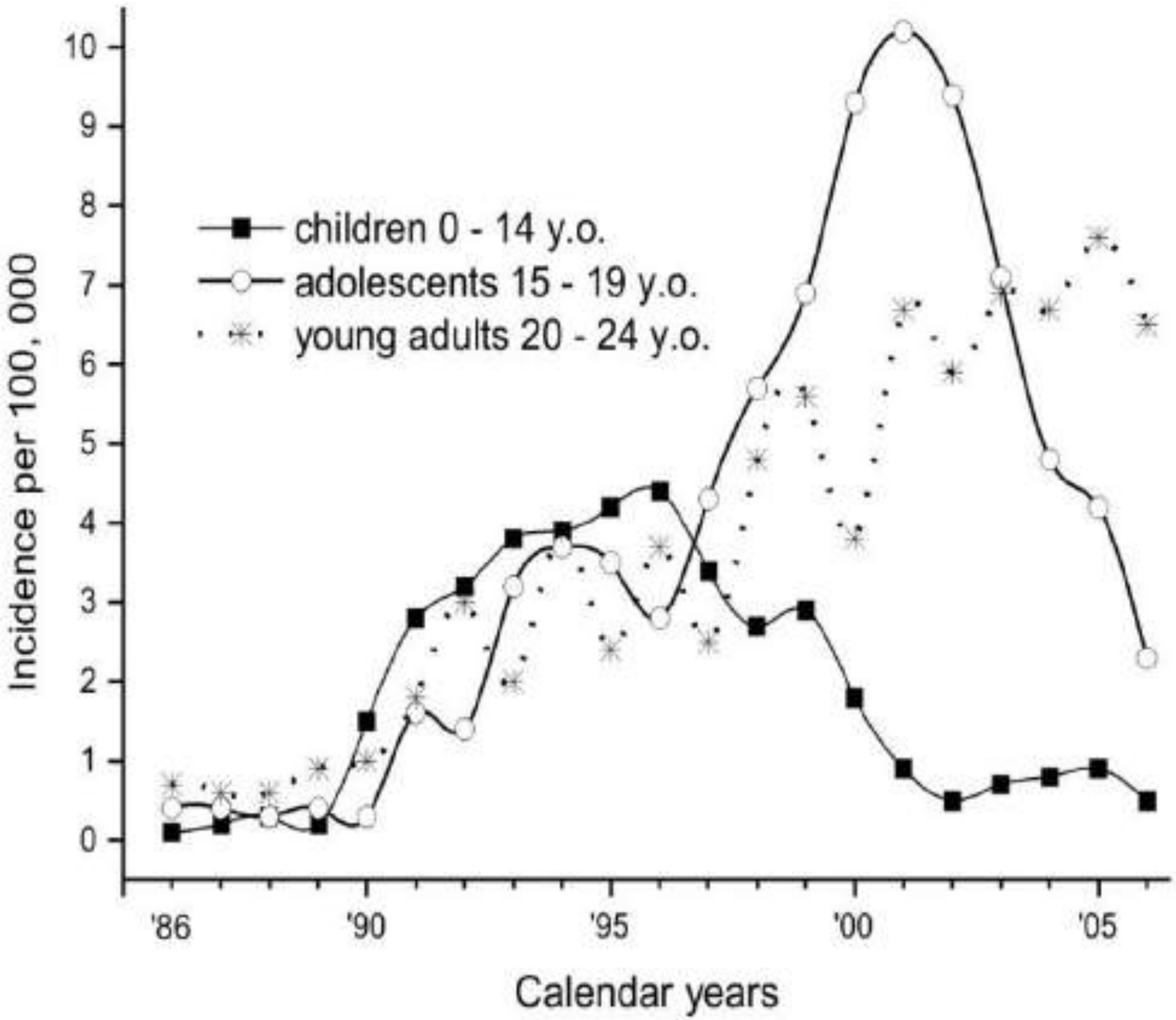
Trends in childhood thyroid cancer incidence in Belarus

Demidchik et al, 2010



Trends in thyroid cancer incidence in young people in Belarus

Demidchik et al, 2010

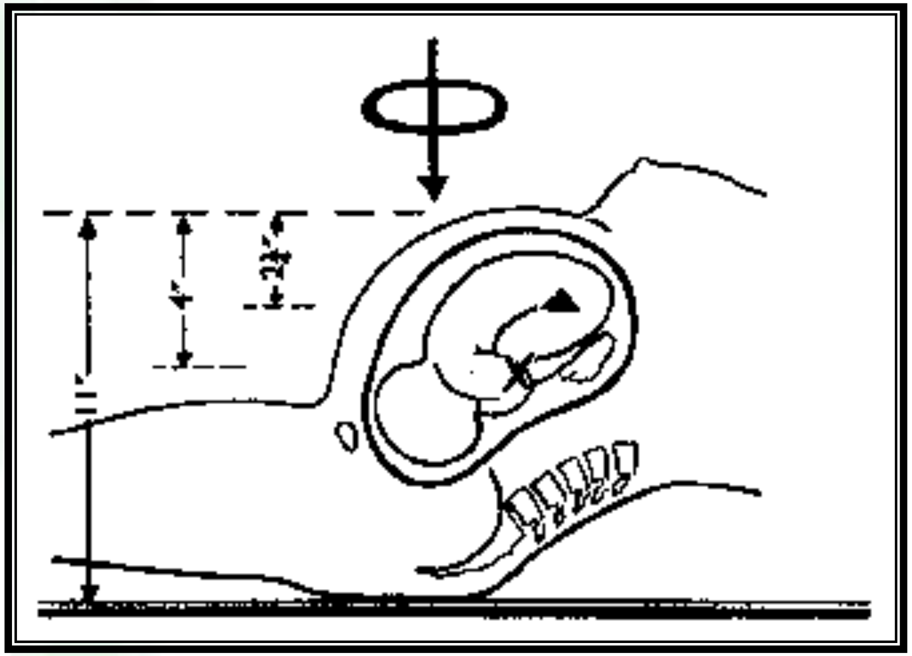


What about exposures in utero ?

- Studies more limited
  - Oxford childhood cancer survey
  - A-bomb
  - Cherobyl
- Small numbers, large uncertainties

Childhood cancer following in-utero x-ray exposure

Pelvimetry or obstetric abdominal exam



Slide courtesy of D. Brenner

Mean dose 6-10 mGy, 80 kVp x rays

Corresponds to a mean of ~1 photon / cell nucleus

The Oxford Survey of Childhood Cancers

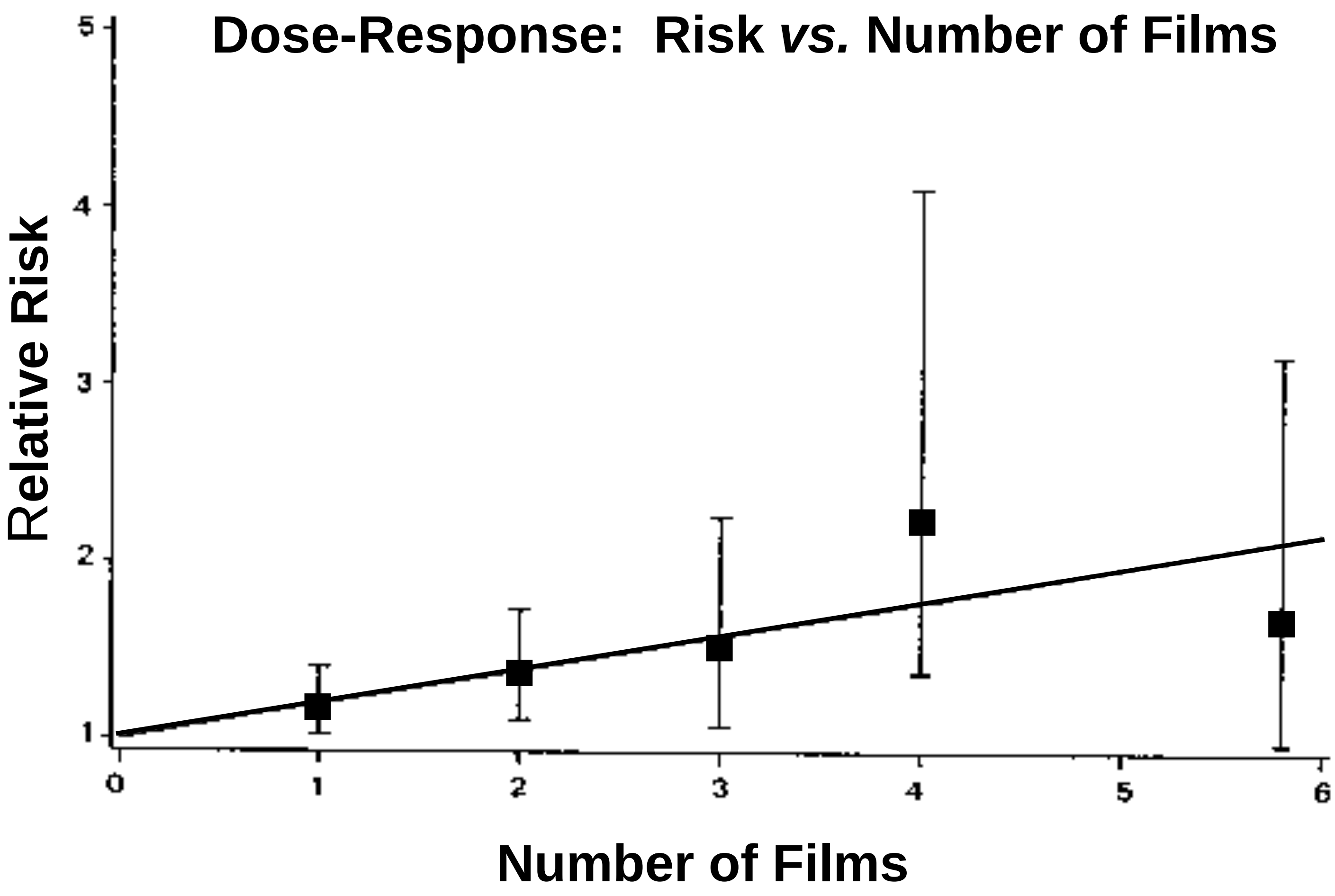
Alice Stewart

"The odds ratio for childhood cancer deaths after X-raying in birth years 1958-61 (1.23, 95% CI 1.04-1.48), and the mean fetal whole body dose from obstetric radiography in 1958 (6 mGy) can each be derived from nationwide surveys in Britain"

Mole (1990)

Slide courtesy D. Brenner

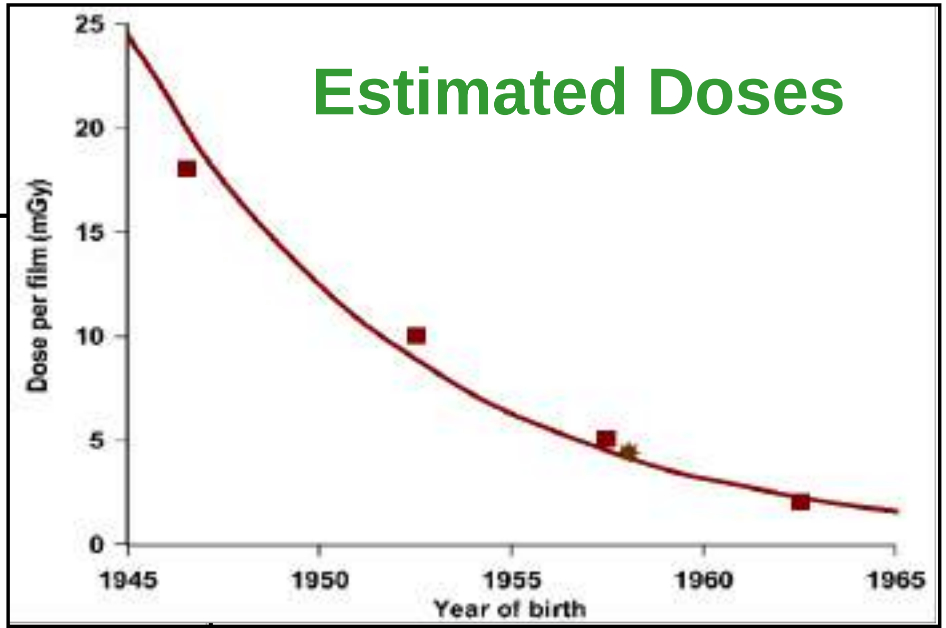
OSCC - Childhood cancer risks after *in-utero* exposure

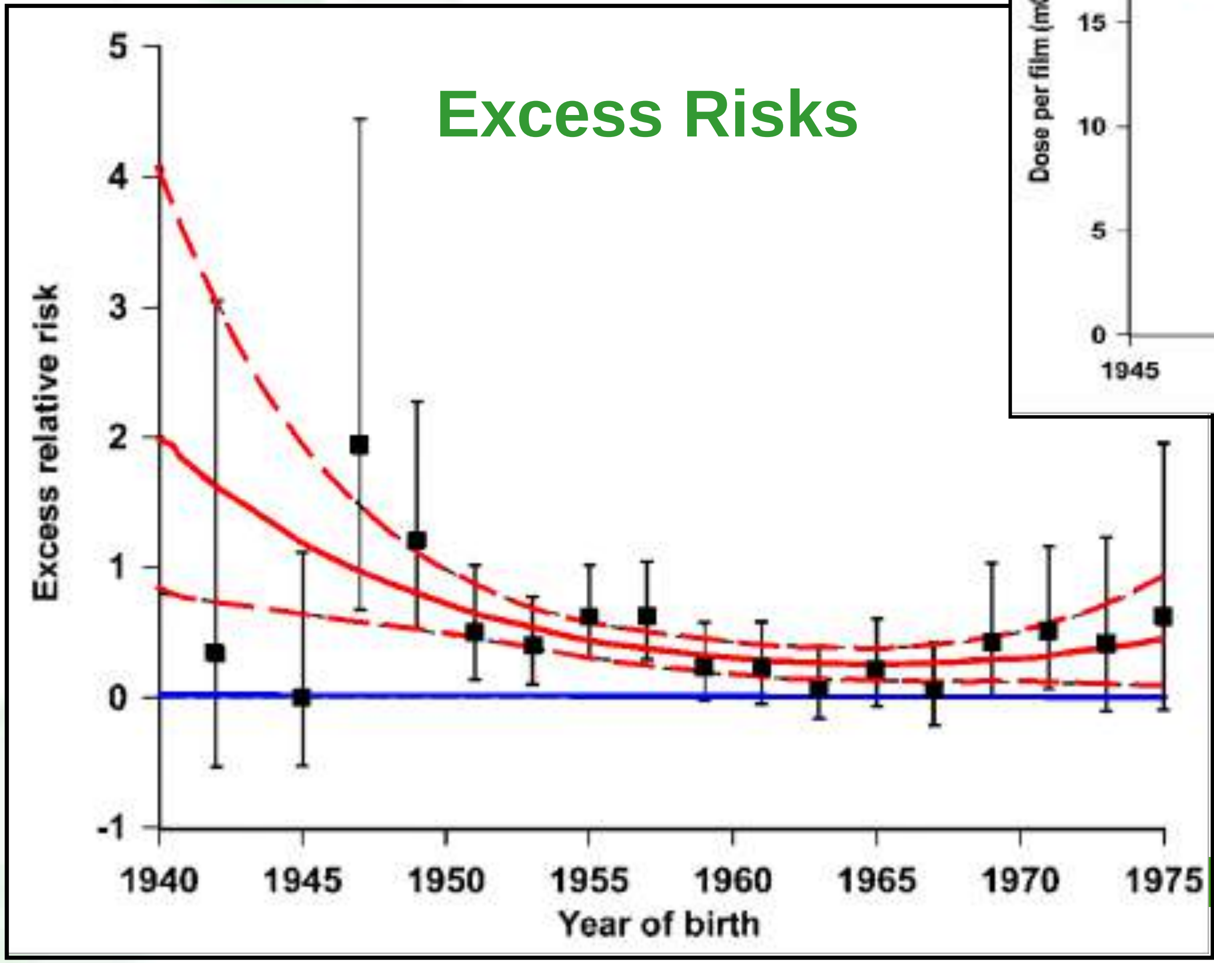


Third Trimester, 1953-72 - *Bithell 1989*

OSCC - Childhood cancer risks after *in-utero* exposure

5,000 case-control pairs for England Wales and Scotland. Cases died in the period 1953-84





Wakeford and Little 2003

Studies of childhood cancer after obstetric x rays

Table 2. Relative risk of cancer in childhood associated with irradiation *in utero* found in different studies (after Bithell [10])

Study (period covered)	Amount of evidence[a]	Relative risk (unadjusted)	95% confidence interval
OSCC (1953–1981)	852.4	1.39	(1.30, 1.49)
NE United States (1947–1967)	114.7	1.47	(1.22, 1.77)
Inter-regional study, UK (1980–1982)	39.0	1.23	(0.90, 1.68)
Los Angeles (1950–1957)	23.9	1.34[b]	(0.90, 2.00)
Louisiana (1951–1955)	18.3	1.70	(1.08, 2.69)
Helsinki (1959–1968)	17.9	1.18	(0.74, 1.87)
California (1955–1956)	17.8	1.68[b]	(1.06, 2.67)
Tri-state (US) (1959–1962)	16.6	1.40[b]	(0.87, 2.27)
Swedish twins (1952–1983)	11.6	1.38	(0.78, 2.46)
Minnesota (1953–1957)	10.2	1.28[b]	(0.69, 2.37)
All other[c]	42.4	1.13	(0.84, 1.53)
All except OSCC	312.4	1.37	(1.22, 1.53)
All	1164.8	1.38	(1.31, 1.47)

[a]A measure of the statistical information contained in a study which is approximately the inverse of the variance of the logarithm of the relative risk [10].
[b]Leukaemia only.
[c]Includes cohort studies other than the Japanese atomic bomb survivor study.

Doll and Wakeford, 1997

Slide courtesy D. Brenner

Consistency with A-Bomb Cancer Mortality Relative Risk Data

1. Comparison of OSCC results with childhood cancer risks in A-bomb survivors exposed ***in utero***

   ERR/Sv (OSCC): 51 (95% CI: 28-76) (Bithell 1993)

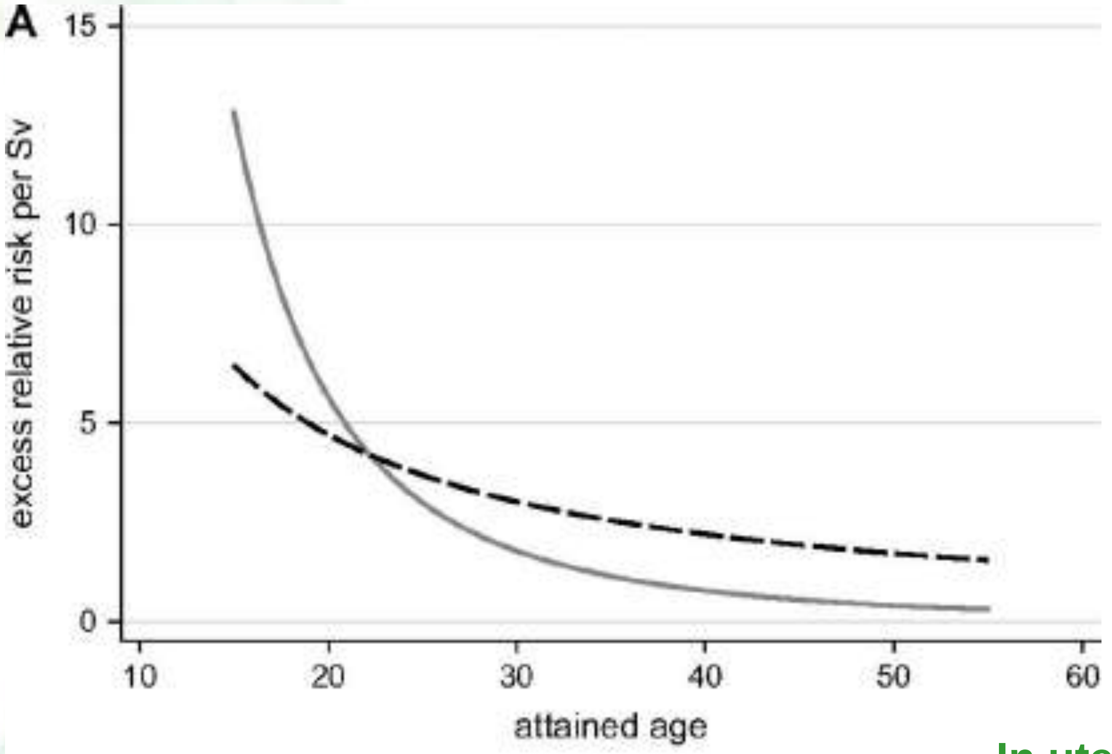
   ERR/Sv (A bomb): 23 (90% CI: 2-88) (Delongchamp 1997)

2. Comparison with of OSCC results with childhood cancer risks in A-bomb survivors exposed ***in childhood***

   ERR/Sv (OSCC): 51 (95% CI: 28-76) (Bithell 1993)

   ERR/Sv (A bomb): 31 (95% CI: 0, 1250) (Wakeford & Little 2003)

Temporal patterns of radiation-associated solid cancer incidence risks among atomic bomb survivors exposed in utero or as young children



in utero (solid lines)
early childhood (dashed)

No statistically significant differences

In utero cohort	2 452	94 cases
<6 years	15 388	649 cases

Preston D L et al. JNCI J Natl Cancer Inst 2008;100:428-436

Thyroid nodules – a-bomb survivors

TABLE 6. ORs of all solid thyroid nodules by mode of exposure

Model	Mode of exposure	n (%)	OR at 1 Gy (95% CI)
Linear logistic model	*In utero* exposure	35/319 (11.0)	2.91 (0.53, 12.18)
	Childhood exposure	63/437 (14.4)	2.65 (1.96, 3.65)
	Combined[a,b]	98/756 (13.0)	2.66 (1.97, 3.63)[b]
Linear EOR model	*In utero* exposure	35/319 (11.0)	2.29 (−0.43, 8.86)
	Childhood exposure	63/437 (14.4)	4.41 (1.95, 10.01)
	Combined[a,c]	98/756 (13.0)	3.79 (1.84, 7.38)[c]

In the analyses of *in utero* or childhood exposure, estimates were adjusted by sex and city but not gestational week or age at the time of bomb
fit better than linear logistic model for all analyses in terms of AIC.

[a] Combined analysis of *in utero* exposure and childhood exposure. The background models include city, sex, *in utero* indicator, and sex by *in ut*

[b] No significant interaction of dose by *in utero* indicator ($P = 0.97$) was observed.

[c] No significance of *in utero* indicator variable in EM part ($P = 0.44$) was observed.

328 screened in 2000-2003

35 nodules

5 malignant tumours

Imaizumi et al., 2008

Chernobyl Nuclear Reactor Accident

Slide courtesy M. Hatch

- **Radioactive releases profoundly affect Northern Ukraine**
- **Principal radionuclide: Iodine-131 (I-131)**
- **I-131 is concentrated and stored in the thyroid gland**

Exposure to the Embryo/Fetus

Slide courtesy M. Hatch

- **I-131 readily crosses the placenta**

- ~10-12 weeks of gestation, fetal thyroid becomes fully active and rapidly accumulates iodine from the maternal circulation
- Late in gestation, levels of iodine in fetal thyroid many-fold higher than those in maternal thyroid
- Small thyroid mass
- High levels of cellular proliferation

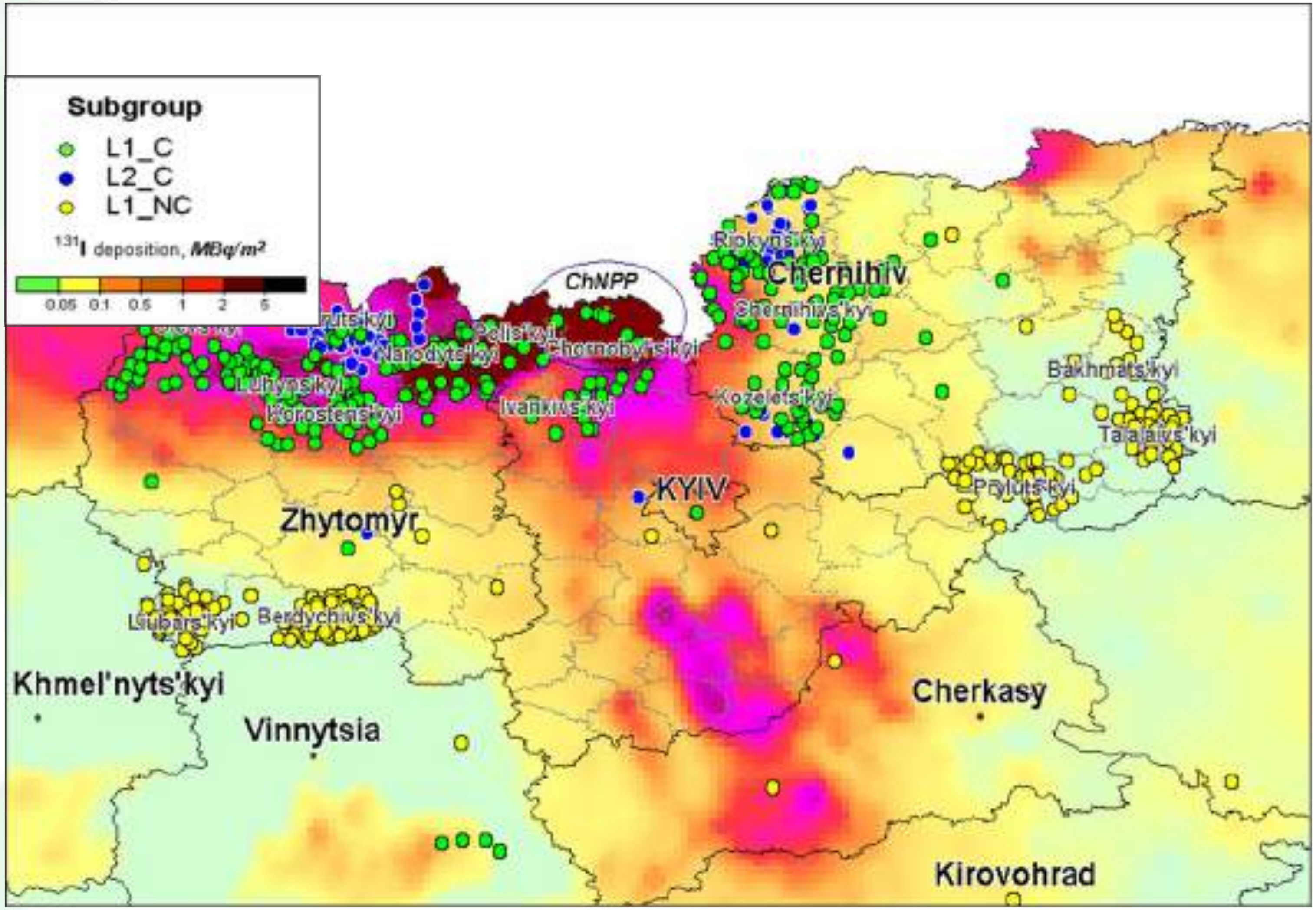
Ukrainian-American *In Utero* Study:

Hatch et al, 2008, Likhtarev et al, 2011

- **Objectives:**
  - Evaluate risk of screening-detected thyroid cancer using individual estimates of fetal thyroid dose (2003-2006)
  - Explore incidence of non-thyroid cancer using registry-based follow-up (1997-2009)
- Design
  - Study area: most affected northern oblasts, (Zhytomyr, Chernihiv, Kyiv)
  - 2,582 mother-child pairs: women pregnant on April 26,1986 or the two months following when fallout still present
- Methods
  - In-depth thyroid screening examination (2003-2006):
    - in-person mother-child interviews:
    - dose reconstruction (residential/dietary history)
    - important risk factors/confounders
  - For non-thyroid cancers, record linkage with the Ukrainian National Cancer Registry, UNCR (1997-2008)

Geographic Distribution of Study Participants

Slide courtesy M. Hatch



Screening Cases with Thyroid Neoplasia

Slide courtesy M. Hatch

#	Dx	Source of dx	Trimester ATA	Sex	Age, yr	I-131 dose, mGy Total	I-131 dose, mGy Postnatal
1	PTC[1]	PMC[4]	3	F	19.9	18.6	4.2
2	PTC	PMC	3	F	19.8	421.2	395.2
3	PTC	PMC	3	F	19.8	453.6	3.6
4	PTC	PMC	3	F	17.7	16.2	0
5	PTC	FNA[5]	2	F	16.5	139.3	0
6	PTC	FNA	2	F	20.9	86.4	0
7	FTC[2]	PMC	1	F	19.4	3.1	0
8	HCN[3]	FNA	2	M	20.8	33.0	0

Results: Thyroid cancer

Slide courtesy M. Hatch

Outcome	EOR[1]/Gy	95% CI	P
In utero			
Thyroid cancer or neoplasia[3] (n=8)	5.35	NE[2]-77.29	0.24
Thyroid cancer[4] (n=7)	11.66	NE-1,982	0.12
1-5 year old			
Thyroid cancer (n=13)	3.24	NE-539	0.01

Case-control and cohort studies of thyroid cancer among those exposed to radio-iodines in childhood – EOR 2-7 / Gy
External exposures 7.7 / GY (Ron et al 1995)

Exclusion of one case with postnatal I-131 dose > 30 mGy or one case exposed during 1st trimester had little influence on EOR/Gy

Registry-linked Non-thyroid Cancers: 1997-2009

Slide courtesy M. Hatch

#	Diagnosis	Trimester ATA	Sex	Age, yr	I-131 dose, mGy
1	Hodgkin's disease	3	M	18.3	309.7
2	Hodgkin's disease	2	F	20.4	18.4
3	Hodgkin's disease	1	M	15.7	0
4	Brain cancer, NOS[1]	3	F	12.3	3.8
5	Diffuse astrocytoma	1	F	14.2	0
6	Choriocarcinoma	2	F	22.1	66.9

Dose from external radiation and long-lived nuclides not yet available

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International Agency for Research on Cancer

World Health Organization

Agenda for Research on Chernobyl Health: ARCH

http://arch.iarc.fr

ARCH

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ARCH is a European Commission FP7 Project to develop a strategic research agenda for the health consequences of the Chernobyl accident

The Chernobyl accident led to the most serious exposure of a normal human population to ionising radiation, apart from the atomic bombings in Japan. **Unlike the bombing, the health impact of Chernobyl has not been comprehensively studied.** In some areas (eg thyroid cancer), research has been intensive and informative; in others, little work has been conducted. The validity of extrapolating radiation risk estimates mainly based on whole body exposures at the atomic bombings to exposures of public health is controversial but of great public concern.

Questions relate to the choice of models for transport of risk between populations; projection of risk over time; extrapolation of risks from external high dose-rate exposure to low dose and low dose-rate exposures from internal radiation. Questions also concern non-cancer risks and the importance of non-targeted effects following low levels of radiation. Chernobyl has an iconic status in the public eye, and the accident provides a unique opportunity to answer these questions, to provide the authoritative studies needed to inform the nuclear debate, and to test novel hypotheses about radiation effects and biology/genetics in general.

Because the range of potential studies is so vast, this project is to develop of a strategic

© ARCH 2008. Radiation map of Europe

ARCH NEWS

- The main deliverable from the ARCH project, the Strategic Research Agenda (SRA) has been submitted to the European Comission.

Internet 100%

What did ARCH recommend ?

- **Chernobyl Health Effects Research Foundation (CHERF)**
  - a mechanism to coordinate and fund studies to enable assessment of the overall long-term health effects of this disaster.
- A key to the success of the ARCH recommendations is
  - the creation, maintenance and follow-up of **Life Span cohorts**, including
    - cohorts exposed to fallout as children in Belarus and Ukraine with detailed thyroid dose measurements *(BelAm, UkrAm cohorts)*
    - cohorts of liquidators
    - ***If feasible, cohorts of evacuees and offspring***
  - Monitoring of time trends using population based registries
  - Conduct of specific analytical studies to address key research questions
- SRA and research priorities available on ARCH website *www.arch.iarc.fr*

CONCLUSIONS

- There is consistent evidence that exposure in utero increases the risk of cancer later in life
- But cohorts are small – little statistical power
- Uncertain at present whether risk is greater to or similar to that from exposure in the first years of life

- *Need further follow-up of appropriate cohorts*