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IRSN
INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

Faire avancer la sûreté nucléaire

Computed paediatric tomography exposure and radiation-induced cancers: Results from a national cohort study in France

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A valuable diagnostic technique

CT scans doses: 20-100 times the conventional radiology doses
10% of examinations
58% of the collective medical dose

Children: High risk group, prolonged life expectancy, lack of optimization

Need for quantifying the potential risk

- *To inform the referees, radiologists, patients*
- *To rationalize the use of examinations*

Pearce et al, Lancet 2012

UK, 179,000 patients undergoing ≥ 1 scan in 1985-2000 <22 years old
7-10 years of follow-up in average
» red bone marrow dose ~50 mGy (5-10 head CT) > risk of leukemia x3
» brain dose ~60 mGy (2-3 Head CT) > risk of cerebral tumors x3
vs exposed to CT scan at < 5 mGy

No individual dosimetric assessment
No clinical information

Mathews et al, BMJ 2013

Australia, 680,000 patients undergoing ≥ 1 scan in 1985-2005 <20 years old
9.5 years of follow-up in average
»all cancers risk x1.2
vs not exposed to CT scan

Various sites of cancer significantly increased
No individual dosimetric assessment
No clinical information

Huang et al, Br J Cancer 2014

Taiwan, 24,418 patients undergoing ≥ 1 head scan in 1998-2006 <18 years old
8 years of total follow-up
risk of cerebral tumors x2.6, significant only for benign tumors
vs not exposed to head CT scan

Exclusion of patients with predisposing factors to cancer
No dosimetric reconstruction

Krille et al, JRP 2015

- 44 584 patients exposed ≥ 1 CT in 1980-2010 <15 years
- SIR all cancer : 1,87 (95% CI, 1,33-2,55)
- SIR leukemia : 1,72 (95% CI, 0,89-3,01)
- SIR brain tumor : 1,35 (95% CI, 0,54-2,78)

Indication of CT scan available for 37 cases and 128 controls
- 22% (8 patients) of cases with predisposing factor to cancer or suspicion of cancer
- 4,7% (6 patients) of controls

No individual dosimetric assessment
Comparison to the general population

Recent epidemiological findings, which interpretation ?

IOP Publishing | Society for Radiological Protection — Journal of Radiological Protection
J. Radiol. Prot. 34 (2014) E1–E5 — doi:10.1088/0952-4746/34/1/E1

Risks from CT scans—what do recent studies tell us?

Serious consideration must be given to the possibility that reverse causation (also known as confounding by indication) is playing an important role in the findings of CT scan studies, a point made recently by UNSCEAR (2013). Reverse causation implies that it is the early symptoms of undetected cancer, or of factors that predispose to cancer, that are the indications for the CT scans, rather than the CT scans *per se* that are causing the apparent excess risk of

Bias by indication?
Bias by reverse causation?

Suspicion of cancer/symptoms related to cancer
Diagnosis/monitoring of diseases predisposing to cancer
Completely unrelated to cancer risk

Cohort Enfant Scanner

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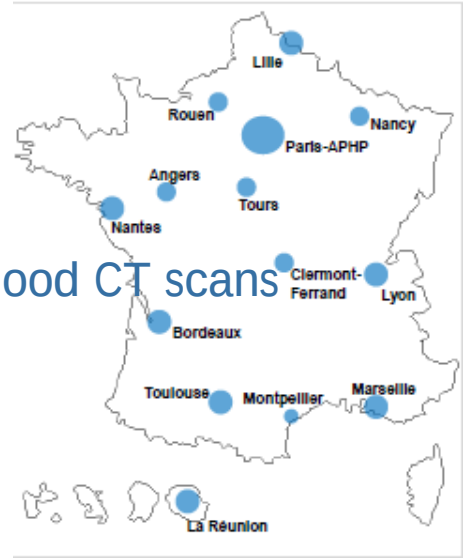
SEVENTH FRAMEWORK
PROGRAMME

CONTRE LE CANCER
LA LIGUE
101 comités
pour la vie

INSTITUT NATIONAL DU CANCER

The « *cohorte Enfant Scanner* » (IRSN)



Main objectives:

Assessment of exposure to CT scans in paediatrics

Analysis of cancer risk related to cumulative doses from childhood CT scans

Study population:

- Children born ≥1995 without cancer diagnosis at the 1st CT scan

  exposed in 2000-2011 to a 1st CT scan < the age of 10 years
- 23 radiology departments of major university hospitals in France
- Follow-up of cancer incidence and mortality through national registries

Grants:

La Ligue contre le cancer (PRE09/MOB)

Institut National du Cancer (2011-1-PL-SHS-01-IRSN-1)

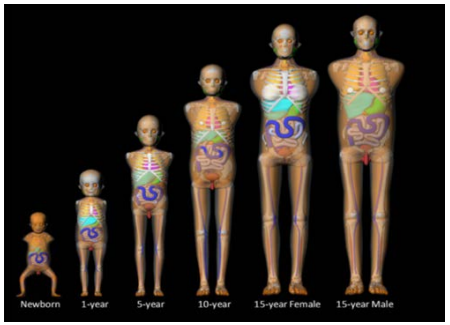
European Community (FP7 No 269912)

Dosimetric reconstruction

- From radiological protocols used in the radiology departments (more than 900 protocols collected)
- Organ dose estimation (IRSN / National Cancer Institute, NIH, USA – Epi-CT)
- NCICT version beta 2.0

Library of paediatric phantoms

More realistic mathematical modelisation of anatomy



Study population

67 274 children included (≥1 year of follow-up) (Journy et al, BJC, 2015)

➡ Median duration of follow-up = 4 years

Follow-up until the age of 15, cancer diagnosis, death, 31 December 2011

Exposures

➡ Young ages at the first examination

median age = 3 years, 31% exposed <1 year old

➡ Low cumulative doses

mean number of CT scan =1.4, median brain dose =18 mGy, bone marrow =7 mGy

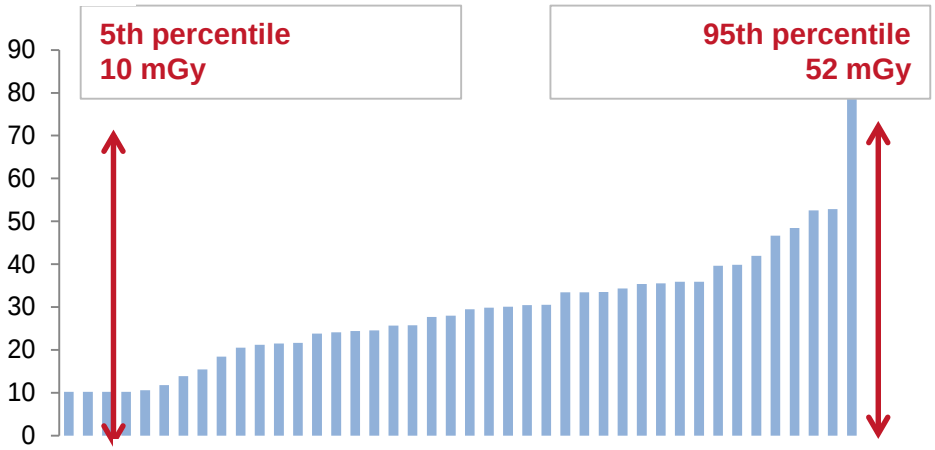
Incident cases (>1 year after the 1st CT scan)

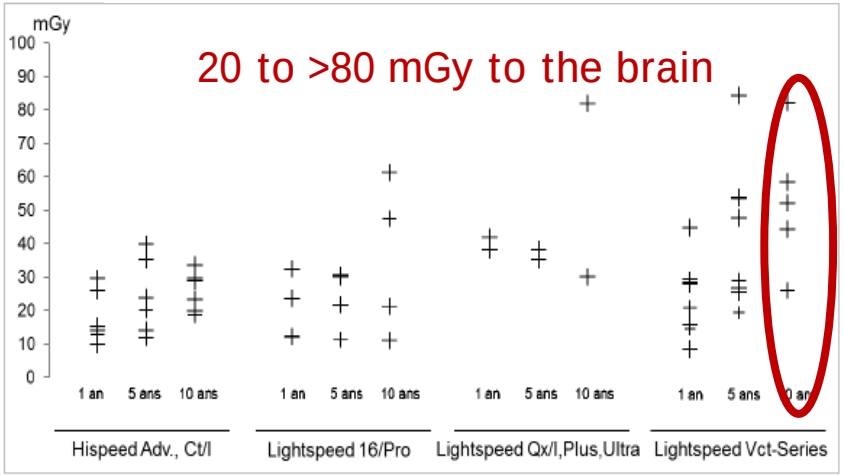
➡ 106 incident cases of cancer

27 tumors of the CNS, 25 cases of leukemia, 21 of lymphoma

Dose variability across the radiology departments

Brain doses from skull/brain CT examinations (2000-2011)





Ratios between the highest/lowest organ doses

Head CT:	5–15
Chest CT:	20–30
Abdominal CT:	10–20

Study population

Clinical conditions predisposing to cancer

Diagnoses retrieved through the hospital discharge databases (period 1995-2012)

Immune deficiencies

- Common variable immune deficiency
- Severe combined immune deficiency
- Wiskott-Aldrich Syndrome
- Organ transplant
- HIV/AIDS

Other genetic defects

- Neurofibromatosis (types 1 et 2)
- Other phakomatoses
- Xeroderma pigmentosum
- Down syndrome
- Noonan Syndrome
- Klinefelter Syndrome
- Bloom Syndrome
- Familial Adenomatous Polyposis
- Multiple endocrine neoplasia (types 1 et 2)
- Retinocytoma (RB1 mutation)
- Fanconi anemia*
- Ataxia telangiectasia*

3% of the included children

32% of the incident cases of cancer

Relative risks:

CNS tumours, RR = 87 (95%CI: 33 to 206)

Leukemia, RR = 24 (95%CI: 8 to 65)

Lymphoma, RR = 32 (95%CI: 14 to 68)

Effect modification or bias by indication?

Leukaemia: ERR per mGy related to cumulative RBM doses (2 years of exclusion)

	No cases	ERR	(95% CI)
In all children	19	0.057	(-0.079; 0.193)
Adjustment for PF ↓			
In all children	19	0.047	(-0.065; 0.159)
In children without PF	12	0.256	(-0.607; 1.118)
In children with PF	5	-0.012	(-0.022; -0.002)

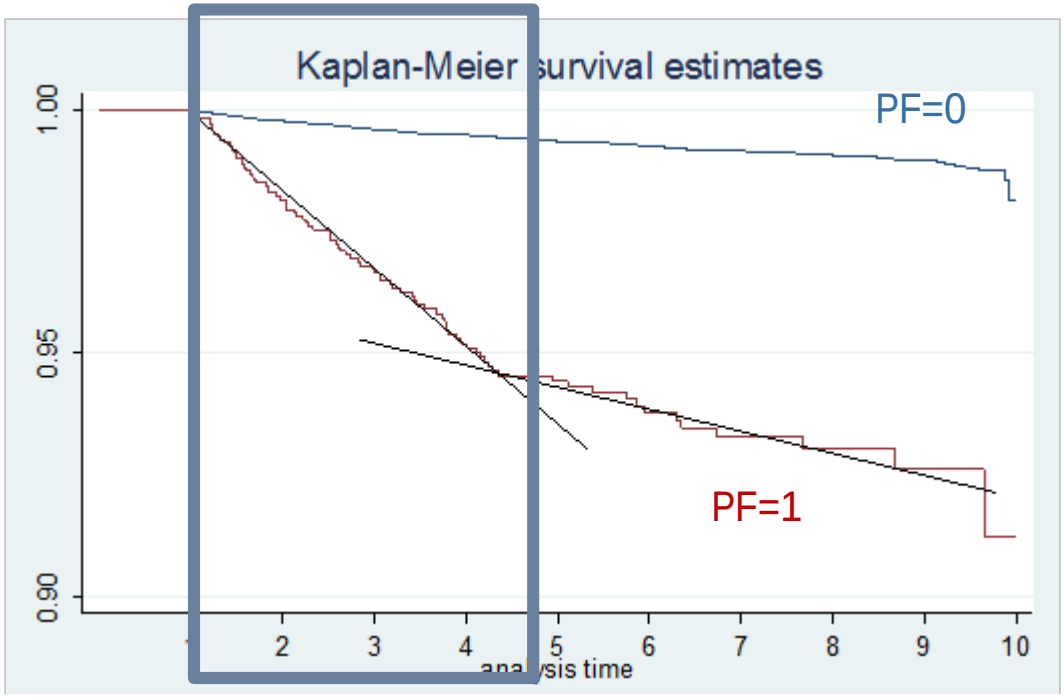
Effect modification or bias by indication?

CNS tumours: ERR per mGy related to cumulative brain doses (2 years of exclusion)

	No cases	ERR	(95% CI)
In all children	22	0.022	(-0.016; 0.061)
Adjustment for PF ↓			
In all children	22	0.012	(-0.013; 0.037)

In children without PF	15	0.028	(-0.036; 0.091)
In children with PF	7	-0.004	(-0.006; -0.003)

Effect modification?



Annual mortality rate
(>1 year after the 1st CT scan)

Cancer deaths
without PF: 4 per 100,000 PYR
with PF: 111 per 100,000 PYR

Non-cancer deaths
without PF: 121 per 100,000 PYR
with PF: 936 per 100,000 PYR

- Increased % of patients with predisposing factors to cancer as compared to the general population
- Risk estimates
  - ↘ with adjustment on predisposing factors
  - very different in patients with PF compared to patients without PF
  - Coherent estimates with previous studies on CT scans
- Period 2000-2011: a duration of follow-up still too short to provide any conclusive results/ no significant excess risk

- The French study is the first one to assess the impact of cancer predispositions on estimates of radiological risk.
- Interpretation of the results of CT studies should take predisposing factors into account
- Prolonged follow-up of the cohort will assess cancer risk linked to CT scan exposure

- *EPI-CT*, a planned collaborative project with other European countries
  - Focus on Dose reconstruction
  - Increased statistical power

SEVENTH FRAMEWORK PROGRAMME

EPI-CT

Unit of Epidemiology of the French Institute of Radiological Protection and Nuclear Safety (IRSN)

- **MO Bernier, S Caër-Lorho, D Laurier:** Setting of the study

Medical Radiation Protection Expertise Unit **(IRSN)**

- **B Aubert, JL Réhel:** Dosimetric estimation

French Society of Paediatric Radiology (SFIPP)

- **H Brisse, C Adamsbaum:** contacts with the departments of radiology

Departments of Paediatric Radiology (23, 21 hospitals)

- Data and protocols used

Registries of Paediatric Cancer (RTSE) and Leukemia (RNHE)

- **B Lacour (RTSE), J Clavel, A Goubin U Inserm754:** Follow-up of the cohort

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CHU de Montpellier : Dr M Saguintaah. CHU de Nancy : Dr M Balde, F Collignon, Dr MA Galloy, E Pozza, Dr E Schmitt. CHU de Nantes : Pr B Dupas, Dr Le François, Mr Salaud, Dr N Surer. CHU Pellegrin Bordeaux : Mme Barat, C Bertini, Pr JF Chateil, Dr M Hajjar. CHU de Rouen : N Baray, Mme Perrier, H Daubert, L Froment.

CHU de Toulouse : Mme Dupont, Dr B Giachetto, Dr L Molinier, Dr J Vial.

Institut Curie : Dr H Brisse

French national register of childhood cancer:

J Clavel, B Lacour, E Nguyen, N Simon

Thank you for your attention

Excess relative risks (ERR) of cancers of the central nervous system (CNS), leukaemia, and lymphoma related to cumulative organ doses in mGy

Exclusion period (years)	1	2	3	4
CNS cancer				
Not adjusted for PF	0.028	0.022	0.005	0.001
	(-0.012; 0.067)	(-0.016; 0.061)	(-0.019; 0.030)	(-0.022; 0.023)
Adjusted for PF	0.017	0.012	0.000	-0.004
	(-0.010; 0.044)	(-0.013; 0.037)	(-0.014; 0.014)	(-0.011; 0.001)
Leukemia				
Not adjusted for PF	0.019	0.057	0.080	3.197
	(-0.043; 0.081)	(-0.079; 0.193)	(-0.136; 0.296)	(-65.08; 71.47)
Adjusted for PF	0.014	0.047	0.056	0.510
	(-0.037; 0.065)	(-0.065; 0.159)	(-0.101; 0.214)	(-2.129; 3.149)
Lymphoma				
Not adjusted for PF	0.009	0.018	0.080	0.068
	(-0.059; 0.077)	(-0.068; 0.104)	(-0.132; 0.292)	(-0.142; 0.277)
Adjusted for PF	-0.002	0.008	0.062	0.048
	(-0.050; 0.046)	(-0.057; 0.073)	(-0.102; 0.227)	(-0.108; 0.205)

CNS: central nervous system; PF: factors predisposing specifically to cancer at that site; 95%CI: Wald-based 95% confidence intervals. ERRs are estimated by Poisson models (maximum likelihood estimates) adjusted for gender, period of birth (1995-2001, 2002-2010), attained age (in years), time since entry into the cohort (in years), as well as the presence of PF (yes/no), unless stated otherwise.

Central Nervous System Tumors		
Mathews 2013	ERR/mGy = 0.021	(0.014-0.029)
Pearce 2012	ERR/mGy = 0.023	(0.010-0.049)
LSS, Preston 2007	ERR/mGy = 0.006	(0.000-0.064)
Leukemia + myelodysplasic syndroms		
Mathews 2013	ERR/mGy = 0.039	(0.014-0.070)
Pearce 2012	ERR/mGy = 0.036	(0.005-0.120)
LSS, Preston 1994*	ERR/mGy = 0.045	(0.016-0.188)
***exclusion of myelodysplasic syndroms. Source : Mathews et al BMJ, 2013**		

Limits :

- Dose reconstruction
- Indication bias