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

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³Pellegrin Hospital, Bordeaux, France
⁴French Society of Prenatal and Radiology.
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
Recent epidemiological findings

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?

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
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)

- 5th percentile: 10 mGy
- 95th percentile: 52 mGy

Ratios between the highest/lowest organ doses

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

20 to >80 mGy to the brain
Study population

Clinical conditions predisposing to cancer

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

<table>
<thead>
<tr>
<th>Immune deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common variable immune deficiency</td>
</tr>
<tr>
<td>Severe combined immune deficiency</td>
</tr>
<tr>
<td>Wiskott-Aldrich Syndrome</td>
</tr>
<tr>
<td>Organ transplant</td>
</tr>
<tr>
<td>HIV/AIDS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other genetic defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis (types 1 et 2)</td>
</tr>
<tr>
<td>Other phakomatoses</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
</tr>
<tr>
<td>Down syndrome</td>
</tr>
<tr>
<td>Noonan Syndrome</td>
</tr>
<tr>
<td>Klinefelter Syndrome</td>
</tr>
<tr>
<td>Bloom Syndrome</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia (types 1 et 2)</td>
</tr>
<tr>
<td>Retinocytoma (RB1 mutation)</td>
</tr>
<tr>
<td>Fanconi anemia*</td>
</tr>
<tr>
<td>Ataxia telangiectasia*</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th></th>
<th>No cases</th>
<th>ERR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all children</td>
<td>19</td>
<td>0.057</td>
<td>(-0.079; 0.193)</td>
</tr>
<tr>
<td><strong>Adjustment for PF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In all children</td>
<td>19</td>
<td>0.047</td>
<td>(-0.065; 0.159)</td>
</tr>
<tr>
<td>In children without PF</td>
<td>12</td>
<td>0.256</td>
<td>(-0.607; 1.118)</td>
</tr>
<tr>
<td>In children with PF</td>
<td>5</td>
<td>-0.012</td>
<td>(-0.022; -0.002)</td>
</tr>
</tbody>
</table>
Effect modification or bias by indication?

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

<table>
<thead>
<tr>
<th></th>
<th>No cases</th>
<th>ERR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all children</td>
<td>22</td>
<td>0.022</td>
<td>(-0.016; 0.061)</td>
</tr>
<tr>
<td><strong>Adjustment for PF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In all children</td>
<td>22</td>
<td>0.012</td>
<td>(-0.013; 0.037)</td>
</tr>
<tr>
<td>In children without PF</td>
<td>15</td>
<td>0.028</td>
<td>(-0.036; 0.091)</td>
</tr>
<tr>
<td>In children with PF</td>
<td>7</td>
<td>-0.004</td>
<td>(-0.006; -0.003)</td>
</tr>
</tbody>
</table>
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
Summary of the study

- 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
Conclusions and perspectives

- 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.
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
Radiologists, clinicians, physicists, technicians of the participating hospitals:
APHP : Pr C. Adamsbaum, J Betout, A Bouette, Pr F Brunelle, P Chambert, Dr Costa, Pr E Dion, Pr H Ducou Le Pointe, Dr S Franchi, Pr G Sebag, Pr G Khalifa, E Maupu, Pr D Musset, Pr D Pariente, Pr Sellier. CHU d’Angers : Dr N Andreu, F Clémenceau, Dr D Loisel, B Ory, Dr D Weil. CHU de Clermont-Ferrand : Pr JM Garcier, Dr J Guersen, S Mangin. CHU Clocheville Tours : Dr S Baron, Mme Charbonnier, C Gaborit, Pr D Sirinelli. CHU de La Réunion : JM Chave, Dr E Chirpaz, Dr O Fels, Dr JF Rouanet. CHU de Lille : Pr N Boutry, Dr A Bruandet, G Potier. CHU de Lyon: D Defez, Dr Perrot, M Teisseire. CHU de Marseille : B Bourlière, Pr P Petit, Dr C Seyler 
CHU de Montpellier : Dr M Saguintah. 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

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

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.
### Recent epidemiological findings

<table>
<thead>
<tr>
<th>Central Nervous System Tumors</th>
<th>ERR/mGy</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Mathews 2013</td>
<td>0.021</td>
<td>(0.014-0.029)</td>
</tr>
<tr>
<td>Pearce 2012</td>
<td>0.023</td>
<td>(0.010-0.049)</td>
</tr>
<tr>
<td>LSS, Preston 2007</td>
<td>0.006</td>
<td>(0.000-0.064)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukemia + myelodysplastic syndroms</th>
<th>ERR/mGy</th>
<th>95% CI</th>
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<td>(0.014-0.070)</td>
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<td>Pearce 2012</td>
<td>0.036</td>
<td>(0.005-0.120)</td>
</tr>
<tr>
<td>LSS, Preston 1994*</td>
<td>0.045</td>
<td>(0.016-0.188)</td>
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</table>


**Limits:**
- Dose reconstruction
- Indication bias