Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France

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Background: Recent epidemiological results suggested an increase of cancer risk after receiving computed tomography (CT) scans in childhood or adolescence. Their interpretation is questioned due to the lack of information about the reasons for examination. Our objective was to estimate the cancer risk related to childhood CT scans, and examine how cancer-predisposing factors (PFs) affect assessment of the radiation-related risk.

Methods: The cohort included 67 274 children who had a first scan before the age of 10 years from 2000 to 2010 in 23 French departments. Cumulative X-rays doses were estimated from radiology protocols. Cancer incidence was retrieved through the national registry of childhood cancers; PF from discharge diagnoses.

Results: During a mean follow-up of 4 years, 27 cases of tumours of the central nervous system, 25 of leukaemia and 21 of lymphoma were diagnosed; 32% of them among children with PF. Specific patterns of CT exposures were observed according to PFs. Adjustment for PF reduced the excess risk estimates related to cumulative doses from CT scans. No significant excess risk was observed in relation to CT exposures.

Conclusions: This study suggests that the indication for examinations, whether suspected cancer or PF management, should be considered to avoid overestimation of the cancer risks associated with CT scans.

Computed tomography (CT) is a valuable imaging technique to help diagnosis and medical management of some medical conditions. Nonetheless, its increasingly widespread use has raised concerns about potential risks of subsequent cancer, for CT leads to effective doses 5–20 times higher than conventional radiology (Shrimpton et al, 1991; Mettler et al, 2008)—corresponding to organ doses of some units to tens of milligrays (mGy) from each scan. In 2007, there were 7.6 million CT examinations in France, overall, and 0.3 examinations per child aged younger than 10 years (Etard et al, 2012).

A reasonable quantitative assessment of potential risks induced by radiation exposure is required to enable physicians to make appropriate decisions about radiology examinations and to provide patients and families with adequate information. One initial approach to such an assessment is to use robust epidemiological results obtained at higher doses to predict the cancer risks related to these low-dose exposures. Although this approach makes it possible to estimate an expected magnitude of potential risks (Brenner and Hall, 2007; Ivanov et al, 2012; Krille et al, 2012; Calandrino et al, 2013; Miglioretti et al, 2013; Journy et al, 2014), its validity has been widely debated in view of hypotheses underlying those extrapolations, in particular of a no-threshold relation between cancer risk and radiation exposure (Brenner and Sachs, 2006; Mothersill and Seymour, 2013; Preston et al, 2013).

Thus, recent studies have been conducted (Pearce et al, 2012; Mathews et al, 2013; Huang et al, 2014) or are underway (Krille et al, 2012; Meulepas et al, 2014) to provide direct risk estimates, from large populations exposed to CT scans. The UK study showed a risk of intracranial tumours and leukaemia three times higher in children and young adults who received mean organ doses of 50 and 60 mGy, respectively, in comparison with patients exposed to doses <5 mGy, after 7–10 years of follow-up on average (Pearce et al, 2012). The Australian study, with a mean follow-up of 9.5 years, reported excess risks of cancer at several sites, and an increase of about 20% in the risk of all cancers, compared with individuals not exposed to CT scans (Mathews et al, 2013). Finally, the Taiwan study suggested a risk of brain tumours in children and adolescents who had head CT scans 2.6 times higher than among unexposed individuals, after 8 years of follow-up (Huang et al, 2014). The leukaemia results were consistent with those expected by extrapolation from previous epidemiological results at higher doses (Hall and Brenner, 2012). However, the risk estimates for tumours of the central nervous system (CNS) were substantially higher than those estimated per unit of dose from moderate- and high-dose studies. The interpretation of these recent results is nevertheless limited by the lack of information about the reasons for scans (UNSCEAR, 2013; Walsh et al, 2014). Overestimates could easily have resulted if these examinations were performed either because of suspected cancer (reverse causation) or for diagnosis or monitoring of conditions themselves related to increased cancer risk (confounding bias). In the absence of information about the indication for the examination, delaying the estimation of cancer incidence beyond various periods of exclusion is one way to assess the consistency of the results when the probability of reverse causation is reduced. The only way to address the confounding bias, however, is to collect data about predisposing factors (PFs) to cancer, such as genetic syndromes and immune deficiencies.

A French retrospective cohort study ('Cohorte Enfant Scanner') is currently assessing cancer risks after CT scans during childhood (Bernier et al, 2012b). To obtain estimates of radiation-related risks not biased by potential confounding factors, it is identifying major PFs among the exposed children. This paper presents preliminary estimates of the risks of CNS cancers, leukaemia and lymphoma, and examines both the possibility of reverse causation and the effect of some genetic defects and other cancer-predisposing conditions on the assessment of the risks attributable to CT scans.

SUBJECTS AND METHODS

Inclusion of children. The cohort includes children born after 1 January 1995 who had a first CT scan before the age of 10 years from 1 January 2000 to 31 December 2010, and had no cancer diagnosis at the first scan. Scans took place in 21 French university hospitals—corresponding to 23 radiology departments with a high volume of paediatric patients—throughout the country, including one in an overseas district. Patients living outside the territory covered by the French national registry of childhood cancers (Registre National des Cancers de l'Enfant (RNCE)) (or who had a CT scan in the overseas department before 2004), even for a limited period, were excluded to ensure correct identification of cancer diagnoses.

Data on CT exposure. Information about exposures to CT scans was retrieved through the electronic radiology information system (RIS) of each department. In one hospital, that information was collected, however, from the hospital discharge database of the Programme de Médicalisation des Systèmes d'Information Médicale (PMSI), which also furnished information for another facility to complete the exposure data for the last year of follow-up. Data were also extracted from the Picture Archiving and Communication System of a third hospital, which had not stored RIS data for the entire study period; agreement between the two sources of information was good for the 4 years of overlap. The following data were collected: patient identifiers, sex, birth date, postal code of birth place, postal code of residence (92% complete), date and type of examination (anatomical area explored, number of sequences of image acquisition for each body part). Linkage of patient identifiers through the different sources of information enabled identification of children who were examined in several departments.

Follow-up. The children were followed from the date of their first CT scan until their exit date, which was the earliest of 31 December 2011, death, first cancer diagnosis, or their 15th birthday. Those whose exit date came before the end of the exclusion period were thus removed from the analyses. Vital status was obtained by linkage with the national registry for the identification of individuals (Registre National d'Identification des Personnes Physiques (RNIPP)).

Case ascertainment. The RNCE has recorded all diagnoses of haematological malignancies, including lymphomas, since 1990, and of solid tumours (all malignancies as well as some borderline/benign tumours, especially of the CNS) since 2000, for the residents of metropolitan (European) France younger than 15 years (Lacour et al, 2010). Linkage with the RNCE enabled us to find diagnoses preceding the first CT scan (to exclude those children) and all incident cases to 31 December 2011. Patients with only a diagnosis of a second tumour recorded in the registry were systematically excluded from the study. For the children living in the overseas department, who were not covered by the national registry, cancer diagnoses were retrieved through the PMSI of the hospital (the only oncology department in the area; some data were available from 1995, with coverage exhaustive starting in 2004), each confirmed afterwards by checking the patients' medical records. Most of the cancer diagnoses for children who lived in this district were nevertheless registered in the RNCE after they were transferred to a hospital in metropolitan France for diagnostic confirmation and/or cancer treatment. Cases of cancer were defined as malignant diseases or CNS tumours regardless of the histology. Topography codes 70–71, 722–729, 751–753 of the International Classification of Diseases (ICD) for Oncology—3rd revision-defined CNS tumours; the morphology codes used for leukaemia (including myelodysplasia) and lymphoma are detailed in Supplementary Table 1. The RNCE also provided the time to diagnosis, defined as the time from the onset of the first symptoms reported by the parents and the date of diagnosis (histological confirmation) (Dang-Tan and Franco, 2007).

Identification of PFs. The list of syndromes or diseases predisposing children to CNS cancer, leukaemia, and lymphoma (Table 1) was determined by experts in paediatric oncology after a literature review. The PF of interest were retrieved among

Table 1. Predisposing factors for CNS cancer, leukaemia, and lymphoma identified by diagnoses in hospital discharge databases and their frequency in 67 274 children included in the cohort

	Predisposing factor for cancer				Frequency in the cohort	
	CNS tumours	Leukaemia	Lymphoma	ICD-10 codes	No children	(Per 1000)
Genetic defects						
Familial adenomatous polyposis	X			D12.6	20	(0.3)
Retinocytoma	X			D31	62	(0.9)
Multiple endocrine neoplasia (MEN1, MEN2)	X			D44.8	3	(<0.1)
Fanconi anaemia[a]		X		D61.0	63	(0.9)
Ataxia telangiectasia[a]		X	X	G11.3	8	(0.1)
Xeroderma pigmentosum	X	X		Q82.1	10	(0.1)
Bloom syndrome		X	X	Q82.8	30	(0.4)
Neurofibromatosis (NF1, NF2)	X			Q85.0	106	(1.6)
Other phacomatoses	X			Q85.1–Q85.9	192	(2.9)
Noonan syndrome		X		Q87.1	94	(1.4)
Down syndrome		X		Q90	202	(3.0)
Klinefelter syndrome			X	Q98	15	(0.2)
Immune deficiencies						
HIV/AIDS			X	B20–B24, R75, Z21 F02.4, O98.7	245	(3.6)
Severe combined immune deficiency (SCID)		X	X	D81.0–D81.2	64	(1.0)
Wiskott-Aldrich syndrome		X	X	D82.0	17	(0.3)
Common variable immune deficiency (CVID)		X	X	D83	57	(0.8)
Transplantation		X	X	N16.5, T86 Y83.0, Z94	749	(11.1)

Abbreviations: AIDS = acquired immunodeficiency syndrome; CNS = central nervous system; HIV = human immunodeficiency virus; ICD-10 = International Classification of Diseases—10th revision.
[a]Genetic variant known to increase radiation sensitivity.

children hospitalised at least once in the hospitals involved in the study, from discharge diagnoses (coded according to ICD—10th revision) recorded in the hospitals' PMSI (discharge database). Those diagnoses were collected regardless of the date of hospitalisation or the performance of any radiology examination at that time. The use of discharge diagnoses to identify PF has previously been assessed (Bernier et al, 2012a). Diagnoses in the RNCE with morphology codes 9384/1 (topography code 692) and 9540/1 (all sites) were also considered to identify, respectively, children with retinocytoma and neurofibromatosis.

Assessment of organ doses. Dose reconstruction was based on the radiological protocols defined by each department—941 protocols for the most common procedures defining image-acquisition parameters for several patient age (or weight) categories. Effective, brain and red bone marrow (RBM) doses were estimated using a dosimetry method, where a series of computational human phantoms were coupled with a reference CT scanner model simulated within a Monte Carlo transport code, MCNPX2.7 (Lee et al, 2012). The dosimetry method was experimentally validated using paediatric and adult physical phantoms (Long et al, 2013). Estimated organ doses are based on an original library of anatomically realistic computational reference phantoms for: newborns, and 1-, 5- and 10-year-olds (Lee et al, 2010), and interpolated for intermediate ages at examination. For all protocols, the scan ranges were standardised over each phantom. Doses from scans of the limbs and shoulders were set at 0; those from scans of the femur were considered equal to doses for the pelvic region. When no protocol was available in the department for a specific procedure, the median dose values estimated for the other departments using the same CT machine were applied; if not available, the median dose values for the other single-detector CT or multi-detector CT machines were assigned. Because very few protocols were available for spine and cervical region scans, median doses for all machines were used. Overall, for 86.8% of the examinations, the doses were estimated according to the specific protocol used at examination.

Data analysis. Analyses were restricted to the cancer sites for which we considered the number of incident cases as sufficient, that is, CNS cancer, leukaemia, and lymphoma. Potential risks of cancer were assessed, first, according to the presence of PF and, then, according to cumulative CT X-ray doses to the brain (for CNS cancer) and to the RBM (for leukaemia and lymphoma). The RBM dose here was considered as a surrogate for exposure to various haematopoietic tissues. For CNS tumours, the dose–response analysis was conducted for two end points: the diagnosis confirmed by histology (the primary end point), and the onset of first signs or symptoms of cancer (the secondary end point). The second criterion ensures that the estimated cumulative doses did not result from CT scans performed for a suspected tumour diagnosed later. For haematopoietic tumours, frequent missing data on time to diagnosis prevented the performance of secondary analyses; only the primary end point was considered.

Relative risks (RRs) for PF were estimated by Poisson models (Breslow and Day, 1987) adjusted for the following covariates: sex, period of birth (1995–2001, 2002–2010), attained age (in years), and time since entry into the cohort (in years). Excess RRs (ERRs) per unit of cumulative organ dose were also estimated with Poisson models, where the background risk of cancer incidence (without exposure to CT scans) was described by the same covariates and the presence of any PF (yes/no) (or the presence of a specific PF in further analyses) (see Supplementary Table 2 for detailed risk models). To investigate the possibility that children were scanned because of a suspected cancer diagnosed later, exclusion periods—during which cancer incidence was not counted—and cumulative dose lagging of, both, 1–4 years were applied. For the analysis of the secondary end point (the onset of first symptoms of CNS tumours), the exclusion period and dose lagging were both set at 1 year. To assess the consistency of the principal results in relation to the ascertainment of cases, sensitivity analyses were conducted by removing children born before 1 January 2000, with at least one CT scan in the overseas district or without any residential data.

Risk estimates were computed by the maximum likelihood method; the confidence intervals (CIs) of the RRs were determined from the likelihood profiles (LPs). For ERR estimates, (left biased)

Wald CIs are presented here because of usual computational problems in defining LP-based CIs when the number of cases and the potential excess risk are small. We used SAS software (SAS Institute, Cary, NC, USA, Version 9.2) to build data sets with exact computation of person-years (PY) and Epicure software (HiroSoft International Corporation, Seattle, WA, USA, Version 1.4, module AMFIT) (Preston *et al*, 1993) to perform risk analyses.

RESULTS

Study population. Among children eligible for the study and traced in the RNIPP, 1.5% were excluded because missing information on the body part scanned at all examinations prevented dose estimation, and 13.4% because their follow-up did not exceed 1 year. After these prior exclusions, 67 274, 58 620, 50 134, and 41 926 children were included for analyses with exclusion periods of, respectively, 1, 2, 3, and 4 years. Girls accounted for 42.9% of all included children. In the overall study population, 366 (0.5%) patients were identified as at risk of CNS cancer, 1162 (1.7%) at risk of leukaemia, and 1091 (1.6%) at risk of lymphoma. Detailed frequencies are given in Table 1. The overall duration of follow-up was 4.4 years in average (median: 4.1 years); it did not substantially differ according to the presence of PF (Table 2). The annual mortality rate was 128 per 100 000 children

with no PF but substantially higher for the children predisposed to CNS tumours (252 per 100 000 PY), leukaemia (1543 per 100 000 PY) or lymphoma (1259 per 100 000 PY).

Computed tomography scan exposures according to PFs. Depending on the exclusion period, the analyses considered 93 640 (1 year), 81 261 (2 years), 68 847 (3 years), and 57 057 (4 years) CT scans. The examinations were of the brain/skull (56.9%), chest (23.1%), sinus and/or middle ear (11.7%), abdomen and/or pelvis (9.1%), cervical region (3.0%), limbs (1.7%), and spine (1.4%) (one CT scan could have explored several body parts). For the overall study period (1-year exclusion), children were exposed to median doses of 18.3 mGy to the brain and 6.9 mGy to the RBM (Table 2). Overall 32.3 and 40.5%, respectively, received cumulative tissue doses to the brain and the RBM < 5 mGy, whereas 2.1 and 0.2%, respectively, were exposed to doses > 100 mGy.

Children at risk of CNS cancer received a first examination at almost the same ages as children without PF (3.2 years *vs* 3.4 in average) but received more scans (1.8 *vs* 1.4 in average) and higher cumulative brain doses (33 mGy *vs* 23 mGy in average) (Table 2). The proportion of highly exposed children was also larger in the presence of PF; 12.0% of the patients predisposed to CNS cancer received cumulative brain doses > 95th percentile (68.0 mGy).

Children with PF for leukaemia or lymphoma were younger at the first examination (2.9 years in average) and underwent more

Table 2. Characteristics of CT scan exposures in the study population according to the presence of PFs for cancer

		Predisposing factors for cancer			
	Overall	None	CNS cancer	Leukaemia	Lymphoma
Number of children	**67 274**	**65 512**	**366**	**1162**	**1091**
Person-years	296 863	288 747	1585	4990	5402
Mean follow-up in years (s.d.)	4.4 (2.9)	4.4 (2.9)	4.3 (2.8)	4.3 (2.8)	5.0 (2.9)
Mean age at the 1st CT scan in years (s.d.)	3.4 (2.9)	3.4 (2.9)	3.2 (2.9)	2.9 (2.7)	2.9 (2.7)
Age at the 1st CT scan (%)					
<1 month	6.0	6.0	6.0	3.3	5.0
⩾1 month—<1 year	24.8	24.6	29.2	31.4	29.0
1–4 years	40.1	40.1	37.2	42.5	42.7
5–9 years	29.1	29.3	27.6	22.8	23.3
Total number of CT scans					
Mean (s.d.)	1.4 (1.2)	1.4 (1.2)	1.8 (1.9)	2.4 (2.6)	2.5 (2.7)
Median	1.0	1.0	1.0	2.0	2.0
Cumulative effective dose (mSv)[a]					
Mean (s.d.)	4.1 (5.2)	3.9 (4.8)	5.7 (6.6)	10.0 (14.5)	10.6 (14.9)
Median	2.6	2.6	3.1	5.8	6.2
Cumulative brain dose (mGy)					
Mean (s.d.)	23.1 (31.8)	23.2 (31.5)	33.0 (51.3)	18.7 (40.5)	19.7 (37.8)
Median	18.3	18.6	22.4	0.9	1.6
Cumulative RBM dose (mGy)					
Mean (s.d.)	8.9 (10.7)	8.8 (10.5)	12.5 (16.5)	10.4 (15.4)	10.9 (14.6)
Median	6.9	6.9	8.4	5.8	6.2
Number of CT scans	**93 640**	**89 722**	**672**	**2822**	**2747**
Anatomical region explored (%)[b]					
Brain/skull	56.9	57.9	63.8	23.8	25.4
Sinus and/or middle ear	11.7	11.8	10.3	8.8	8.0
Cervical region (except spine)	3.0	3.0	3.0	2.7	2.5
Chest	23.1	22.5	15.6	44.1	43.2
Abdomen and/or pelvis	9.1	8.2	13.2	37.8	38.8
Spine	1.4	1.4	1.6	1.0	0.7
Limbs	1.7	1.7	1.6	0.9	0.8

Abbreviations: CNS = central nervous system; CT = computed tomography; RBM = red bone marrow. The categories of predisposing factors (defined for each specific site of cancer) are not exclusive, as children may be at risk of cancer at several sites. The results are given for an exclusion period of 1 year.
[a]Conversion factors from the ICRP 103.
[b]Each single CT scan could have explored several body parts.

scans (2.5 in average) than patients without PF (Table 2). They were mainly exposed for scanning of the thoracic or the abdominal region (43.6 vs 22.4% of the CT scans performed in patients without PF or having PF for CNS tumours only) resulting in the highest effective doses. Despite of the total number of scans, patients with PF for leukaemia or lymphoma received similar cumulative RBM doses than patients without PF due to a lower proportion of head scans. The patterns of CT exposures varied, however, according to each PF (Supplementary Table 3).

Cancer incidence and risks associated with PFs. During the overall study period, 106 children were diagnosed with a primary tumour, including 27 with CNS cancer (of which 14 malignant diseases), 25 with leukaemia, and 21 with lymphoma. Supplementary Table 4 details the incidence of CNS cancer, leukaemia, and lymphoma by histological subgroups for various exclusion periods. Other incident cases were neuroblastoma ($n = 8$), kidney tumours ($n = 8$), liver tumours ($n = 3$), retinoblastoma ($n = 2$), and tumours of other sites ($n = 12$). Incidence rates (IRs) of CNS cancer (about 9–10 per 100,000 PY) did not vary substantially with the exclusion period; for leukaemia, however, IR decreased from 8.4 to 5.3 per 100 000 PY, and for lymphoma, it increased from 7.1–9.0 per 100 000 PY, for 1–4 years of exclusion

(Supplementary Table 4). Median time from first symptoms to diagnosis of CNS cancer was 8 weeks but varied depending on the histology (Table 3). It exceeded 1 year for 9 (34.6%) children and 3 years for 4 (15.4%) (the time to diagnosis was unknown for one case). On the basis of a 2-year exclusion period, the RRs were 86.8 (95% CI 33.1–205.9) for CNS cancer, 24.2 (95% CI 7.7–65.2) for leukaemia, and 31.7 (95% CI 13.9–68.4) for lymphoma in patients with PF compared with children without them (Table 4).

Computed tomography scans-related risks of cancer. For all the outcomes, the adjustment for PF lowered the estimates of ERR associated with the cumulative organ doses from CT scans (Table 5). The adjustment for each single PF led to different estimates of the ERR per mGy.

For an exclusion period of 2 years after the first CT scan and adjusting for all PFs, the ERR per mGy was 0.012 (95% CI − 0.013 to 0.037) for CNS cancer, 0.047 (95% CI − 0.065 to 0.159) for leukaemia, and 0.008 (95% CI − 0.057 to 0.073) for lymphoma. Although a dose–response trend was suggested for the risk of CNS cancer (but not for haematopoietic cancers) (Supplementary Table 5), no significant effect was actually observed.

For haematopoietic tumours, the ERR increased with the exclusion period (Table 6). Inversely, for CNS cancer, the ERR tended towards 0 when the exclusion period was 3 years or longer. The adjusted ERR of CNS cancer per mGy up to the onset of the first symptoms (the secondary end point), that is, 0.007 (95% CI − 0.017 to 0.032), was lower than the estimate for the primary end point with a 2-year exclusion period, even after adjusting for PF (Table 5). The modifying effects of characteristics at exposure, attained age, and time since examination on the estimates of ERR (for the primary end points) are presented in Supplementary Table 6. Supplementary Table 7 reports the results of the sensitivity analyses.

DISCUSSION

This paper reports the frequency of different PF in children who underwent CT scans in France and examines the impact of those predisposing conditions on preliminary estimates of radiation-related risks in the *Cohorte Enfant Scanner*. In this population, 0.5, 1.7, and 1.6% of children, respectively, had medical conditions known to predispose them to CNS cancer, leukaemia, and lymphoma. Subsequently to RRs of 87 (95% CI 33–206) (CNS

Table 3. Time from first symptoms to diagnosis of tumours of the CNS

	Number of cases	Time to diagnosis (weeks)	
		Median	Value for each case
Overall	27	8	
Pilocytic astrocytoma	2	35	5, 64
Other astrocytic and oligodendroglial tumours	5	3	1, 1, 4, 8, NA*
Neuronal and mixed neuronal-glial tumours	4	65	30, 65, 67, NA*
Medulloblastoma	7	4	1, 2, 4, 4, 8, 17, NA
Meningioma	2	92	27, 156
Other	7	25	2, 4, 13, 36, 104, 260, NA*

Abbreviations: NA = not available. NA* = not exactly known but > 156 weeks.

Table 4. Number of cases (N) of primary CNS tumours of the CNS, leukaemia, and lymphoma, incidence rates (IRs) per 100 000 PY, and relative risks (RRs) of cancers associated with PFs

Predisposing factors	CNS cancer				Leukaemia				Lymphoma			
	N	IR	RR	(95% CI)	N	IR	RR	(95% CI)	N	IR	RR	(95% CI)
None	15	6	1	Reference	12	5	1	Reference	12	5	1	Reference
All specific PF	7	566	86.8	(33.1; 205.9)	5	128	24.2	(7.7; 65.2)	7	160	31.7	(13.9; 68.4)
NF1, NF2	5	1389	206.0	(67.2; 526.8)	NA				NA			
Other phacomatoses	3	493	59.2	(13.9; 174.2)	NA				NA			
Retinocytoma	1	448	45.8	(2.5; 219.9)	NA				NA			
Down syndrome	NA				1	175	24.4	(1.3; 120.5)	NA			
CVID, SVID	NA				1	252	36.9	(2.0; 181.2)	0	0	0.0	—
Transplantation	NA				4	152	26.8	(7.5; 75.8)	5	190	31.4	(10.1; 82.3)
Ataxia telangiectasia	NA				0	0	0.0	—	2	5717	597.1	(91.7; 2241)

Abbreviations: 95% CI = likelihood profile-based 95% confidence intervals; CNS = central nervous system; CVID = common variable immune deficiency; IR = incidence rate per 100 000 person-years; NA = not applicable (the disease does not particularly predispose the affected individuals to cancer at that site); NF1, NF2 = neurofibromatosis type 1, type 2; PF = factors predisposing specifically to cancer at that site; RR = relative risk; SVID = severe combined immune deficiency. RRs are estimated by Poisson models (maximum likelihood estimates) adjusted for gender, period of birth (1995–2001, 2002–2010), attained age (in years), and time since entry into the cohort (in years). The results are given for an exclusion period of 2 years. No cancer was diagnosed in the patients affected by the other predisposing factors considered in the study.

Table 5. Excess relative risks (ERRs) of CNS tumour, leukaemia, and lymphoma related to cumulative organ doses in mGy, adjusted or not for the presence of PFs for cancer for the primary and secondary end points

	CNS cancer		Leukaemia		Lymphoma	
	ERR	(95% CI)	ERR	(95% CI)	ERR	(95% CI)
Primary end point (2-year exclusion period)						
Not adjusted for any PF	0.022	(−0.016; 0.061)	0.057	(−0.079; 0.193)	0.018	(−0.068; 0.104)
Adjusted for all specific PF	0.012	(−0.013; 0.037)	0.047	(−0.065; 0.159)	0.008	(−0.057; 0.073)
Adjusted for one specific PF						
NF1, NF2	0.019	(−0.016; 0.053)	NA		NA	
Other phacomatoses	0.014	(−0.015; 0.042)	NA		NA	
Retinocytoma	0.020	(−0.016; 0.057)	NA		NA	
Down syndrome	NA		0.068	(−0.087; 0.222)	NC	
CVID, SVID	NA		0.054	(−0.076; 0.184)	NC	
Transplantation	NA		0.045	(−0.065; 0.155)	0.008	(−0.057; 0.073)
Ataxia telangiectasia	NA		NA		−0.010	(−0.035; 0.014)
Secondary end point						
Not adjusted for any PF	0.015	(−0.022; 0.052)	Not available		Not available	
Adjusted for all specific PF	0.007	(−0.017; 0.032)				

Abbreviations: 95% CI = Wald-based 95% confidence intervals; CNS = central nervous system; CVID = common variable immune deficiency; NA = not applicable (the disease does not particularly predispose the affected individuals to cancer at that site); NC = not computed (no cancer was diagnosed in patients with that PF); NF1, NF2 = neurofibromatosis type 1, type 2; PF = factors predisposing specifically to cancer at that site; SVID = severe combined immune deficiency. 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. No sufficient cases allowed providing risk estimates for other predisposing factors considered in the study. For the primary end points, the results are given for a 2-year exclusion period; for the secondary end point, the exclusion period is 1 year. The analysis for the secondary end point is performed from 296 831 persons-years and 21 cases of CNS tumours (one case with a missing time to diagnosis was removed).

Table 6. Number of cases (N) and excess relative risks (ERRs) of primary tumours of the CNS, leukaemia, and lymphoma related to cumulative organ doses in mGy, adjusted for the presence of PFs for specific cancers, for exclusion periods of 1, 2, 3, and 4 years

	1			2			3			4		
Exclusion period (years)	N	ERR	(95% CI)	N	ERR	(95% CI)	N	ERR	(95% CI)	N	ERR	(95% CI)
CNS cancer	27	0.017	(−0.010; 0.044)	22	0.012	(−0.013; 0.037)	17	0.000	(−0.014; 0.014)	13	−0.004	(−0.011; 0.001)
Leukaemia	25	0.014	(−0.037; 0.065)	17	0.047	(−0.065; 0.159)	12	0.056	(−0.101; 0.214)	7	0.510	(−2.129; 3.149)
Lymphoma	21	−0.002	(−0.050; 0.046)	19	0.008	(−0.057; 0.073)	14	0.062	(−0.102; 0.227)	12	0.048	(−0.108; 0.205)

Abbreviations: CNS = central nervous system; 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), and the presence of PF (yes/no).

cancer), 24 (95% CI 8–65) (leukaemia), and 32 (95% CI 14–68) (lymphoma), children with PF accounted for 32% of all tumours diagnosed during the study period (Table 4). Specific patterns of CT exposures were observed according to the PFs. In particular, children with PF for hematopoietic tumours received a first examination at younger ages than children with no PF, and those predisposed to CNS tumours received higher cumulative brain doses. These results confirm the need to consider the existence of these PF in estimating the cancer risks potentially induced by CT scans. Indeed, the preliminary estimates of ERR associated with CT exposures were reduced by 17–56% (based on a 2-year exclusion period), depending on the site of cancer, after adjusting the risk estimates for PF (Table 5).

Adjusted ERR per mGy was 0.012 (95% CI − 0.013 to 0.037) for CNS cancer, 0.047 (95% CI − 0.065 to 0.159) for leukaemia, and 0.008 (95% CI − 0.057 to 0.073) for lymphoma at the end of a median follow-up of 4 years (median attained age = 9 years, 2-year exclusion period) (Table 5). Extending the exclusion period beyond 2 years substantially reduced the risk estimates of CNS cancer, a finding suggesting that an indication bias persists even after adjustment for PF. A mean duration of follow-up of 4 years was nevertheless too short to provide any conclusive results about radiation-induced risks in the study. Indeed, a long latency period (at least 5 years) is usually assumed for radiation-induced CNS cancer, and excess risk of leukaemia may be expressed > 25 years after exposure (UNSCEAR, 2013). For hematopoietic tumours, the estimates were also limited by the small range of cumulative RBM doses. In addition, the interpretation of the lymphoma results remains uncertain as inconsistent estimates were obtained in the sensitivity analyses (Supplementary Table 7).

The ERR estimated here for leukaemia, without any adjustment for PF (Table 5), appears compatible with the estimates from the UK study (Pearce et al, 2012) for children under 10 years of age at the first scan. Our results for CNS cancer are also very similar to those obtained from the Australian study with a 1-year exclusion period (Mathews et al, 2013). Here, however, the excess risks diminished markedly as the exclusion period increased, resulting in estimates much lower than those published from the UK study after a 5-year exclusion period (Pearce et al, 2012). The excess risk of lymphoma is compatible with the most recent findings for survivors of the Hiroshima and Nagasaki atom bombs (ERR per mGy for non-Hodgkin lymphoma (NHL) was > 0.02 in men when attained age at exposure was < 25 years (Hsu et al, 2013)). The increased risk among boys observed in our study (Supplementary Table 6) is also consistent with all previous estimations, although there is little evidence so far that NHL may be radiation induced, and none for Hodgkin disease (UNSCEAR, 2013).

This study made it possible to assess for the first time the cancer risks associated with exposures to CT scans while taking into

account major PF, including rare genetic defects and acquired immune deficiencies. The results emphasise that these factors affected the estimation of radiation-related risks during the first years after childhood CT scans. Adjusting the analyses for only one single-risk factor showed that none of them alone explained the decrease in ERRs. Conditions other than principal risk factors such as NF1 and Down syndrome should be therefore considered, although they were rarer. Furthermore, the results may suggest a lower radiation-related risk in children with PF (Supplementary Table 6). The very small cases observed in each group of PF prevent nevertheless the interpretation of a potential modification of effect in the current study. In addition, a similar pattern observed for each outcome associated with various PF may not support a potential biological effect. Finally, quantifying the effect of adjustment of the estimated excess risk should provide useful information to support the interpretation of results from studies without medical diagnoses or history. It should, however, be noted that the indication bias is likely to be less important among populations exposed at older ages than it is here, or when the duration of follow-up would be increased. There would be indeed a lower prevalence of PF in such populations and a more frequent use of CT scans for other reasons than PF.

Reverse causation may have biased the estimates of excess risk of CNS cancer from CT scans. The decrease in the ERR as the exclusion period increased (Table 6) and for time since first examination > 5 years (Supplementary Table 6) suggests that the excess risk was due to situations where signs of cancer initiation ultimately explained, rather than followed, the use of CT scans. Nonetheless, no such trends were observed for leukaemia or lymphoma when the exclusion period was extended. A major issue in the interpretation of results of studies of CT scans is therefore to be able to provide risk estimates that are not affected by the scans performed due to cancers only diagnosed later (UNSCEAR, 2013; Walsh *et al*, 2014). As observed here, numerous studies have reported short mean times from symptom onset to diagnosis of CNS tumours (except for ganglioglioma), as short as 4–20 weeks depending on histology (Brasme *et al*, 2012). However, the time to diagnosis may exceed several years; for instance, 15% of the cases reported here had a time to diagnosis > 3 years. After removing CT exposures after the date of the first symptoms, the ERR per mGy (adjusted for PF) of CNS tumours was 0.007 (95% CI − 0.013 to 0.028), which suggests that a 2-year exclusion period would not be sufficient for estimating unbiased radiation-induced risk. This estimate is consistent with the excess risk found for the Hiroshima and Nagasaki survivors exposed before the age of 15 years (ERR mGy-1 = 0.003 (95% CI 0.001–0.007) through the age of 50 years, according to the data used in (Preston *et al*, 2007), especially when considering the decrease in excess risk with attained age (Preston *et al*, 2002). Analyses restricted to exposures before the onset of first symptoms may thus provide estimates free of indication bias and thus help to determine appropriate exclusion periods to compensate for the unavailability of data about the indication of examinations.

Here, we devoted substantial effort to the estimation of the cumulative organ doses using > 900 radiology protocols from the participating departments. The risk estimation is thus based on detailed French practices in paediatrics and reflects their variability over time among 23 radiology departments. From those protocols, organ dose were estimated using a CT dosimetry method based on Monte Carlo radiation transport (Lee *et al*, 2012), which is reported to provide more accurate estimations than older numerical tools, as the body contour and internal anatomy of patients are described by realistic paediatric phantoms (Lee *et al*, 2010). Dose estimation is thus thought to be as accurate as possible, although the technical parameters actually used at each image acquisition may vary from the protocol. Note that doses may have been reduced since the early 2000s, thanks to technological advances in CT and better optimisation of procedures. Uncertainties in exposure assessment remain, however, because of missing doses for CT examinations with unknown anatomical areas (3.4% of all examinations in the participating departments), their performance in radiology departments not involved in the study, or because of incomplete storage of radiology data. In addition, assessment of the cohort's exposure to other diagnostic examinations was not possible. A previous study showed, however, that CT accounted for 83% of the dose from all diagnostic examinations of children exposed to CT scans in France (Etard *et al*, 2014). Although undefined doses would account for only a limited proportion of the total exposure from diagnostic procedures, we cannot rule out their possible effect on risk estimates. Sensitivity analyses show that a bias in risk estimation due to under-ascertainment of cases is unlikely (Supplementary Table 7).

Overall, the results reported here showed that studies estimating cancer risks after CT scans should consider the reason for these examinations to obtain convincing risk estimates. By extending the follow-up, the *Cohorte Enfant Scanner* should be able to provide more robust risk estimates in the future and to investigate whether a confounding bias related to the PFs persists at older ages. This cohort, as well as the UK study mentioned above, is participating in the Epi-CT collaborative project that includes nine national cohorts intended to obtain powerful results about cancer risks after CT scans and aims at enhancing strategies to optimise CT procedures. The Epi-CT project is focusing especially on exposure assessment and consideration of the uncertainties in dose estimation for risk analyses (Thierry-Chef *et al*, 2013). Valuable information (although for higher exposure levels) could also be obtained by studies on interventional procedures that use X-rays to treat benign conditions, especially as the indication for treatment is generally known with precision (Baysson *et al*, 2013). In clinical practice, all of those results should help to determine the situations in which the expected benefits do not outweigh the risks and clarify the information given to patients and parents. So far, no evidence has invalidated the risk predictions extrapolated from studies at high doses under the linear dose–response assumption. The promotion of the optimisation of CT procedures and the use, as often as possible, of non-irradiating techniques such as magnetic resonance imaging must continue, especially in paediatrics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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