Childhood leukaemia and CT scans: recent results and perspectives

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Séminaire ASN «Risques de leucémies et exposition aux rayonnements ionisants»
Montrouge le 9 juin 2015

outline

- summary of recent reports on computed tomography (CT) exposure early in life and leukaemia (the UK, Australia and Taiwan):
  - epidemiological methods
  - dosimetry
  - main findings
  - limitations
- efforts to address limitations of the previous studies:
  - French study
  - German study
  - joint European perspective - EPI-CT

CT: major concerns

- CT is a powerful diagnostic tool with immediate benefit to the patient, however:
  - The use of CT scans has grown rapidly since the 1980s
  - Children are generally more sensitive to the effects of radiation
  - Children have a longer life-span to express health effects
  - Radiation doses are substantially greater than from conventional X-rays
  - Children may have received higher doses than adults, particularly in the earlier years

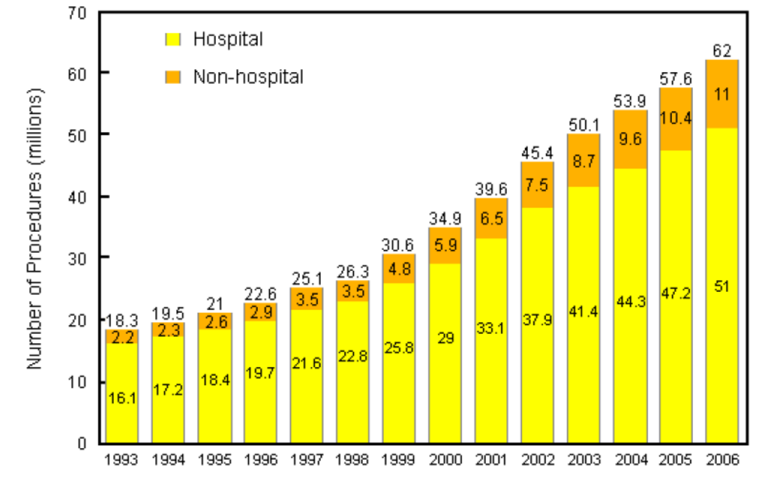


Fig. 4.1. Number of CT procedures per year in the United States (millions), 1993 to 2006. Average growth: >10 % y^{-1}.

NCRP REPORT No. 160, 2009

recent CT studies: epidemiological design

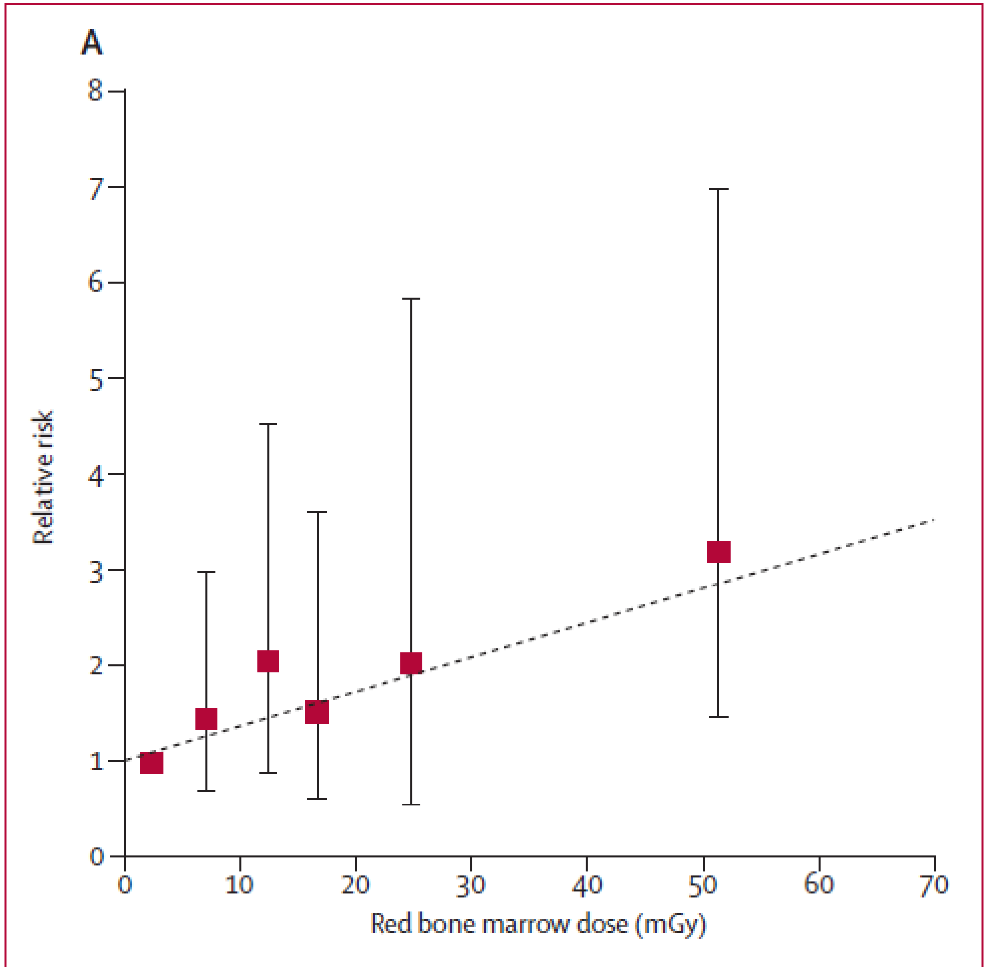
Study	CT exp period	Study population				Follow-up		Lag period (y)
		AAE	Size	Source	Procedure	Period	Procedure	
UK Pearce at al, 2012	1985-2002	<22	178,604	81 NHS regional services of GB	RIS, paper records, films	1985-2008	linkage NHSCR	2
Australia Mathews et al, 2013	1985-2005	<20	10.9M 680,211 exp	Medicare	Records	1985-2007	Ca Database & Nat. Death Index	1(2)
Taiwan Huang et al, 2014	1998-2006	<18	24,418 exp (head CT) 97,668 unexp (1:4)	50% randomly selected insured children	NHI ResData base	1998-2008	NHIRD and CICD	2

summary: dosimetry

- UK study:
  - ❖ estimated absorbed average bone marrow dose for each examination type (range 0.0-9 mGy/scan)
  - ❖ based on typical CT machine settings from UK surveys in 1989 an 2003, dose estimates before 2001 were 2–3 times higher than were those after
- Australian study:
  - ❖ average effective dose per scan by site and year of scan and age
  - ❖ obtained from literature for two periods before 2001 and after, converted into bone marrow dose
  - ❖ Average bone marrow dose per scan (4.2-4.6 mGy)
- Taiwan study: exposed vs. non-exposed

summary: UK study findings

- 74 leukaemia cases (including 9 MDS)
- ERR/1mGy for leukaemia 0.036 (95%CI 0.005-0.12)
- per 10.000 head CT scans before 10 y of age in the 10 years after the CT scan will occur 1 extra case of leukaemia
- no effect of age at exposure, time since exposure, sex
- little evidence of non-linearity



Relative risk of leukaemia in relation to the RBM dose

Pearce *et al*, 2012

summary: Australian study findings

- Excess of 48 leukaemia cases, including MDS, exposed vs. non-exposed
- IRR 1.23 (95% CI 1.08-1.42)
- ERR/1mGy:
  - 1 year lag: 0.039 (95% CI 0.014-0.07)
  - 2 year lag: 0.042 (95% CI 0.01-0.08)
- No effect of time since first exposure
- IRR increased with increasing age at exposure (P=0.06 for trend)
- No effect of sex
- Effect of exposure did not differ according to socioeconomic status

summary: Taiwan study findings

- **17** cases of leukaemia among exposed
- HR 1.90 (95% CI 0.82-4.40)
- results are difficult to interpret:
  - short follow-up period
  - absence of dosimetry
  - missing exposures to RBM (only head CT included)

limitations

- lack of information about indications for the CT scans and the consequent potential for '**reverse causation**'*

However, leukaemia seldom causes medical conditions in young patients that are prompting CT scans

- No information available on leukaemia predisposing syndromes (e.g. Down's syndrome, neurofibromatosis type 1)

However, these account only for a small proportion of cases

*UNSCEAR 2013: EFFECTS OF RADIATION EXPOSURE OF CHILDREN

limitations: dosimetry

- Pearce *et al*:
  - potential for large uncertainties in dose estimates due to the use of typical protocols (group-averaged estimates instead of individual scan parameters)
  - arbitrary year (2001) used as the demarcation of the high exposures in the past (conventional CT) and the lower exposures currently used (helical CT)
- Mathews *et al*:
  - average effective dose instead organ dose used
  - average doses per CT scan type from literature

other limitations

- Missing exposures:
  - CTs in non-included hospitals - e.g. tertiary hospitals)
  - doses from other diagnostic procedures
  - CTs before 1985
  - repeated scans
- Short follow-up:
  - Australian study mean duration after exposure 9.5y
  - UK <15 years since exposure (max 23 y)

efforts to address limitations

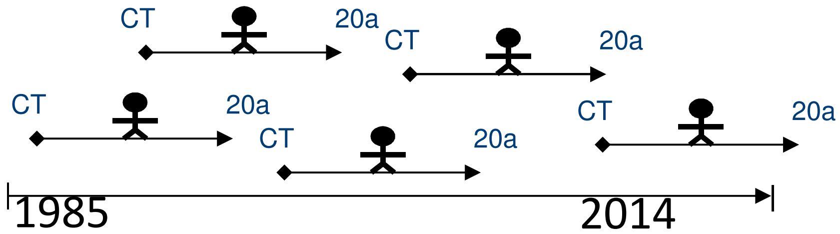
- French study (Journy *et al*, 2014):
  - 67,274 children with a CT scan before 10y from 2000 to 2010
  - mean follow-up 4 years (till 2011)
  - RBM absorbed dose estimated according to the specific protocol (for 86.8%)
  - 25 leukaemias and 21 lymphomas
  - PF retrieved from hospital discharge databases
  - 1.7% were at risk for leukaemia, 1.6% - for lymphoma
  - adjustment for PF lowered ERR/mGy (2y lag):
    - ✓ for leukaemia from 0.057 to 0.047 (both non-significant)
    - ✓ for lymphoma from 0.018 to 0.008 (both non-significant)

efforts to address limitations (2)

- German study (Krille et al, 2015):
  - 44,584 children <15 years who received CT between 1980 and 2010
  - Review of medical records for suspicion of cancer
  - Mean follow-up 4.1 years
  - 12 leukaemias, including MDS (5 excess cases)
  - SIR = 1.72 (95% CI 0.89-3.01), after excluding children with symptoms SIR=1.79 (0.92-3.12)
  - HR/1 mGy=1.01 (95%CI 0.98-1.04)
  - Average doses from published report used

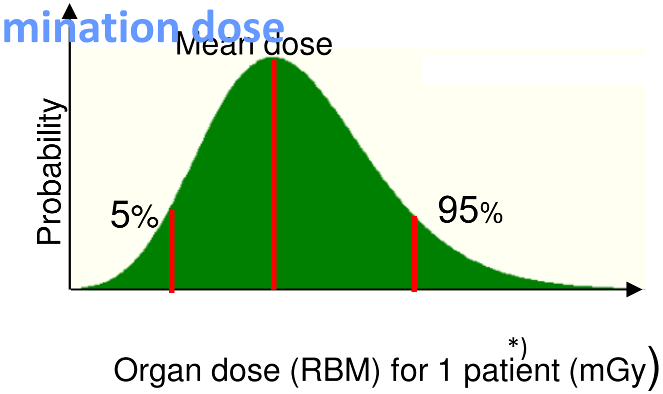
European cohort of paediatric CT patients (2011-2016)

- Establish a multinational cohort of paediatric patients who received CT scans
- Evaluate the radiation-related risk of cancer and leukaemia in this cohort

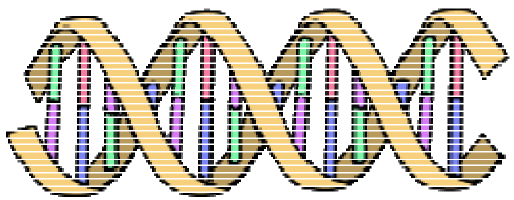


- Develop individual estimates of organ-specific doses from paediatric CT using improved methods for dose estimation
- Develop methods to characterize quality of CT images in relation to the corresponding examination dose

EPI-CT



- Test biological markers of CT-irradiation effects



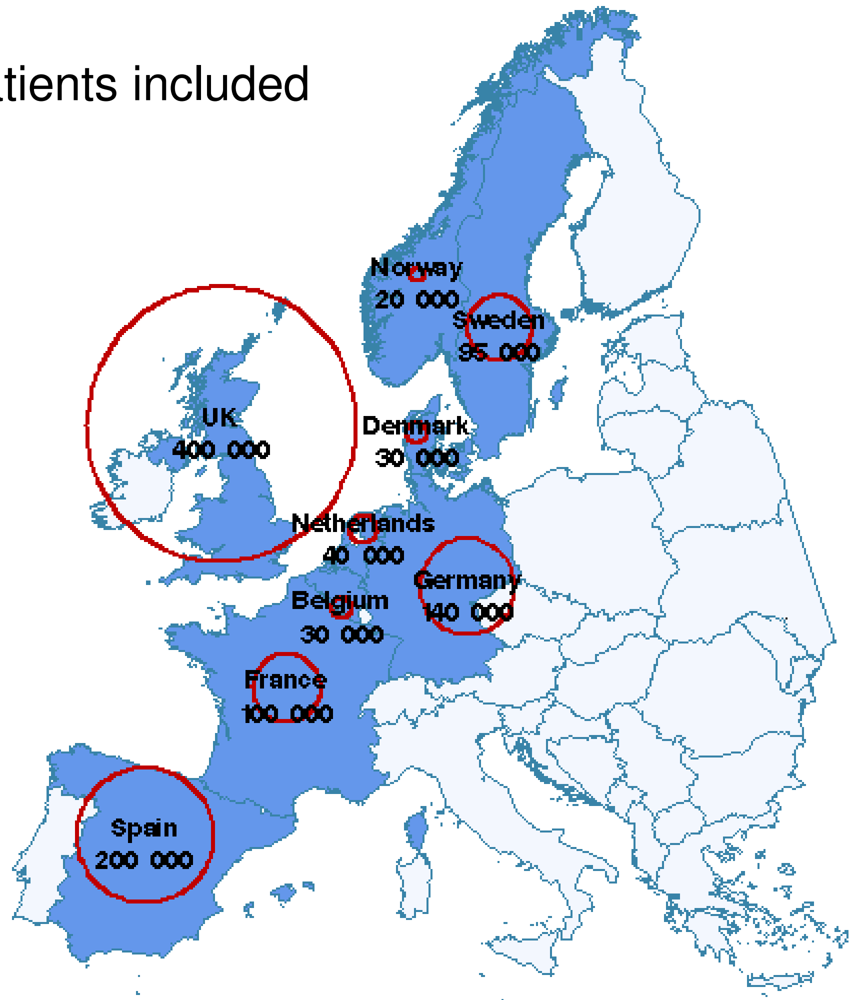
International Agency for Research on Cancer

World Health Organization

Slide adapted from L. Krille

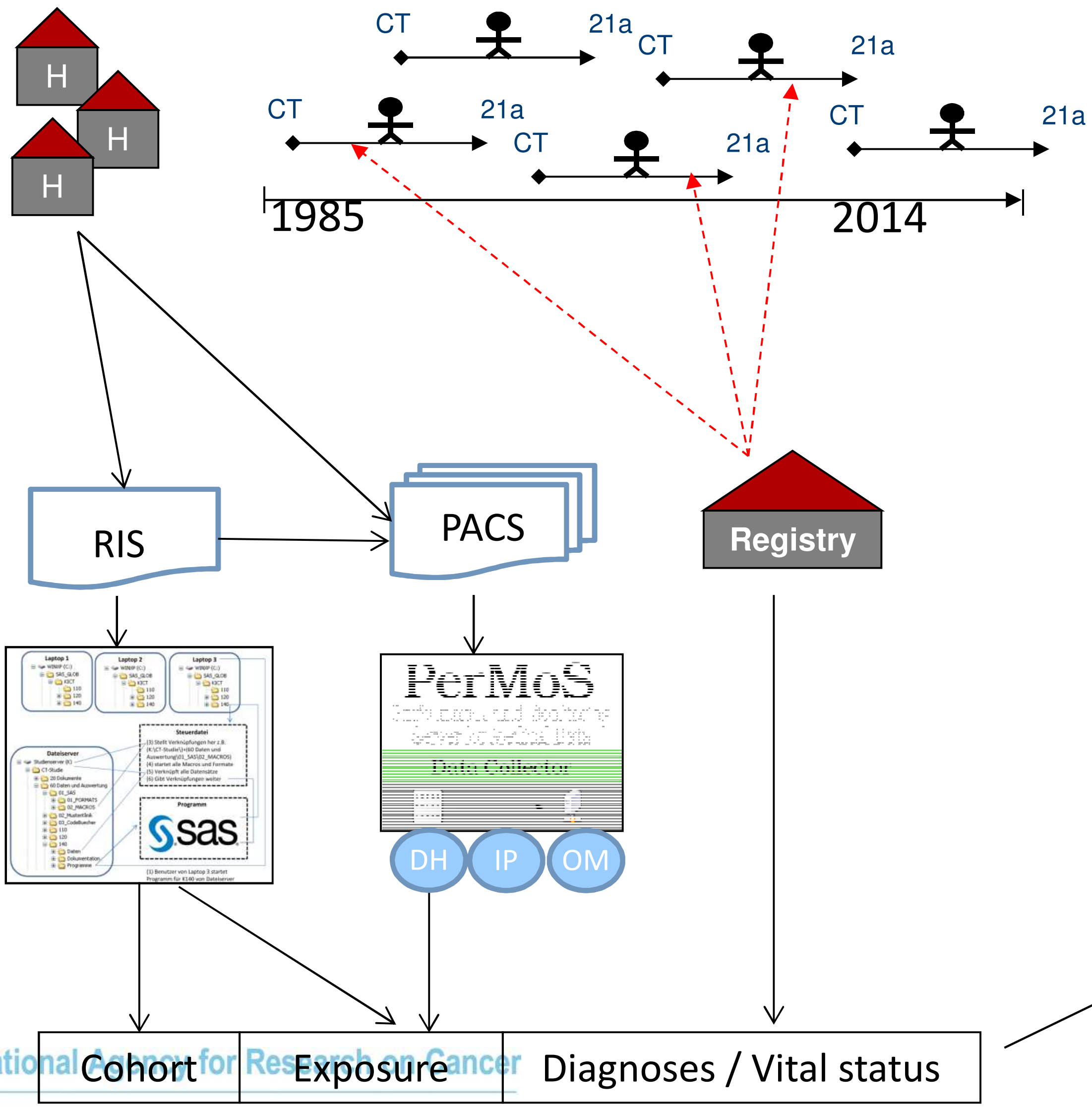
EPI-CT

~1,100,000 patients included



EPI-CT: cohort study

Slide courtesy of L. Krille



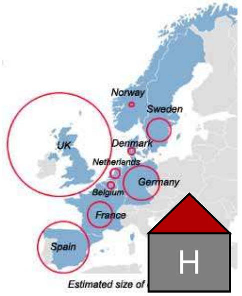
- Dose Response

EPI-CT today: national cohorts

Country	Patients	Period	Age	Cancer incidence
Belgium	17,506	2000-2012	0-15	Yes
Denmark	9,800	2001-2012	0-18	Yes
France	136,138	2000-2012	0-10	Childhood + adolescence
Germany	83,000	1983-2010	0-15	Childhood + adolescence?
Netherlands	162,886	1979-2014	0-18	Yes
Norway	87,477	1980-2013	0-20	Yes
Spain	170,000	1981-2014	0-20	Yes
Sweden	96,229	1982-2013	0-18	Yes
UK	405,211	1985-2013	0-21	Yes
Total	1,168,247	1979-2014		

EPI-CT: dosimetry

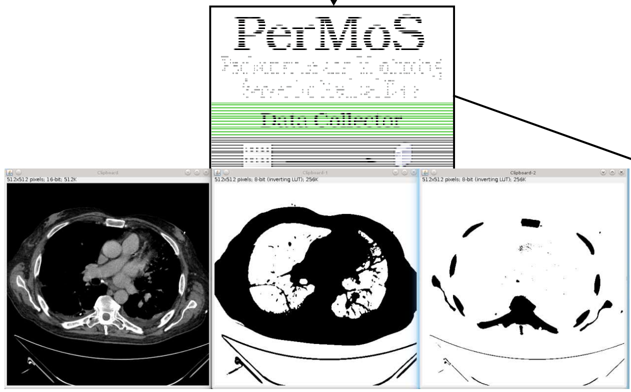
Slide adapted from L. Krille



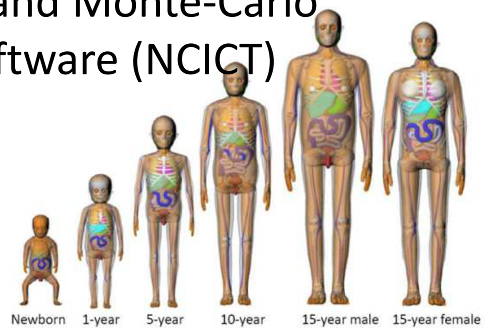
PACS

RIS

from typical protocols - a questionnaire was developed to obtain historical information on: scanner models used over time, protocols implemented for the main examination types



New phantoms and Monte-Carlo simulation software (NCICT)



automated organ detection and classification

Jahnen 2012

Courtesy of C.Lee

EPI-CT: uncertainties on doses

- The problems in EPI-CT are mainly "missing data":
  - height and weight
  - machine types (scanner models)
  - exposed area
  - machine settings for specific protocols
- Patients have shared attributes
  - use of the same machine for groups of patients in the same hospital (same age, same examination type)
- 2DMC simulation method provides alternative realizations of possibly true sets of doses
  - 'm' sets of doses for the entire cohort instead of 1 point estimate of dose for each of 'n' study subjects

EPI-CT: challenges and solutions

- Potential sources of bias and uncertainty:
  - reverse causation (sub-studies in France, Germany)
  - SES (sub-studies in the UK, Netherlands, Belgium)
  - cancer predisposing syndromes (CPS) (sub-studies):
    - ✓ through medical birth registries (in Norway)
    - ✓ diagnosis for hospitalisation (in France)
    - ✓ analyses of a sample of medical records (in Germany)
    - ✓ a sub-study in the Netherlands – simulation of potential impact of CPS on risk estimate
  - missing doses from CT scans
  - missing doses from other IR procedures

Conclusions

- Uncertainties remain, but major improvement in dose (and uncertainty) estimation compared to previous studies is expected
- Potential sources of bias and uncertainty:
  - being addressed through sub-studies and simulations to evaluate potential impact

EPI-CT is a unique cohort suitable for long-term follow-up of cancer and possibly non-cancer outcomes (cataracts, cardiovascular disorders, school performance)

more information: http://epi-ct.iarc.fr

Many thanks to all collaborators in Europe and US NCI