Age-related variation in radiogenic cancer risk with a focus on childhood CT studies

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MHB MEDIZINISCHE HOCHSCHULE BRANDENBURG

Overview

1. Age-related radiation effects from LSS & other (low dose) studies
2. General results of CT studies, particularly EPI-CT
3. Age and radiation effects in CT studies

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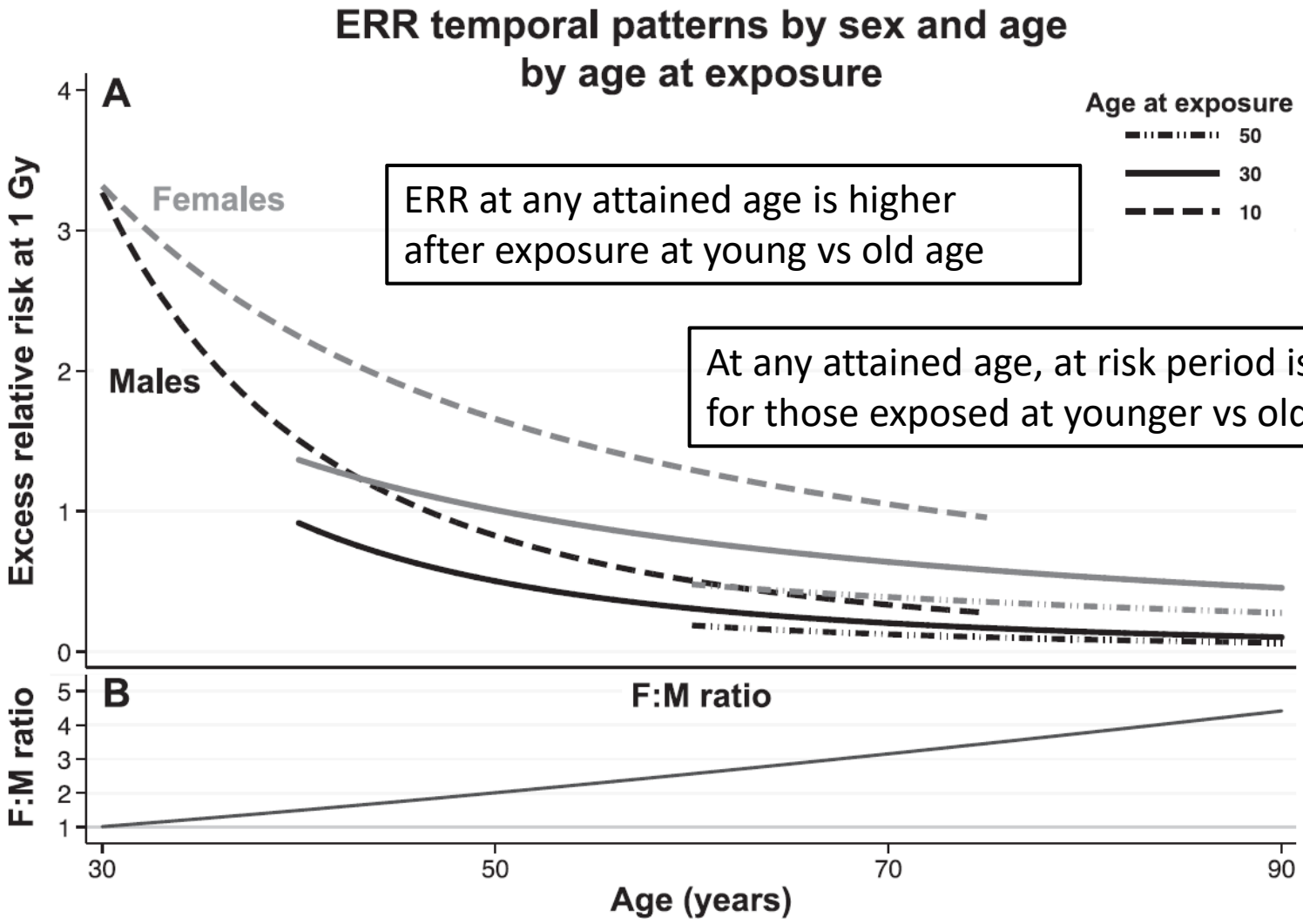
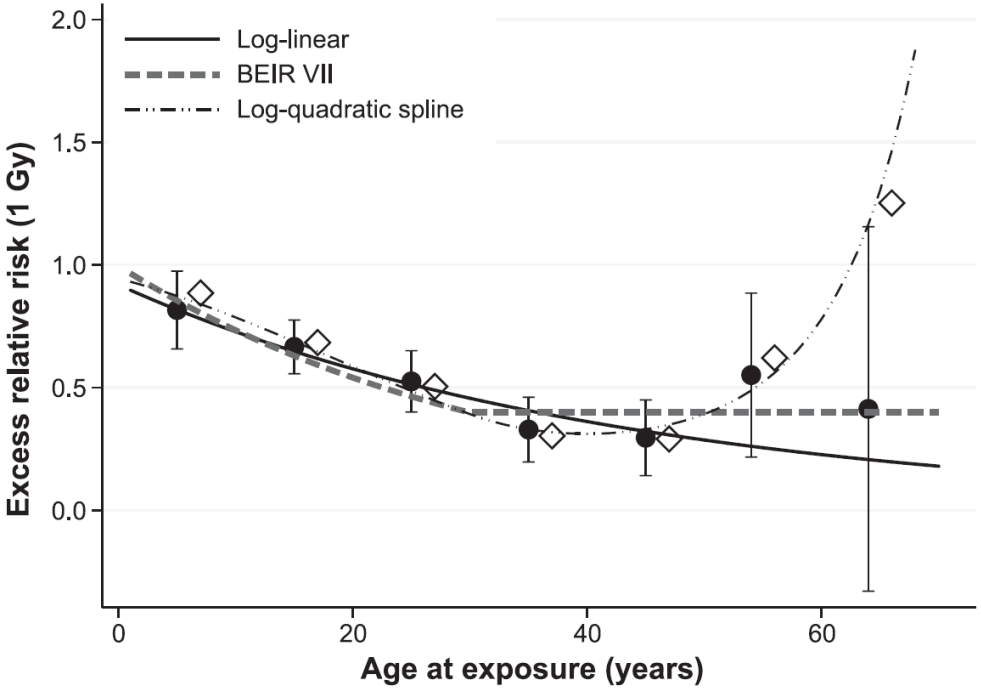
Solid cancer in LSS 1958-2009



Grant et al 2017

Age at exposure effect

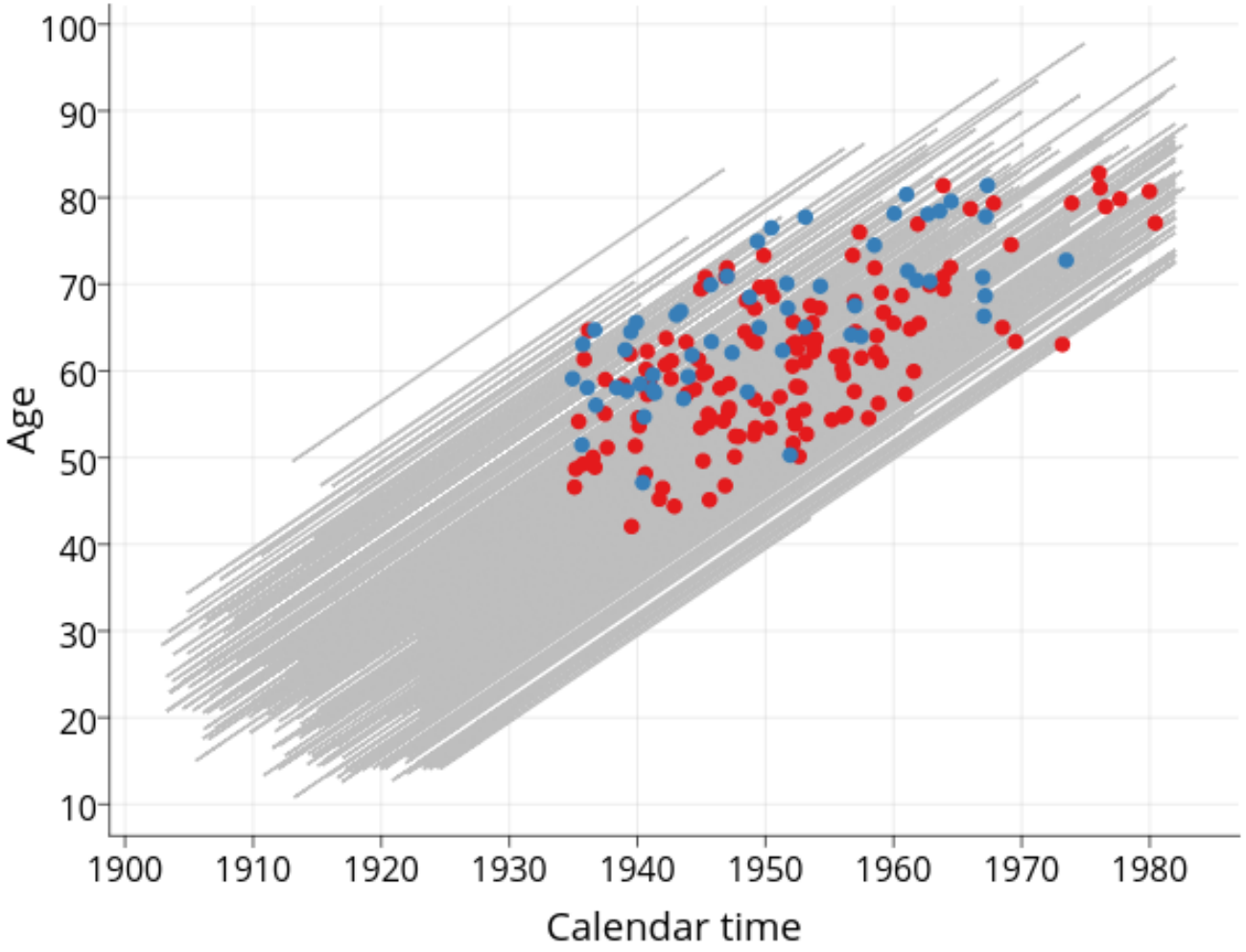


Grant et al 2017

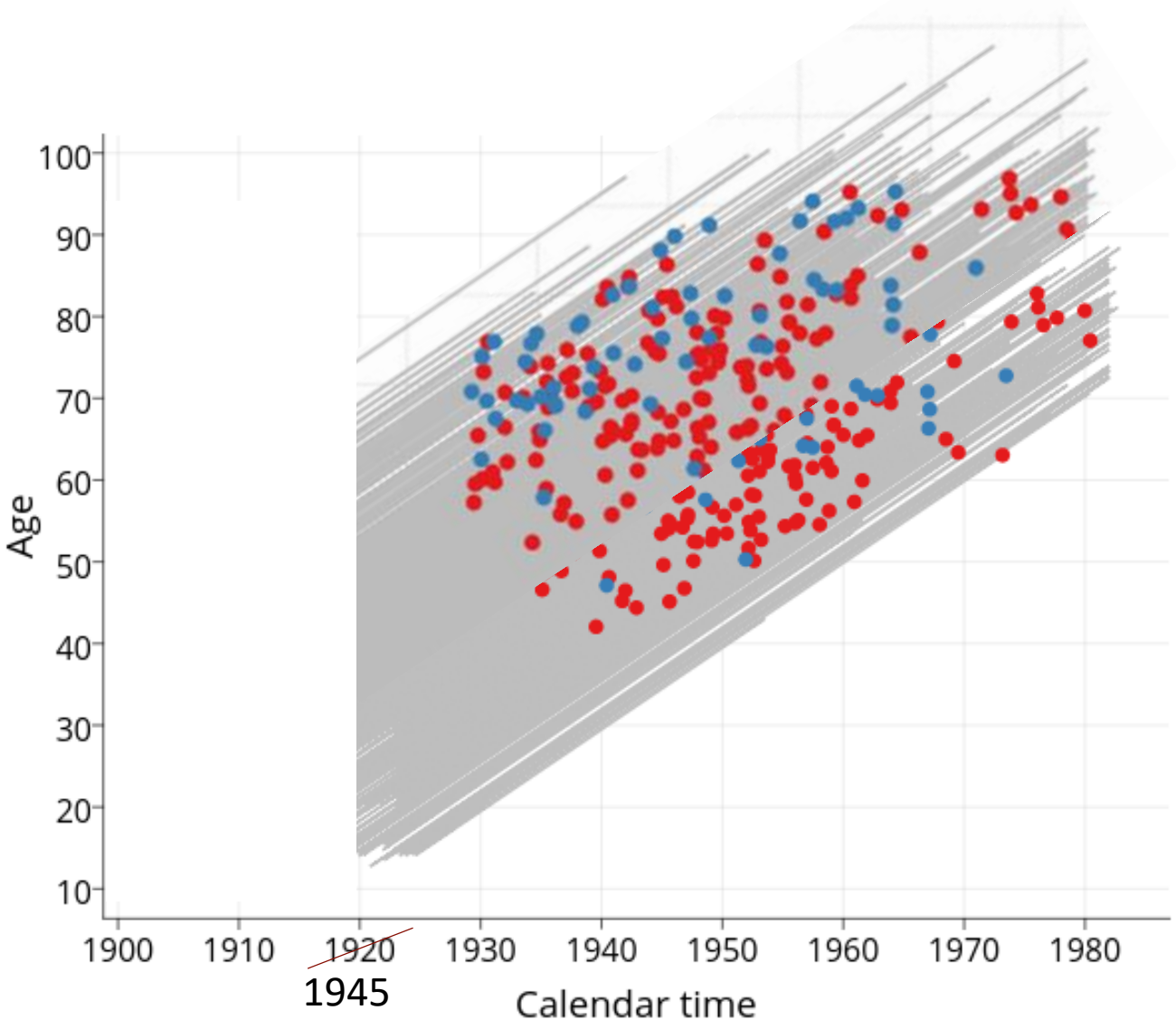
Site-specific findings

- Strongest evidence for higher ERR with childhood vs. adult exposure for thyroid, NMSC, salivary gland
- No or opposite variation: lung, colon
- More complex patterns for leukemia, with increasing ERR with AAE for some subtypes (AML)

Lexis diagram of an occupational cohort



Approximate Lexis diagram of the LSS cohort



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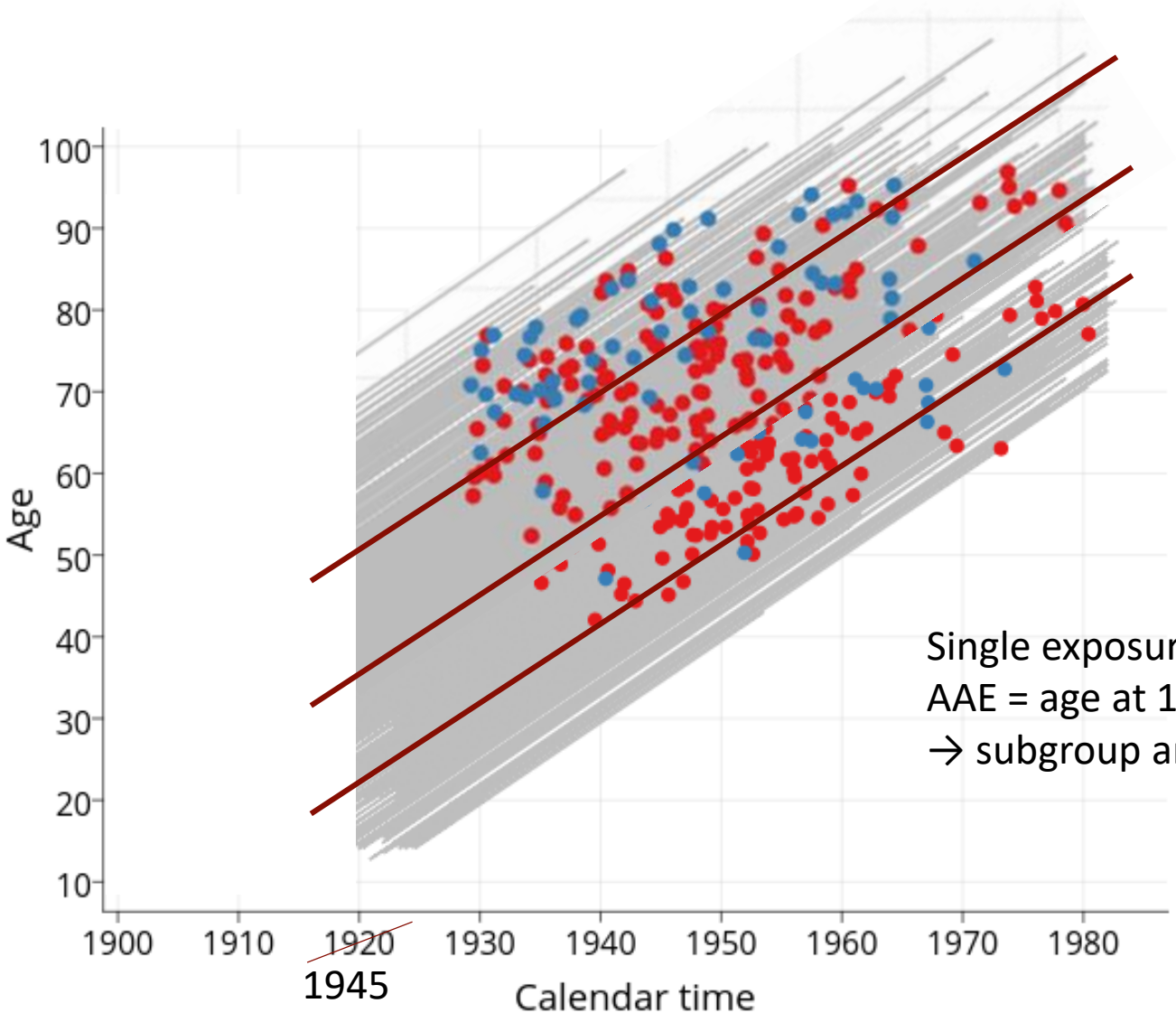


Single exposure:
AAE = age at 1st exposure
→ subgroup analysis by AAE

Age at exposure & attained age distributions

Age at exposure (years)	Number of subjects	Observed person-years	Number of deaths[a]	Alive
0–9	17,833	910,347	2,200	88%
10–19	17,563	848,826	4,887	72%
20–29	10,891	494,021	5,178	52%
30–39	12,270	462,694	10,410	15%
40–49	13,504	365,240	13,397	1%
50+	14,550	213,079	14,548	0%
Total	86,611	3,294,210	50,620	42%

	Both sexes			
	No. of subjects	Person-years	No. of cases	Rate per 10^4
Attained age (years)				
<40	56,657	646,102	450	7.0
40–	15,260	486,309	1,178	24.2
50–	16,637	614,709	3,210	52.2
60–	11,258	651,170	6,491	99.7
70–	4,649	457,149	6,990	152.9
80–	983	224,046	4,219	188.3

Grant et al 2017

Pooled analysis of leukemia after childhood low dose exposure

- 9 cohorts
- ABM dose<100 mGy
- 1st exposure < 21 yrs
- N=262,573
- 20 yrs avg. follow-up

Endpoint	Age at first exposure: Modification of ERR per year age at exposure (+95% CI)	*p*-value[b]
Acute myeloid leukaemia +myelodysplastic syndromes	1.000[c] (0.896[d], 1.116[d])	0.964[c]
Acute myeloid leukaemia	1.000[c] (0.887[d], 1.127[d])	0.924[c]
Chronic myeloid leukaemia	1.030 (0.864[d], 1.226[d])	0.696
Acute lymphoblastic leukaemia	1.057 (0.902[d], 1.467)	0.483
Acute leukaemia	1.000[c] (0.928[d], 1.078[d])	0.869[c]
Leukaemia excluding chronic lymphocytic leukaemia	1.000[c] (0.935[d], 1.069[d])	0.950[c]

We also examined risk by age at exposure, in which the expected number of cases or deaths for stratum j and dose group k with average RBM doses $D_{ijk,e=0-4}$, $D_{ijk,e=5-9}$, $D_{ijk,e=10-14}$, $D_{ijk,e=15+}$ for age at exposure groups, 0-4, 5-9, 10-14 and ≥15 was given by:

$$PY_{ijk}\gamma_{ij}\left[1+\alpha_{0-4}D_{ijk,e=0-4}+\alpha_{5-9}D_{ijk,e=5-9}+\alpha_{10-14}D_{ijk,e=10-14}+\alpha_{15+}D_{ijk,e=15+}\right] \quad \text{(C4)}$$

Age at exposure (years)	RR at 100 mSv (95% CI)	*p*-value, heterogeneity
	Acute myeloid leukaemia + myelodysplastic syndromes (*n*=87)	
0 - 4.99	3.01 (0.85, 7.77)	
5 - 9.99	4.03 (0.06, 14.07)	0.979
10 - 14.99	3.43 (0.57, 9.34)	
≥15	2.52 (0[b c], 8.64)	
	Acute myeloid leukaemia (*n*=79)	
0 - 4.99	2.23 (0.54, 6.07)	
5 - 9.99	3.06 (0[b c], 12.11)	0.957
10 - 14.99	3.37 (0.54, 9.35)	
≥15	2.11 (0[b c], 8.34)	
	Chronic myeloid leukaemia (*n*=36)	
0 - 4.99	2.23[d] (0.54[b], 6.07[b])	
5 - 9.99	3.06[d] (0[b c], 12.11[b])	0.957[d]
10 - 14.99	3.37[d] (0.54[b], 9.35)	
≥15	2.11[d] (0[b c], 8.34[b])	
	Acute lymphoblastic leukaemia (*n*=40)	
0 - 4.99	2.68 (0[b c], 24.73)	
5 - 9.99	11.57 (1.07, 58.05)	0.549
10 - 14.99	5.13 (0[b c], 27.50)	
≥15	6.78 (0.27, 36.15)	

Little et al 2018

Other studies

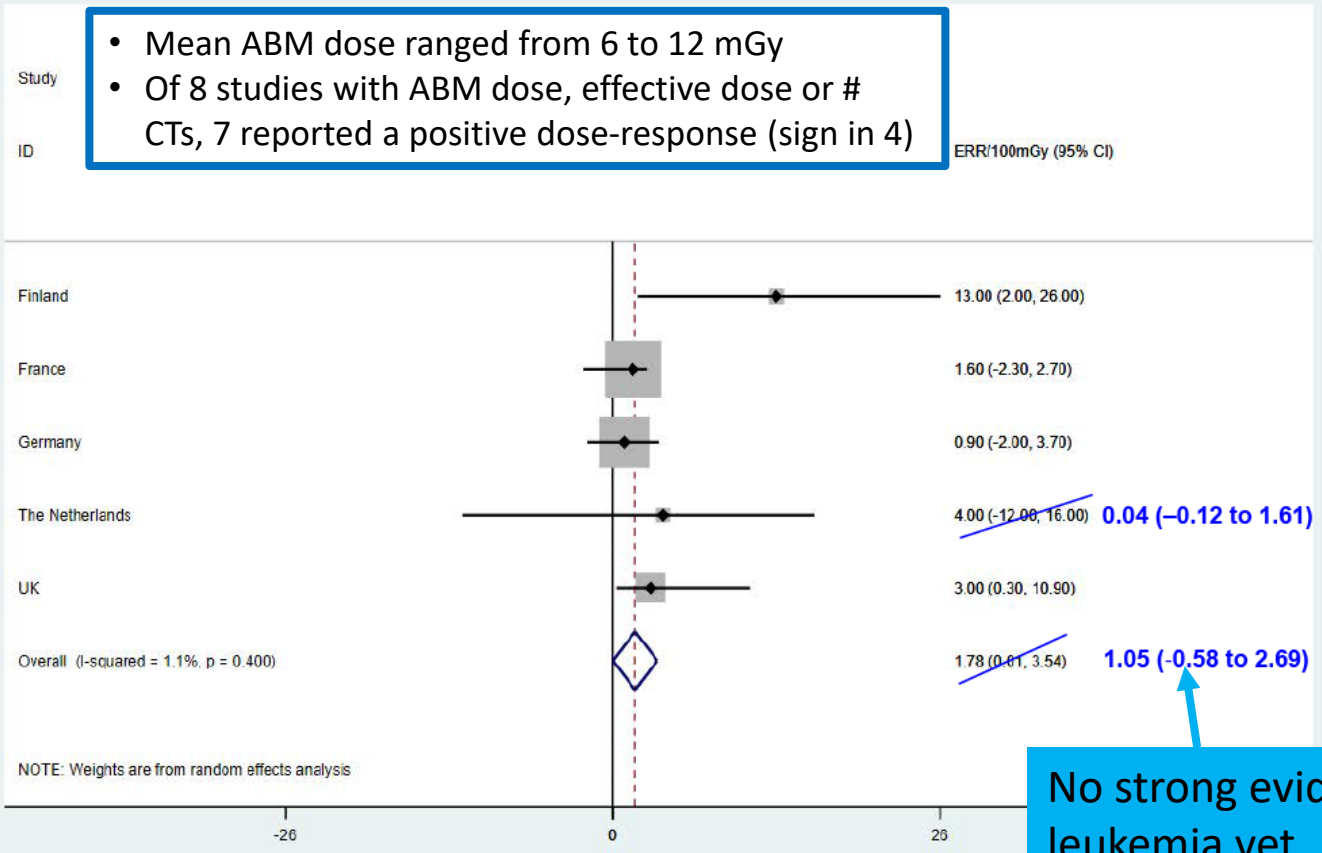
- Early life exposure at low/moderate doses: excess cancer risk associated with radiation doses < 100 mGy
  (Little et al 2022)
- Childhood low-dose exposure & thyroid cancer: stronger dose-response at younger AAE in pooled analysis of 9 cohorts
  (Lubin et al 2017)
- Therapeutic radiation: second cancer risk highest at young treatment age
  (Wakeford & Hauptmann 2022)
- Exposure during pregnancy & childhood cancer: consistent evidence for elevated cancer risk at doses ~30 mGy from OSCC & other studies
  (Wakeford & Bithell 2021)
- Natural background radiation & childhood cancer: no clear patterns
  (Kendall et al 2021)

Overview

1. Age-related radiation effects from LSS & other (low dose) studies
2. **General results of CT studies, particularly EPI-CT**
3. Age and radiation effects in CT studies

Meta-analysis for leukemia/MDS per red bone marrow dose from pediatric CT scans

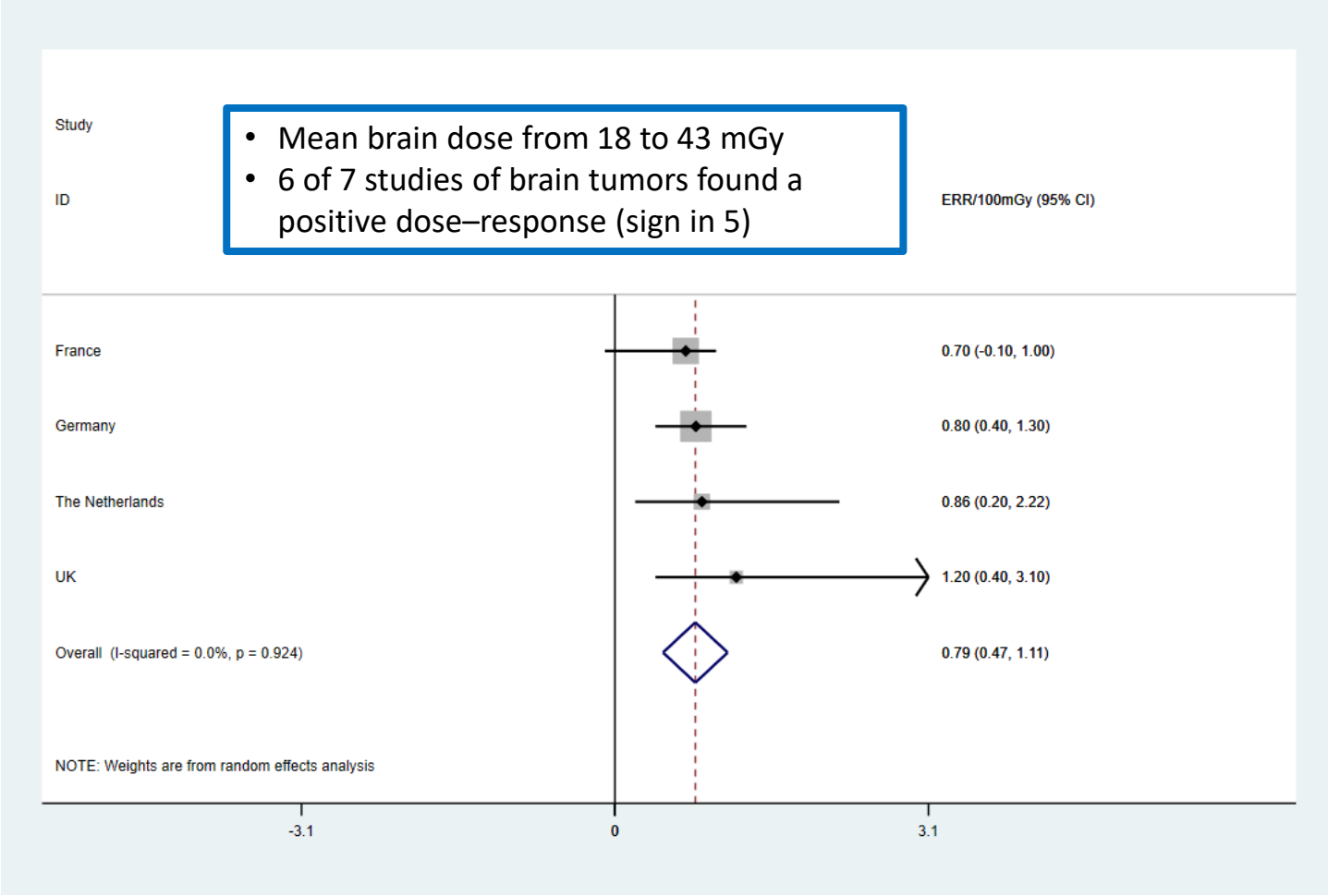
- Mean ABM dose ranged from 6 to 12 mGy
- Of 8 studies with ABM dose, effective dose or # CTs, 7 reported a positive dose-response (sign in 4)



No strong evidence for leukemia yet (with or without MDS)

Berrington et al 2021

Meta-analysis for brain tumors per brain dose from pediatric CT scans



Berrington et al 2021

EPI-CT Consortium

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Country	Hospitals	Patients	Period
UK	91	322,125	1985-2013
Netherlands	42	148,135	1979-2015
Sweden	29	121,805	1977-2013
France	24	119,399	2000-2011
Norway	27	77,252	1980-2021
Spain	36	84,592	1991-2013
Germany	20	47,096	1983-2010
Denmark	6	17,696	1999-2014
Belgium	2	10,074	2000-2015
Total	278	948,174	1977-2015

Bernier et al 2018

worldwide cancer research formerly known as AICR

European Commission

Brain cancer in the EPI-CT cohort

MEDIZINISCHE HOCHSCHULE BRANDENBURG

Characteristics		All subjects N (%)	Cases N (%)	Person-years N (%)
Overall		658,752 (100)	165 (100)	4,536,716 (100)
Sex	Male	368,721 (56)	95 (58)	2,524,786 (56)
	Female	290,031 (44)	70 (42)	2,011,930 (44)
Country	United Kingdom	267,677 (41)	94 (57)	2,200,590 (49)
	The Netherlands	107,034 (16)	29 (18)	831,615 (18)
	Sweden	98,415 (15)	28 (17)	812,508 (18)
	France	63,994 (10)	3 (2)	201,760 (4)
	Norway	50,770 (8)	9 (5)	277,060 (6)
	Spain	36,439 (6)	0 (0)	102,447 (2)
	Germany	21,890 (3)	1 (1)	71,472 (2)
	Denmark	9,289 (1)	1 (1)	30,349 (1)
	Belgium	3,244 (0)	0 (0)	8,915 (0)
Birth cohort	<1980	64,480 (10)	46 (28)	972,233 (21)
	1980-<1990	219,575 (33)	65 (39)	1,837,084 (41)
	1990-<1995	138,993 (21)	35 (21)	802,363 (18)
	≥1995	235,704 (36)	19 (12)	925,037 (20)

CT-exposure in the EPI-CT cohort

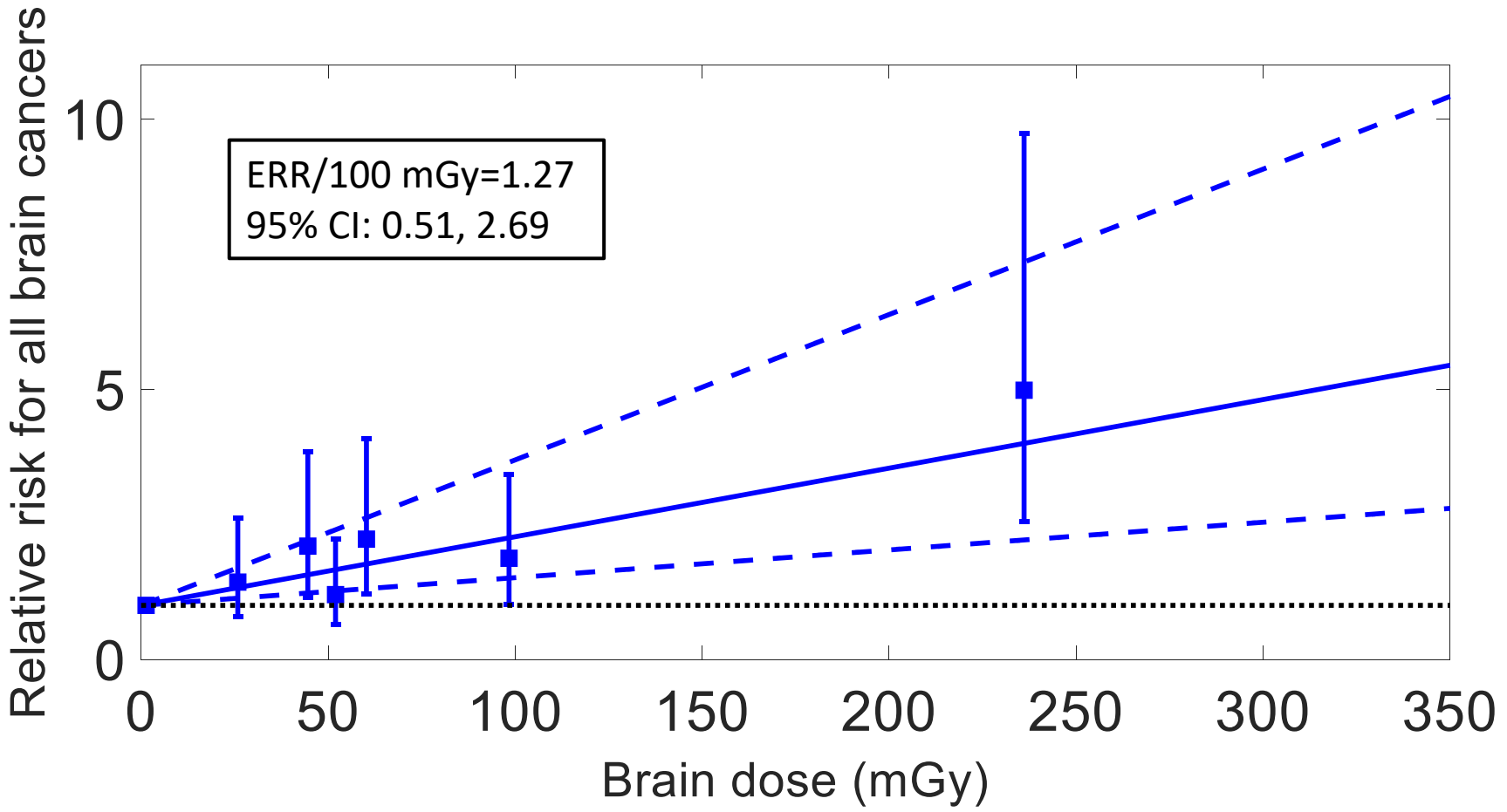
Characteristics	All subjects N (%)	Cases N (%)	Person-years N (%)
Cumulative number of head/neck CT examinations			
0	174,968 (27)	24 (15)	1,089,643 (24)
1	384,335 (58)	102 (62)	2,828,828 (62)
2-3	80,918 (12)	24 (15)	505,152 (11)
4+	18,531 (3)	15 (9)	113,092 (3)
Cumulative brain dose (mGy, lagged by 5 years)			
Mean	49.3	98.1	
Interquartile range	12.9-57.5	41.5-106.1	
Follow-up duration after 5 years since the first CT examination (years)			
Mean	6.9	5.4	

Risks by brain dose

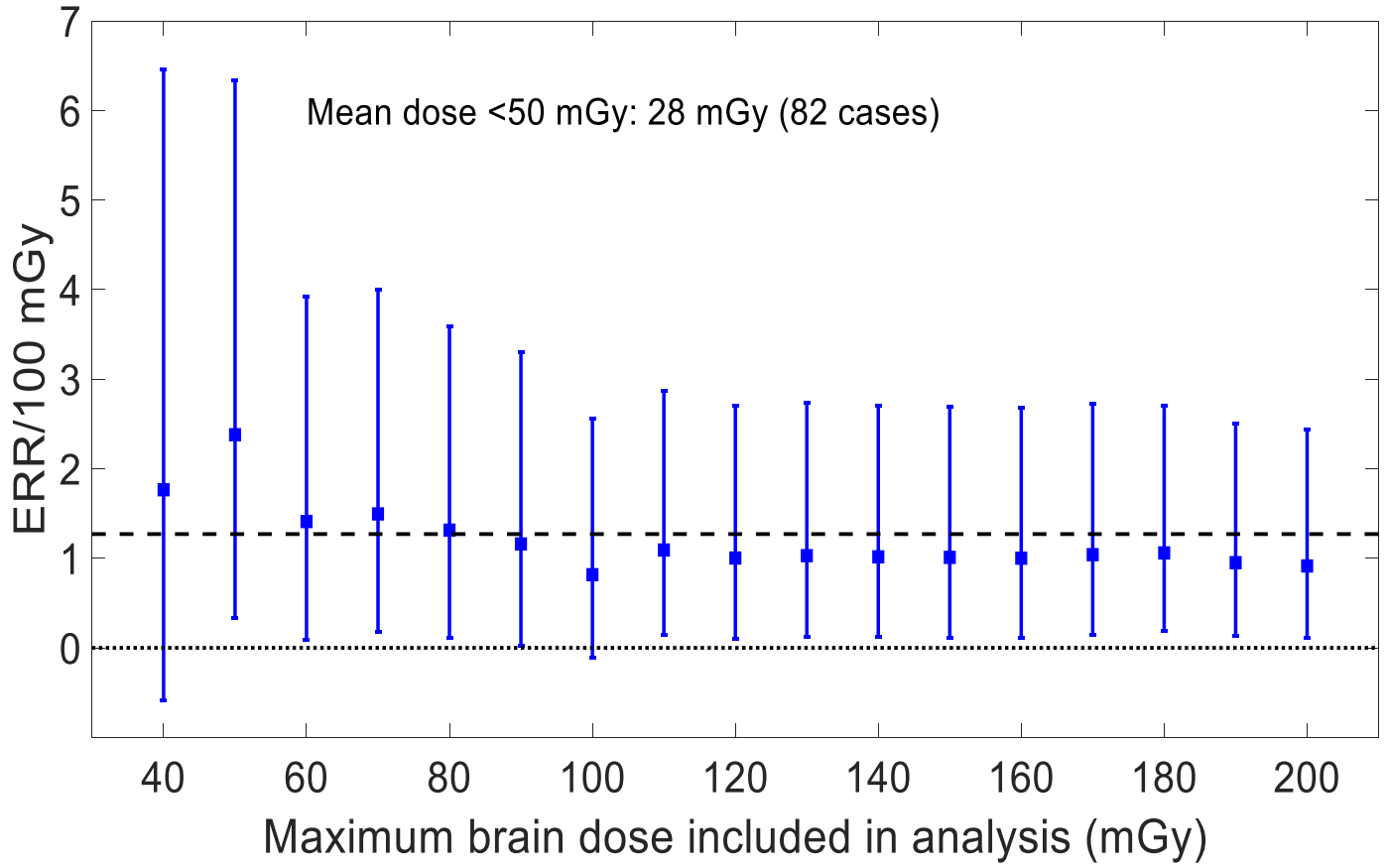
	All brain cancers		Glioma	
	Cases	RR (95% CI)	Cases	RR (95% CI)
Cumulative brain dose (mGy)				
0-<5	18	1.0 (ref)	16	1.0 (ref)
5-<41	27	1.4 (0.8, 2.6)	18	1.1 (0.5, 2.1)
41-<48	26	2.1 (1.1, 3.8)	21	1.9 (1.0, 3.7)
48-<56	23	1.2 (0.6, 2.2)	17	1.0 (0.5, 2.0)
56-<65	27	2.2 (1.2, 4.1)	18	1.7 (0.9, 3.4)
65-<150	27	1.9 (1.0, 3.4)	19	1.5 (0.8, 3.0)
150+	17	5.0 (2.5, 9.7)	12	4.1 (1.9, 8.8)
p-value	<0.001		0.007	
ERR/100 mGy (95% CI)	1.27 (0.51, 2.69)		1.11 (0.36, 2.59)	

No evidence of non-linearity, p=0.849 for all brain cancers & p=0.371 for glioma

Brain cancer dose-response



Analyses limited to lower doses



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UK pediatric CT study

- Opposite AAE effect than expected: brain tumor risk higher if exposed at older vs. younger age
- Note: multiple CTs can occur → separate ERRs per dose received during AAE windows
- Different from subgroup-like LSS analyses

	Leukaemia		Brain tumours	
	ERR per mGy	p value	ERR per mGy	p value
Sex				
Male*	0·031	0·6300	0·016	0·0850
Female	0·042		0·028	
Years since first exposure				
0–<5	0·048	0·8061	0†	0·6468
5–<10	0·033		0·025	
≥10	0·026		0·021	
Years since last exposure				
0–<5	0·052	0·3004	0†	0·1976
5–<10	0·015		0·026	
≥10	0·014		0·016	
Number of CT scans				
1	0·013	0·8013	0·007	0·1213
2–4	0·028		0·021	
≥5	0·035		0·018	
Age at exposure (years)‡				
0–<5	0·030	0·5381	0·005	0·0003
5–<10	0·072		0·028	
10–<15	−0·002		0·037	
≥15	0·049		0·041	
Years since exposure‡				
2–<5	0·055	0·5357	..	0·2399
5–<10	0·021		0·026	
10–<15	0·005		0·023	
≥15	0·026		0·005	

ERR=excess relative risk. ..=not applicable (follow-up started at 5 years).
*Includes individual of unknown sex. †Aliased parameter, set to zero.
‡Time-dependent variable.

Table 4: Excess relative risk per mGy for leukaemia and brain tumours, by various personal characteristics

Pearce et al 2012

Trend somewhat weakened in corrected analyses

Exclusion	None	Brain-tumor related conditions	Brain-tumor related and possible related conditions	Previous cancers	Previous cancers & possible previous cancers
Age at exposure					
0-4 yrs	0.006	0.004	0.004	0.0003	0.0009
5-9 yrs	0.032	0.039	0.039	0.03	0.023
10-14 yrs	0.038	0.035	0.035	0.036	0.036
15-21 yrs	0.038	0.03	0.03	0.03	0.015
p-heterog	*0.02*	*0.02*	*0.02*	*0.0003*	*0.01*
Time since exposure					
5-9 yrs	0.026	0.023	0.023	0.019	0.012
10-14 yrs	0.023	0.018	0.018	0.015	0.015
15+ yrs	0.005	0.004	0.004	0.002	0.003
p-heterog	*0.30*	*0.34*	*0.34*	*0.30*	*>0.5*

Berrington et al 2016

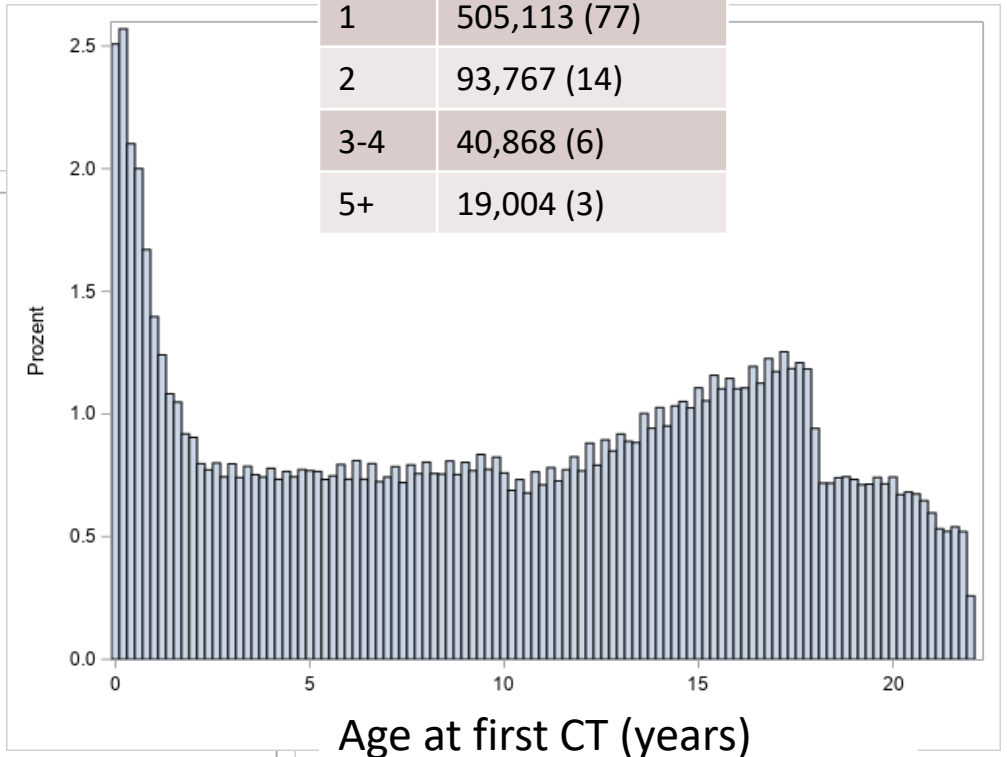
Brain tumors in the Dutch pediatric CT Study

Outcome	ERR per 100 mGy*	P†
Sex		
Male	0.68	.62
Female	1.16	
No. of head CT scans		
1	0.78	.71
2 to 3	1.09	
≥4	1.02	
Years since exposure		
5 to <10	1.56	.13
10 to <15	0.80	
15+	0.10	
Age at exposure, y		
0 to <10	0.44	.43
10 to <15	1.44	
15+	0.88	

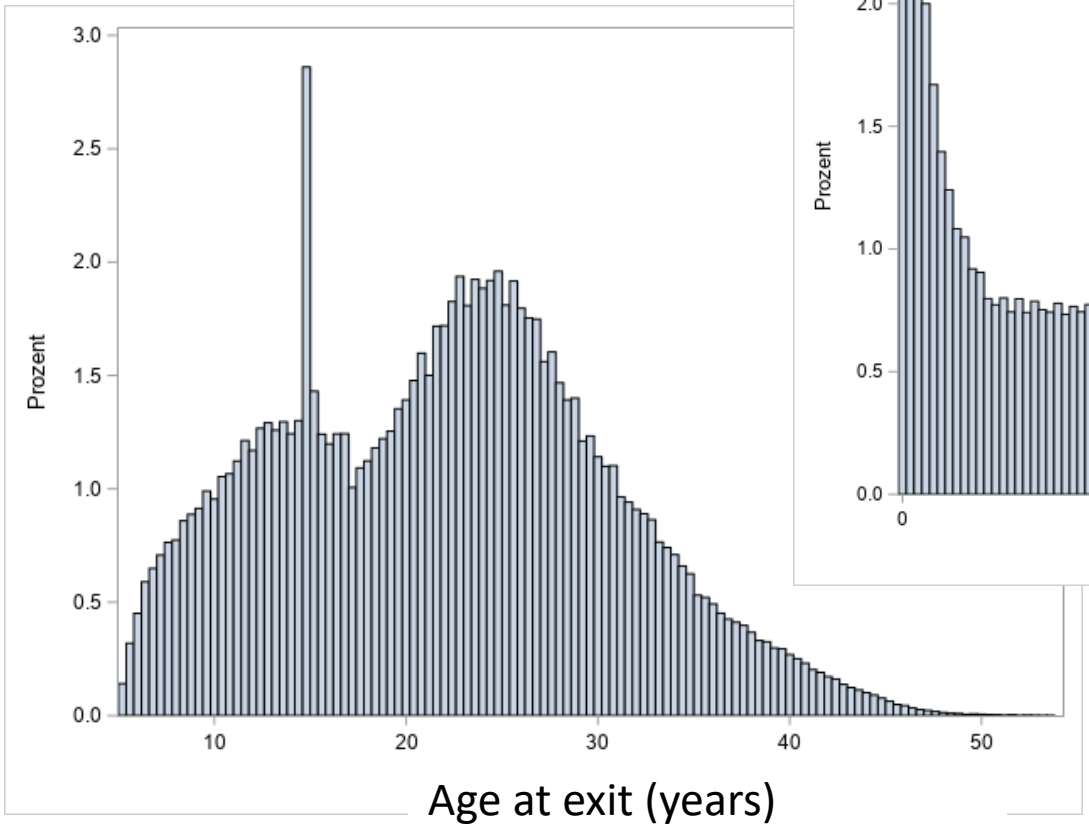
Meulepas et al 2019

Age at 1st CT & age at exit in EPI-CT

# CTs	N (%)
1	505,113 (77)
2	93,767 (14)
3-4	40,868 (6)
5+	19,004 (3)

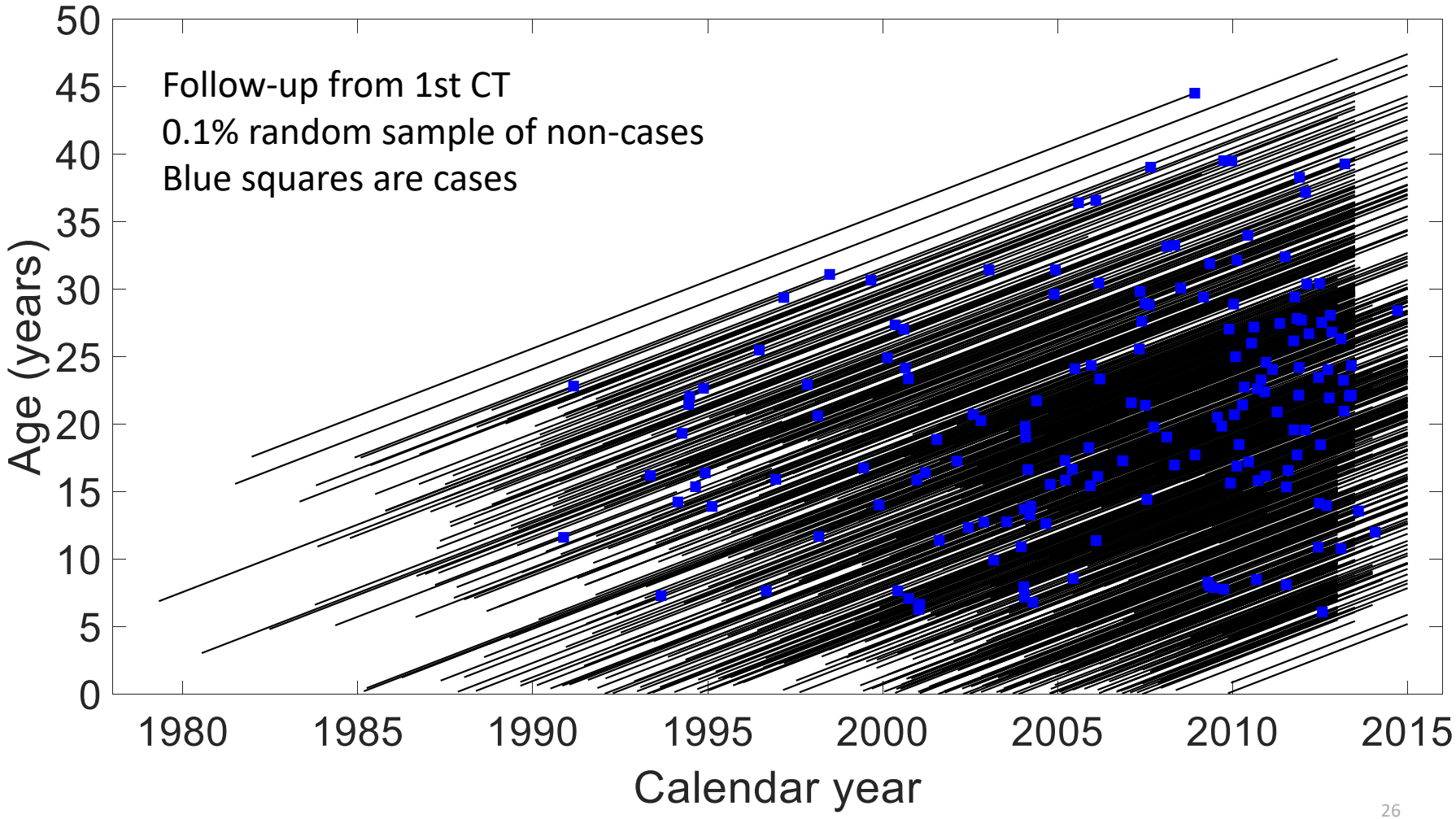


Age at first CT (years)



Age at exit (years)

Lexis diagram for EPI-CT brain cancer analyses



Limited attained age range

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EPI-CT

Attained age	Person-years	Cases
5-10	479,265	18
10-15	742,514	23
15-20	816,549	37
20-25	1,055,000	38
25-30	853,734	26
30-35	400,249	14
35-40	148,638	8
40-45	40,655	1
45+	116	0

LSS

	Both sexes			
	No. of subjects	Person-years	No. of cases	Rate per 10^4
Attained age (years)				
<40	56,657	646,102	450	7.0
40–	15,260	486,309	1,178	24.2
50–	16,637	614,709	3,210	52.2
60–	11,258	651,170	6,491	99.7
70–	4,649	457,149	6,990	152.9
80–	983	224,046	4,219	188.3

Age & time effects for brain cancer in EPI-CT

	ERR/100 mGy (95% CI)	P hom
Age at CT exposure (years)		
0-<6	0.40 (<-0.40, 1.79)	
6-<12	1.98 (0.60, 4.48)	
12+	1.62 (0.40, 4.09)	0.156
Attained age (years)		
5-<18	3.30 (0.87, 16.07)	
18-<25	1.33 (0.11, 5.30)	
25+	0.33 (-0.19, 1.75)	0.119
Time since exposure (years)		
5-<10	1.84 (0.78, 3.76)	
10-<15	1.34 (0.26, 3.23)	
15+	-0.12 (<-0.91, 1.12)	0.020

Conclusions

Radiation-related cancer risk is higher if exposure occurs at younger age

- Strong direct evidence from LSS study spanning all ages at exposure & with long follow-up
- Strong indirect evidence that observed RRs are higher in studies of early life vs adult exposures (exception: natural background exposure)

Pediatric CT studies show inconclusive patterns for brain cancer & leukemia

- Limited by narrow range of age at exposure & attained age
- Limited by short follow-up
- Imprecise estimates of AAE-specific ERRs (small numbers of cases)

Upcoming: Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) Study

- North America (Kaiser Permanente) & Canada (Ontario)
- Diana Miglioretti, Rebecca Smith-Bindman
- Children exposed to diagnostic medical radiation in utero & during childhood

	RIC		EPICT
	Fetal-exposure cohort	Childhood-exposure cohort	
Children	3,474,000	3,724,632	1,170,186
Cancers	6,606	6,358	
Leukemias	2394	2,372	
Average follow-up (yr)	10.8	9.7	9.3
Exposed to CT	17,370	219,753	1,170,186

Kwan et al 2022

Acknowledgements

Patients

Radiology departments

Cancer registries

IARC, Lyon (coordination)

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