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Report on results of dose-response analyses from case-control study

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1. Introduction

To better understand the magnitude of the actual health risk that might be associated with low-dose diagnostic ionising radiation (IR) exposure from CT examinations in paediatric and adolescent patients, epidemiological and modelling investigations have been conducted and have suggested increased risk of haematological malignancies and brain cancers, following cumulative low-dose CT exposure (1–6). In 2011, the EPI-CT cohort was set up with the objective to explore these associations in a large-scale (nearly 1 Million patients) multi-national cohort and improve the direct estimation of radiation-related cancer risk (7). A major focus of the study was the improvement of the estimation of individual doses from CT scanning, using detailed information on the characteristics of each scan received by the study subjects collected from all participating radiology departments (8). The first follow-up of the EPI-CT cohort has confirmed the results of previous individual studies, demonstrating an increased risk of haematological malignancies and of brain cancers in relation to radiation dose from CT scanning. A number of possible factors may, however, bias the results of this study and cannot be elucidated in the framework of large-scale record-based cohort studies like EPI-CT as they require collection of much more detailed information from many different sources, something that is logistically not feasible in a study of nearly a million patients. The main factors include (9):

- The reason for performing the CT: in most instances radiological records contain no or little information about this. In the absence of such information, there is a potential for a bias called "reverse causation", that is counting as a risk factor a CT actually performed for the diagnosis or surveillance of a cancer. Reverse causation can, in principle, be effectively minimised in cohort studies by applying various lag periods – not taking into account scans conducted 2, 5 or more years before diagnosis and efforts have been made in the UK (10) and German cohorts (4) to review medical records to collect relevant information, but this is a logistically complex task in the framework of large cohort studies;
- Factors that may modify the risk of radiation induced cancer: if a subset of study participants are at higher risk of cancer and of undergoing a CT scan because of some underlying condition, this could lead to "confounding by indication" (11). The underlying conditions include genetic conditions such as Down syndrome, Fanconi anaemia, Neurofibromatosis and Ataxia-telangiectasia. Various efforts have been made in the UK study (12) and the French paediatric CT cohort (6) to collect information on such conditions, though it is very difficult to ensure completeness of the information, particularly over time. Results of the UK and French study, as well as a risk prediction study in the Netherlands (13) suggests that such syndromes are unlikely to substantially bias risk estimates, but further information is needed to verify this.
- Missing dosimetric information: the CT cohorts collected information about CT scans from radiological records of the participating hospitals. It is possible that study subjects received CT scans in other places; further, they may have received substantial doses from other types of procedures for which no information could be collected in the cohorts. The effect of missing doses can be varied – non-differential dose misclassification will tend to bias the risk estimates towards the null; differential misclassification, however, can lead to biases in different directions (11).

In order to improve the estimation of risk of haematological malignancies and brain tumours from radiation CT doses, therefore, a nested case-control (NCC) study was established in WP5 of MEDIRAD in the French, Spanish and Swedish EPI-CT cohorts, where contacting patients was felt feasible and in agreement with national regulation. This approach allows the collection of additional information on cases and matched controls to address the issues mentioned above and hence improve the risk estimates.

2. Methods

2.1 Objective

The overall objective of this study was to estimate haematological and brain cancers risk from medical ionising radiation exposure in a paediatric and young adult population, subjected to CT at least once before the age of 22 years (with maximum age varying between countries). The influence of potential confounding factors or individual susceptibility modifiers (such as: age at exposure, sex, family history of cancer, genetic factors, SES…) will be also investigated.

The specific objectives of the study were to:

- Conduct a case-control study of leukaemia and brain cancer nested within the French, Spanish and Swedish EPI-CT cohorts, the three largest EPI-CT cohorts in countries where it was felt is would be legally and logistically possible to contact study subjects;
- Collect necessary detailed personal and medical information through a questionnaire and from medical and radiological records, disease registries and hospital discharge databases, in particular:
    - more detailed information about diagnostic radiation exposures to improve CT dose reconstruction and estimate doses from other sources of medical ionizing radiation exposure (diagnostics, interventional cardiology, among others).
    - personal and medical information about possible confounders (socioeconomic data, other potential risk factors...)
    - information about underlying diseases and syndromes (such as: Down syndrome, ataxia telangiectasia, neurofibromatosis, immunodeficiency) thought to influence the risk of haematological and brain malignancies or the probability of undergoing a CT scan.
- Derive improved estimates of the risk of leukaemia, lymphoma and brain tumours related to radiation dose from CT scanning in childhood, adolescence and young adulthood;
- Study the impact of genetic and epigenetic variants on the risk of leukaemia, lymphoma and brain tumours following childhood and adolescent exposure to ionizing radiation from CT scans and other medical procedures (not presented here).

2.2 Study design

The study was designed as a case-control study, nested within three of the national EPI-CT cohorts of paediatric CT patients, from France, Spain and Sweden. The cohorts were defined based on the radiological records of the hospitals with the largest paediatric populations in each study region and country. Details of these cohorts are presented in Bernier et al 2018 (7) and the age-range and period of inclusion of patients and scans are shown, by country in **Table 1**.

Table 1 – Characteristics of the cohorts on which the nested case-control study was based.

Country	France	Spain	Sweden
Age range of patients at inclusion	0-9	0- 20	0-17
Dates of 1st CT scan	2000-2013	1991-2013	1977-2013
Dates of cancer incidence follow-up	2000-2016	1991-2018	1977-2014
Size of cohort[1]	119 399	31 258	44 954

[1]For logistic reasons, the nested-case control study was restricted to the sub cohorts from Catalonia and Madrid in Spain (the two autonomous communities which contributed the most patients to the Spanish study) and the Karolinska Institute in Stockholm in Sweden.

Definition of cases

Eligible cases were patients from the cohorts mentioned above with a primary diagnosis of haematological malignancy at least 2 years after their first CT or malignant brain tumour at least 5 years after their first CT. Subjects with a previous cancer or benign tumours were not eligible. Cases who have died were included (where feasible) to prevent a possible selection bias related to prognosis.

Control selection

For each case, two controls were selected from the cohort from patients who were at risk (alive and cancer-free and under follow-up) at the time of diagnosis of the case (**Figure 1**), matched with cases on sex, year of birth and region of residence. Follow-up began at the time of the first registered CT procedure in the EPI-CT cohort and a lag period of two years for haematological malignancies and five years for brain tumours was applied.

One additional control per case was included, using the same criteria and matched further on estimated dose in order to increase considerably the statistical power to test for interactions with genetic or epigenetic factors (not analysed here) (14).

Sampling was with replacement, that is additional controls were selected and approached until the required number of participating controls is reached if the initially selected controls could not be traced or refused participation. It should be noted that a control may serve as a control for more than one case, though given the size of the cohort, this is likely to be infrequent. In addition, a control from one matched set may later be found to be a case, at which point the appropriate control will be selected for the new set. For each participating control, a reference date is set as the date on which their matched case was first diagnosed with the endpoint of interest (haematological malignancy or brain tumour).

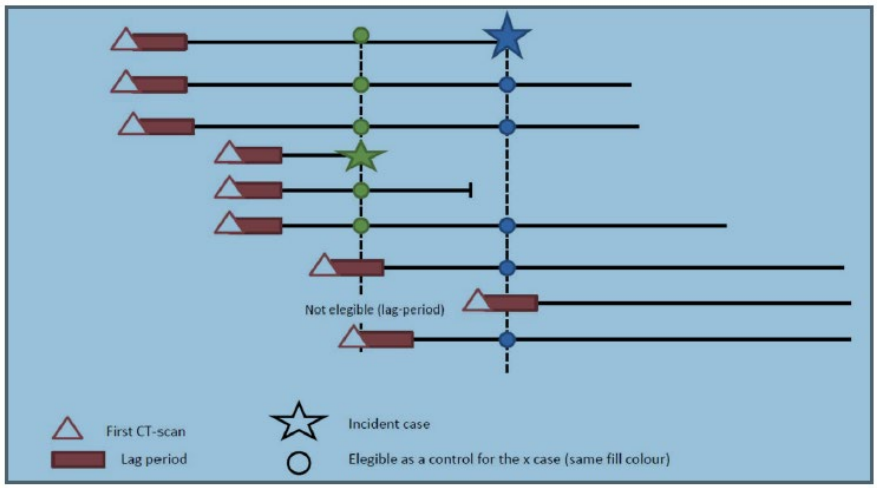

Figure 1. Example of control selection from risk set

2.3 Data collection

The study was approved by relevant ethics review authorities: Ethics Committee Parc de Salut MAR gave approval on March 1st, 2018 for the study in Spain, the approval by CNIL (France) was obtained on April 19th, 2018 and the Swedish Ethics Review Authority (Etikprövningsmyndigheten) provided approval on September 16th, 2019. The study complies with the EU General Data Protection Regulation 2016/679.

In France and Spain, participation in the study was voluntary and those agreeing signed an informed consent (IC) form. In Sweden, for logistic reasons, it was not possible to contact individual subjects and all information was obtained from radiological records, providing exhaustive information on CTs and other radiological procedures but not on other possible risk factors.

Patient contact and collection of information

Spain and France

Cases and potential controls were initially contacted by letter from IRSN (France) and the Departments of Health (Madrid, Catalonia), informed about the study and asked whether they were interested to participate. Those willing to participate (or their parents/legal guardian in the event the subject was < 18 years) signed the informed consent (Annex I) indicating which parts of the study they wished to participate in: 1) provide personal information through a questionnaire, 2) allow collection of specific information from radiological, medical records and from hospital-based and population-based registries 3) allow the study investigators to contact their general practitioner or oncologist / haematologist and 4) permit collection of information about their preconception period, in utero and early life period through a questionnaire addressed to their parents and 5) provide a biological sample (saliva). **Table 2** summarises the information collected from different sources.

Table 2 – Information to be collected for all cases and controls selected for the study.

Source of information	Type of information collected
EPI-CT cohort study database	General information such as sex, date of birth, vital status, place of residence, and information regarding cancer diagnosis.
Participant questionnaire	General information: including sex, age, socioeconomic status, present, and past residences. Individual and familial medical history, including cancer and **cancer-predisposing conditions** (see Annex II for details). Ionizing radiation exposure: including medical exposures (CTs, radiotherapy, other diagnostic procedures) and, where applicable, occupational ionizing radiation exposure. Lifestyle factors: such as smoking and alcohol drinking habits.
Parents' questionnaire	Preconception, pregnancy and early life period of the subject
Medical records	Validation of medical data (medical history, medical radiation exposure) collected through the questionnaire.

Sweden

The case-control study was nested within the sub cohort of patients from Karolinska Institute in Stockholm and information on radiological procedures was collected from radiological records at the Karolinska University Hospital, the hospital where the study subjects had their CT scans performed. Radiological Information System (RIS) and Picture Archiving System (PACS) were searched for information on radiological exams for cases and controls. The following information was collected for each individual: date of birth, sex, exam date, type of radiological exam. Examinations were grouped in the following categories: CT scans, conventional X-ray, fluoroscopic examinations, nuclear medicine, and mammography. They were grouped by time period and coded by anatomical region following the coding strategy implemented within the EPI-CT study (8). For nuclear medicine,

information on tracers was also considered as the organ doses depend on the injected activity of specific tracers.

2.4.1 Dose reconstruction

For each examination, doses delivered to the organs of interest (bone/active marrow (BM) and brain) were estimated from a large matrix of organ dose data which we built from the literature. The matrix provides a summary of reported BM or brain doses for typical radiological protocols from various time periods and age categories (8,15–29). Details on the relevant publications, strategy implemented, assumptions and doses per modality, time period and age category are provided in Deliverable 5.5. For each individual, the cumulative BM and brain doses were estimated by summing doses from all radiological procedures performed over time. Procedures performed two or five years prior to the haematological or brain cancer diagnosis (or reference date) were excluded to account for latency between exposure to IR and cancer diagnosis and ensure that exams were not taken due to a cancer suspicion.

Comparison of EPI-CT cohort CT exposure data which was extracted from archived patient information from the Radiology Information System (RIS) of Karolinska university hospital coupled with anautomatic extraction of data from the Picture Archiving and Communication System (PACS) using a dedicated software (PerMoS) (8) and CT exposure data extracted manually for cases and controls was performed to assess the impact of missed CT doses.

2.4.2 Statistical analysis

Descriptive analyses of numbers of exams, doses (to the bone marrow and brain) and age at first exposure were performed for cases (haematological and brain cancers) and controls, overall and by modality..

Conditional logistic regression was used to estimate the relative risk of haematological and brain malignancies. The dose was modelled both continuously and as a categorical variable (< 24, 25-49, and >50 mGy). Dose to the bone marrow was used for analyses of haematological malignancies risk and dose to the brain for analyses of brain cancer risk; doses were cumulative, lagged by 2 and 5 years respectively.

Possible effect modification by sex and age at first exposure (<5, 5-9, >10 years old) was tested by adding an interaction term between dose (modelled continuously) and these variables. Heterogeneity of risk by sex and by age at first exposure was tested using a likelihood ratio test.

A Spearman's correlation was also performed to assess the relationship between CT exposure and non-CT procedures which include: radiography, fluoroscopy, nuclear medicine procedures. As a sensitivity test, we determined the additional number of CT procedures and respective doses from the case-control compared to the cohort. Furthermore, a conditional logistic regression analysis was performed with and without additional CT doses.

All tests were performed using R version 1.4.1717.

3. Results

3.1 Cases ascertained

Table 3 shows the distribution of cases ascertained per country and region, as well as the current status of data collection.

Data collection is complete in Sweden and ongoing elsewhere.

In France, first contact with cases and controls was performed by mail between March and June 2019 but follow-up calls were delayed by the pandemic. Efforts to include additional cases and controls have been made in the second half of 2021.

In Spain, the start of the study was delayed significantly due to uncertainties at the level of the health authorities in applying the GDPR and then to the COVID pandemic as the Departments of Health in the Autonomous Communities of Madrid and Catalonia are responsible for making the contacts with potential study participants. Contacts started in Madrid in late 2020 and are expected to start in Catalonia in December 2021.

Given the status of data collection in France and Spain, the rest of this deliverable focuses on the results of the analysis of the nested case-control studies of haematological malignancies and of brain cancers in Sweden.

Table 3 – Data collection status at 30 October 2021

	Cases ascertained	Cases recruited	Controls recruited
Sweden			
Haematological cancers	39	39	79
Brain cancers	8	8	17
France			
Haematological cancers	36	2	2
Brain cancers	22	0	0
Spain			
Haematological cancers	84	3	3[1]
Brain cancers	25	2	1

3.2 Results of the case-control study in Sweden.

Descriptive analyses

The numbers of cases and controls for which radiological data were collected is shown in **Table 3**. For the purpose of the dose-response analyses, the controls matched on dose are excluded as overmatching on dose would bias the risk estimates (matching on dose will be used in the genetic and epigenetic analyses).

The analyses shown here are based on 39 cases of haematological malignancies and 79 controls, and 8 cases of brain cancer and their 17 matched controls.

A total of 1,629 radiological procedures were included in the current study. Because of missing information on either date of examination, modality or isotope used, doses could not be estimated for 2% of the recorded examinations. Doses were estimated for 1,583 examinations.

A description of patient and exposure characteristics can be found in **Table 4 and Appendix Table 1**. There were more males than females in the haematological malignancy analyses, while the proportions were similar for brain cancer cases. 28% of cases of haematological cases were below the age of 10 years at diagnosis compared to 12% of brain tumour cases; the percentages of cases diagnosed at ages 20 years or above were 28 and 50%, respectively.

Cases tended to be slightly younger at the time of their first radiological procedure, particularly in the brain cancer study (Table 4). The median number of radiological procedures was higher in cases than controls, both overall and for procedures other than CTs. The median dose was similar though slightly higher overall, for CTs and for other radiological procedures among cases of haematological malignancies than among their controls. It was lower among brain cancer cases than controls. Though

[1] These controls are not matched with participating cases.

some subjects had repeated CT scans (and one control had as many as 22), the median number of CTs was 1 in cases and in controls in both the haematological malignancies and brain cancer studies.

The distribution of cumulative doses was very skewed, with most subjects having received doses below 50 mGy (**Figures 2 and 3**). The median dose was higher in the brain than in the bone marrow and was mainly attributable to CT scanning. Most study subjects also underwent at least X-ray in their life (Appendix Table 1), but the doses were low, with a median dose to the brain of 0 mGy from X-rays. Few study subjects had undergone fluoroscopy or nuclear medicine procedures and the doses from these procedures were very low.

Table 4 – Characteristics of subjects and exposure **–** number of subjects and median and range of age, number of exams and doses. Doses are individual cumulative dose estimated to the red/active bone marrow dose (BM) for haematological malignancies and to the brain for brain cancers. *Number of procedures and doses are lagged by 2 years for haematological malignancies and 5 years for brain tumours.*

	Haematological cancers		Brain cancers	
	Cases	Controls	Cases	Controls
Distribution of number of study subjects				
Total	39	79	8	17
Gender				
Male	24	49	4	8
Female	15	30	4	9
Attained age				
<10	11	22	1	2
10-19	17	35	3	6
20-29	9	18	4	9
>=30	2	4	NA	NA
Age at first radiological procedures				
<5	19	36	4	4
5-9	9	16	2	8
>=10	11	27	2	5
Median and range of age at exposure, number of examinations and dose				
All procedures				
Age first exam (yrs)	5.7 (0.003-17)	6.0 (0.008-18)	5.3 (0.01-15)	8.7 (0.1-14)
Exams/patient	5 (1-43)	3 (1-24)	4.5 (1-29)	4 (1-10)
Dose (mGy)	20 (2.7-109)	16 (2.7-427)	42 (0.05-90)	46 (0.07-301)
All CTs				
Age first exam (yrs)	5.7 (0.20-17)	6.0 (0.01-18)	5.3 (0.01-15)	8.7 (0.1-14)
Exams/patient	1 (1-5)	1 (1-22)	1 (1-4)	1 (1-6)
Dose (mGy)	16 (1.4-85)	14 (1.4-426)	42 (0.05-90)	46 (0.07-301)
Other procedures				
n subjects	30	61	5	15
Age first exam (yrs)	5.3 (0.002-17)	5.5 (0.1-18)	7.5 (0.01-18)	8.8 (0.14-16)
Exams/patient	6 (1-42)	2 (1-22)	7 (1-25)	3 (1-8)
Dose (mGy)	2.5 (0-44)	1.8 (0-16)	0[2] (0-6)	0 (0-2)

[2] Note that doses to parts of the body other than the brain deliver low to 0 doses to the brain, thus the median dose to the brain for cases and controls is 0.

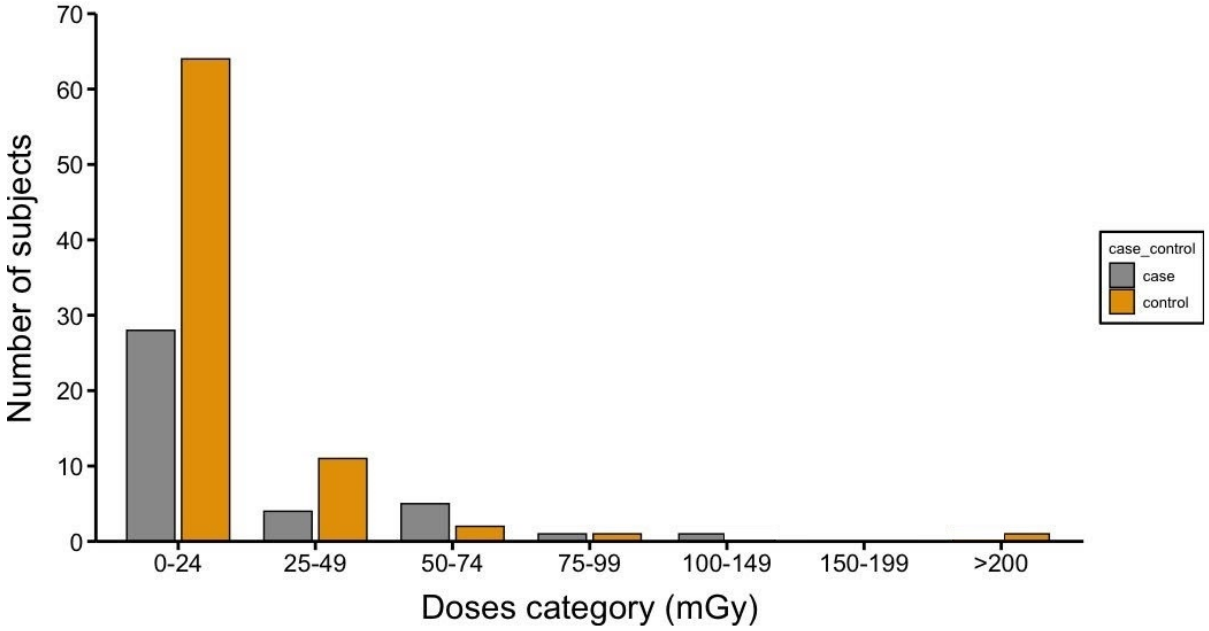

Figure 2. Distribution of dose to the bone marrow doses from all procedures (mGy)

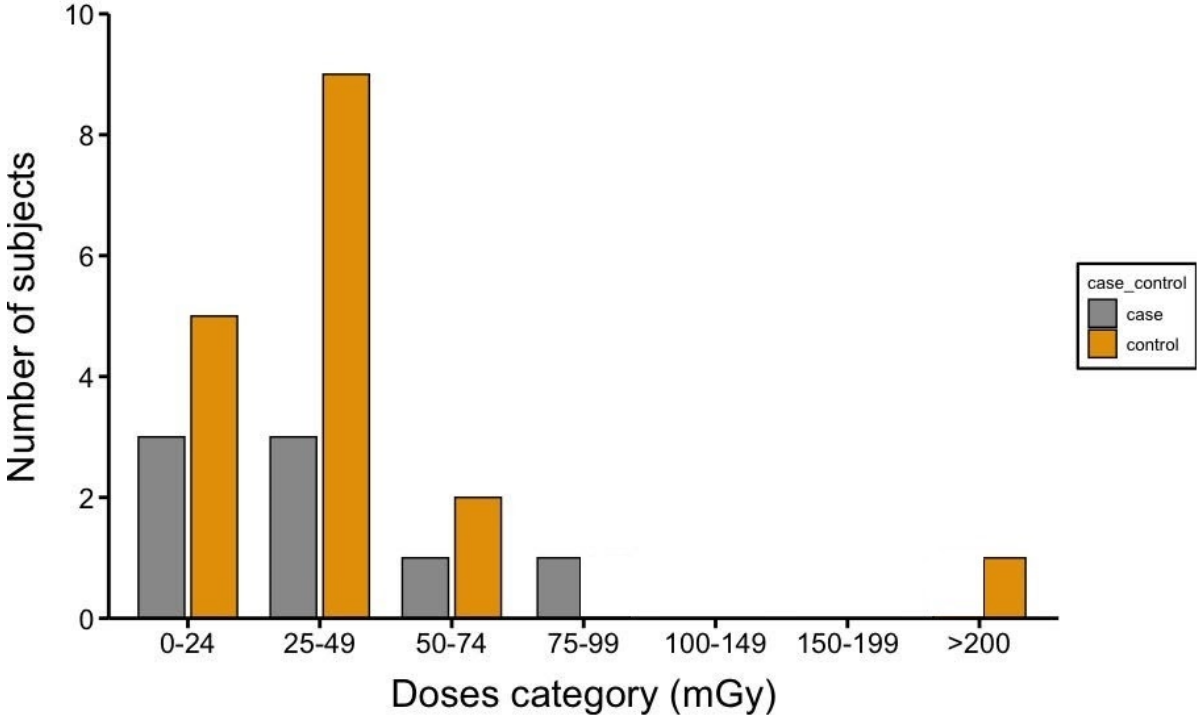

Figure 3. Distribution of dose to the brain from all procedures (mGy) among cases and controls

Analyses of risk in relation to total dose from radiological procedures

The odds ratio (OR) for haematological malignancies was estimated to be 1.25 (95% CI 0.5-2.9) for a cumulative dose at 100 mGy (**Table 5**). The risk was highest in the highest dose category (>= 50 mGy) based on 7 cases and 4 controls. There was no evidence of heterogeneity of risk by age at first exposure (p= 0.68 for interaction),

For brain cancer, there was no evidence for a dose-response relationship for brain tumours, though the OR in the 50 mGy and above category was close to 2, but not statistically significantly elevated, based on small numbers of subjects.

Table 5 – Estimated OR and 95% CI. For all radiological procedures.

Dose (mGy)	Haematological cancer			Brain cancer		
	Cases	Contr.	OR (95% CI)	Cases	Contr.	OR (95% CI)
Continuous – OR at 100 mGy	39	79	1.25 (0.5-2.9)	8	17	0.61 (0.09-4.0)
Categorical:						
<25	28	64	1	3	5	1
25-49	4	11	0.89 (0.3-3.2)	3	9	0.60 (0.1-3.2)
>= 50	7	4	4.31 (1.1-17)	2	3	1.79 (0.1-29)

Effect of missing doses

A major advantage of the nested case-control study compared to the original record linkage based cohort study conducted in EPI-CT is the feasibility of reviewing radiological records and interviewing study subjects to ascertain CTs and other radiological procedures which might have been missed in the cohort study.

Reviewing the radiological records for all cases and controls in Sweden led to the identification of 5 additional CT in 4 subjects (all controls) in the haematological malignancy study. The median bone marrow dose among these missing CTs was 16.5 mGy and the highest was 40.6 mGy.

In the brain tumour study, 3 additional CTs were found in the radiological records: 1 in a case, with a brain dose of 1 mGy and 2 in controls (brain doses respectively 1 and 100 mGy).

Review of records also allowed identification of a total of 696 other radiological procedures which had been conducted in 135 individuals.

Table 6 compares the doses of the cases and controls in both studies, estimated from the CT data available in the EPI-CT cohort study, to the doses estimated in the current nested case-control studies from all CTs and from all radiological procedures identified in the radiological records. The additional CTs found in the case-control studies had little to no effect on the median doses, though the maximum dose increased among controls both for haematological malignancies and brain cancer. Doses from radiological procedures other than CTs had no effect on brain doses but resulted in a small increase in median bone marrow dose, and an increase in the maximum dose among cases of haematological malignancies.

Table 6 – Comparison of doses (mGy) depending on radiological procedures included.

	Dose from CT scans in cohort median (range)	Dose from all CTs median (range)	Dose from all procedures median (range)
Haematological malignancy case-control study			
Cases	17 (1.4-85)	16 (1.4-85)	20 (2.7-109)
Controls	14 (1.4-386)	14 (1.4-426)	16 (2.7-427)
Brain cancer case-control study			
Cases	42 (0.05-90)	42 (0.05-90)	42 (0.05-90)
Controls	46 (0.07-201)	46 (0.07-301)	46 (0.07-301)

Missing procedures/doses from missing CTs and from other radiological examinations can only confound the association between radiation dose and risk of cancer if they are associated not only with the risk of cancer but also with the number of procedures/doses available in the cohort.

In the **haematological malignancies case-control study**, we found that the number of missing CTs was moderately correlated with the numbers of CTs in the cohort study (Spearman's correlation coefficient: 0.40, $p<0.0001$) and that the number of other radiological procedures was also correlated with the number of CTs (Spearman's correlation coefficient 0.29, $p=0.0014$). Correlation between doses were somewhat lower: 0.22 ($p= 0.014$) for the correlation between missing dose from missing CTs and dose from CTs included in the cohort study and 0.21 ($p=0.024$) for the correlation between dose from other radiological procedures and dose from CTs. **Table 7** compares the risk estimates derived in the case-control study with those which we would have obtained if we had considered only CT scans or only the CT scans identified in the cohort study.

While the risk estimates in all three analyses are statistically compatible (given the small number of cases and wide confidence intervals), we see a shift of the distribution of cases and controls towards higher dose categories when we include dose from missing CTs and, for cases, doses from other procedures, with an increased OR at 100 mGy in the continuous analysis (not statistically significant) and a higher OR in the highest dose category, possibly leading to a stronger conclusion on the risk of haematological malignancies from CT radiation. These results need to be verified using a larger sample size and the analyses will be repeated once the nested case-control study is completed in France and Spain.

Table 7 – Comparison of risk estimates for haematological malignancies depending on the procedures included.

	Main analysis - all radiological procedures			**Analysis based only on dose from CT scans**			**Analysis based only on CT scans identified in the cohort study**		
	Cases	Cont.	OR (95%CI)	Cases	Cont.	OR (95%CI)	Cases	Cont.	OR (95%CI)
Continuous @ 100 mGy	39	79	1.25 (0.5-2.9)	39	79	0.92 (0.3-2.8)	39	79	1.01 (0.3-3.1)
Categorical: Reference - < 25	28	64	1	30	67	1	31	67	1
25-49	4	11	0.89 (0.3-3.2)	3	9	0.67 (0.2-3.1)	5	10	1.12 (0.3-3.8)
>= 50	7	4	4.31(1.07-17)	6	4	3.60 (0.9, 15)	3	2	3.34 (0.5-20)

In the **brain cancer case-control study**, while we found a moderate correlation between the number of missing CTs and the numbers of CTs in the cohort study (Spearman's correlation coefficient: 0.50, $p=0.01$), there was no indication of a correlation between the number of other radiological procedures and the number of CTs (Spearman's correlation coefficient 0.04, $p=0.90$) or between doses: -0.09 ($p=$

0.70) for the correlation between missing dose from missing CTs and dose from CTs included in the cohort study and -0.07 (p=0.70) for the correlation between dose from other radiological procedures and dose from CTs.

Table 8 compares the risk estimates derived in the case-control study with those which we would have obtained if we had considered only CT scans or only the CT scans identified in the cohort study. As expected given the absence of correlation between CT dose in the cohort and either missing CT dose or dose from other radiological procedures, inclusion of these additional doses has virtually no effect on the continuous risk estimate. The impact appears to be greater for the categorical risk estimate in the highest dose category, but this is mainly due to the instability of the risk estimate in this category due to the very small number of subjects.

Table 8 – Comparison of risk estimates for brain cancer depending on the procedures included.

	Main analysis - all radiological procedures			**Analysis based only on dose from CT scans**			**Analysis based only on CT scans identified in the cohort study**		
	Cases	Cont.	OR (95%CI)	Cases	Cont.	OR (95%CI)	Cases	Cont.	OR (95%CI)
Continuous @ 100 mGy	8	17	0.61(0.09-4.0)	8	17	0.59 (0.1-4.0)	8	17	0.61 (0.1-5.9)
Categorical: Reference - < 25	3	5	1	3	5	1	3	5	1
25-49	3	9	0.60 (0.1-3.2)	3	9	0.60 (0.1-3.2)	3	10	0.58 (0.1-3.0)
>= 50	2	3	1.79 (0.1-29)	2	3	1.79 (0.1, 29)	2	2	$1e^7$ (0- inf)

4. Discussion

The implementation of the GDPR regulation in May 2018 has greatly impacted the conduct of this study in all countries, despite the careful planning of the study, mainly because of legal concerns in the participating hospitals and health departments related to the collection of personal information, even with all appropriate informed consent and security measures. These concerns, in particular in Spain, led to numerous changes to the approach for the conduct of the nested case-control studies. When the situation became clearer and approaches were agreed, the COVID-19 pandemic caused further, major delays as field work had to be stopped in all three countries, thus preventing/delaying the collection (with appropriate informed consent) of the needed information from questionnaire and medical records.

While the MEDIRAD project is now coming to an end, field work is now underway in Spain and additional cases and controls have been identified and are being contacted in France in relation to the extension of the follow-up of the French and Spanish cohorts in WP5. While numbers of subjects recruited in both countries are much too low at present to be included in the analyses, the partners are committed to continue fieldwork at own cost and to conduct the analysis of this study.

Preliminary results based on the nested case-control study in Sweden, suggest a possible relationship between the radiation dose at the bone marrow from radiological procedures and risk of haematological malignancies, though numbers of subjects are too limited to draw any firm conclusions. Importantly, we found a moderate correlation between the CT bone marrow dose estimated from the cohort study alone and dose from missing CTs as well as dose from other radiological procedures. This translates in differences in risk estimates for haematological malignancies, with a stronger dose-response relationship when all doses are taken into account in the

case-control study. If these preliminary results are confirmed in the full study including cases and controls from the three countries, this observation suggests that missing doses could confound the relationship between radiation dose and risk of haematological malignancies in the full cohort.

Numbers of brain tumour cases and controls in the study were very low and hence risk estimates are very uncertain. Caution is therefore required while interpreting our results. There is no evidence for a dose-response relationship in the continuous analyses, though an increased OR was seen in the highest dose category but based on only 2 cases and 3 controls. As expected, given the absence of correlation between the CT bone marrow dose estimated from the cohort study alone and dose from missing CTs as well as dose from other radiological procedures, the inclusion of these missing doses had little effect on the risk estimate as a function of radiation dose. While the study subjects could have received non-negligible numbers of X-rays, most of these were to parts of the body other than the brain, hence brain doses were considerably lower than doses from CT scanning.

In both the haematological malignancies and brain cancers case-control studies, very few subjects had ever undergone fluoroscopy or nuclear medicine procedures and the resulting doses from these procedures to the bone marrow and to the brain were close to zero.

Until the case-control studies in France and Spain are completed, it will not be possible to address the impact of predisposing syndromes and of genetic and epigenetic variants on the estimates of cancer risk from doses from radiological procedures.

5. Conclusions

We have successfully developed the protocols for case-control studies of haematological malignancies and brain tumours within the EPI-CT cohorts aimed at improving the estimates of risk of these malignancies from CT scanning and studying the role of factors which may modify these risks. Changes in the data protection regulations and the COVID-19 pandemic have severely delayed the conduct of these studies, however, and only the study in Sweden is complete at present and, in that study, it was not possible to collect information other than from radiological records. Work in France and Spain will continue beyond the MEDIRAD grant, however, and analyses of risk based on the data from the three countries are foreseen.

Preliminary results from Sweden suggest a possible dose-response relationship for haematological malignancies (numbers of cases and controls in the brain tumour study are too small to draw any inference) which will need to be verified in the full study.

Importantly, we found that, for bone marrow dose, there is a correlation between the CT dose estimated in the cohort and dose from missing CTs and from other radiological procedures. If confirmed, this has important implications, as it suggests that these missing doses may confound the association between CT doses and haematological cancer risk in record-based cohort studies and lead to an underestimation of risk. This appears to be less of a concern for analysis of brain tumour risks as many of the other radiological procedures deliver little to no dose to the brain.

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Appendix Table 1

Characteristics of subjects (using mean, range) exposed and associated doses for cases and matched controls. Age at first procedure is expressed in years. Doses are expressed as cumulative doses individual doses using, mean (min-max). Organ exposure includes red bone marrow for Haematological malignancies and brain for brain cancers.

	Haematological cancers		Brain cancers	
	Cases	Controls	Cases	Controls
Median and range of age at exposure, number of examinations and dose				
X-rays				
n subjects	30	61	5	15
Age first exam (yrs)	5.3 (0.2-17)	5.5 (0.008-18)	7.5 (0.01-18)	8.8 (0.1-16)
Exams/patient	5.5 (1-33)	2.0 (1-18)	7 (1-23)	2 (1-8)
Dose (mGy)	2.5 (0-29)	1.9 (0-15)	0 (0-6)	0 (0-2)
Fluoroscopy				
n subjects	10	2	1	1
Age first exam (yrs)	1.1 (0.03-14)	8.1 (0.8-15)	4.6	9.8
Exams/patient	2 (1-6)	1.5 (1-2)	2	1
Dose (mGy)	1.1 (0.2-10)	1.8 (1.0-2.5)	0	0.5
Nuclear medicine				
n subjects	7	2	0	1
Age first exam (yrs)	3.6 (0.2-18)	1.0 (0.2-1.7)	NA	9.9
Exams/patient	2.0 (1-6)	1.5 (1-2)	NA	1
Dose (mGy)	0.9 (0.2-22)	0.5 (0.5-0.6)	NA	0.1

Annex 1 – Informed Consent Forms

Madrid

Consentimiento Informado Participación Estudio EPI-CT NCC

(1_adultos casos controles)

(ejemplar para el participante)

- Confirmo que he leido y entendido la hoja de información del estudio EPI-CT NCC y que he tenido la oportunidad de hacer todas las preguntas que creía necesarias.
- Entiendo que mi participación en el estudio caso control EPI CT NCC es voluntaria y que soy libre de retirarme en cualquier momento, sin dar explicaciones y sin consecuencias legales o en la atención médica

Por favor marca las casillas

Autorizo a que mis datos personales sean utilizados por el personal responsable del estudio en la Subdirección General de Epidemiología e ISGlobal con el fin de participar en este estudio	☐

	Sí	No
Consiento en responder un cuestionario personal	☐	☐
Consiento a que mis padres (tutores legales) respondan a un cuestionario dirigido a ellos	☐	☐
Autorizo a los investigadores del estudio a acceder a mi historial médico	☐	☐
Autorizo a los investigadores de ISGlobal a contactar con los departamentos de radiología para acceder a las imágenes diagnósticas y a obtener una copia anonimizada para análisis futuros con el objetivo de mejorar la estimación de dosis de radiación en distintos órganos	☐	☐
Autorizo a los investigadores a hacer cruces de la base de datos del presente estudio con diferentes registros poblacionales de datos de salud y demográficos	☐	☐
Estoy de acuerdo en donar unas muestras de saliva a los investigadores del estudio EPI-CT NCC para análisis genéticos y epigenéticos. (En caso de aceptar les mandaremos junto con los kits toda la información sobre el tratamiento de las muestras y el consentimiento informado específico para el tratamiento de sus datos)	☐	☐
Otorgo mi consentimiento al tratamiento de mis datos personales para llevar a cabo proyectos de investigación afines al presente o de la misma área de investigación	☐	☐

Datos de contacto:

_____

Dirección postal

_____ _____

Teléfono correo electrónico

_____ _____

Nombre y apellidos del participante Fecha y Lugar

Firma del participante a partir de 12 años	**Firma del padre, madre o tutor legal**	**Firma del investigador**

Consentimiento Informado Participación Estudio EPI-CT NCC

(3_CasosExitus)

(ejemplar para la Comunidad de Madrid)

- Confirmo que he leído y entendido la hoja de información del estudio EPI-CT NCC y que he tenido la oportunidad de hacer todas las preguntas que creía necesarias.
- Entiendo que la participación en el estudio caso-control EPI-CT NCC de mi hijo/a - menor del que era responsable- (en adelante el participante) es voluntaria y que somos libres de retirarnos en cualquier momento, sin dar explicaciones y sin consecuencias legales.

Por favor, marca las casillas

Autorizo a que los datos personales del participante sean utilizados por el personal responsable del estudio en la Subdirección General de Epidemiología e ISGlobal con el fin de participar en este estudio	☐

	Si	No
Consiento participar respondiendo un cuestionario sobre el participante y otro dirigido a los padres o tutores legales	☐	☐
Autorizo a los investigadores del estudio a acceder al historial médico del participante	☐	☐
Autorizo a los investigadores a hacer cruces de la base de datos del presente estudio con diferentes registros poblacionales de datos de salud y demográficos	☐	☐
Estoy de acuerdo en que, si el hospital donde el participante fue atendido/a de forma regular ha conservado algunas muestras biológicas en su biobanco, se pueda usar una pequeña muestra para el estudio EPI-CT NCC para análisis genéticos y epigenéticos.	☐	☐
Otorgo mi consentimiento al tratamiento de los datos personales del participante para llevar a cabo proyectos de investigación afines al presente o de la misma área de investigación	☐	☐

Datos de contacto:

Nombre y apellidos del participante

Nombre y apellidos del padre/madre/ tutor legal

Teléfono

correo electrónico

Dirección postal

Fecha y Lugar

Firma del padre/madre/tutor legal	**Firma del investigador**

FORMULAIRE DE CONSENTEMENT (PARTICIPANT MAJEUR)

Etude Enfant Scanner

Impact des irradiations médicales sur la santé des enfants et des jeunes adultes

PROMOTEUR DE LA RECHERCHE : **Institut de Radioprotection et de Sureté Nucléaire (IRSN)**
INVESTIGATEUR PRINCIPAL : **Dr Marie-Odile Bernier, Médecin-Chercheur de l'IRSN**

FORMULAIRE DE CONSENTEMENT

Je soussigné(e) _____*(nom, prénom)* certifie avoir lu et compris la lettre d'information que j'ai reçue par courrier.

J'ai bien compris les informations décrites sur cette lettre d'information et j'ai eu la possibilité de poser toutes les questions que je souhaitais en contactant l'investigateur principal de l'étude, Dr Marie-Odile Bernier.

Je connais la possibilité qui m'est réservé(e) d'interrompre la participation de mon enfant à cette recherche, à tout moment, sans avoir à justifier ma décision en informant pour cela le Dr Marie-Odile Bernier, dont les coordonnées figurent à la fin de ce document.

L'investigateur principal de l'étude peut décider de l'arrêt de ma participation à cette recherche, pour des raisons scientifiques ou pratiques.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes de l'Ile de France X, le ..... et a été autorisée par la Cnil, le …….

Dans le respect des règles de protection des données personnelles et de confidentialité formulées dans la loi n°2004-801 du 6 août 2004 modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, j'accepte que les données collectées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte.

J'accepte que seules les personnes qui collaborent à cette recherche ou qui sont mandatées par le promoteur, ainsi qu'éventuellement le représentant des Autorités de Santé, aient accès aux données collectées dans cette recherche, dans le respect le plus strict de la confidentialité.

J'ai bien noté que, conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, je dispose d'un droit d'accès et de rectification des données me concernant.

Je dispose également d'un droit d'opposition à la transmission des données susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du médecin, investigateur principal de l'étude, Dr Marie-Odile Bernier, qui connait mon identité.

Je peux également accéder à tout moment, au cours ou à l'issue de la recherche, à l'ensemble de mes données personnelles, en application des dispositions de l'article L1111-7 du code de la santé publique.

Mon consentement ne décharge en rien l'investigateur principal et le promoteur de la recherche de leurs responsabilités à mon égard. Je conserve tous les droits garantis par la loi.

Conformément à la loi du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé, les résultats globaux de la recherche me seront communiqués directement si je le souhaite.

Ayant disposé(e) d'un temps de réflexion suffisant avant de prendre ma décision, j'accepte librement et volontairement de participer à l'étude Enfant Scanner (nom complet : étude cas-témoins Enfant Scanner), dans les conditions établies par la loi et telles que précisées dans la lettre d'information qui m'a été remise.

⋆ Oui **⋆ Non**

Je donne mon accord pour fournir des données personnelles me concernant à travers des questionnaires et une fiche de coordonnées et que ces données puissent faire l'objet d'un traitement informatique, conformément aux recommandations de la loi relative à l'informatique, aux fichiers et aux libertés.

⋆ Oui **⋆ Non**

Je souhaite remplir le questionnaire en ligne sur Internet (en cas de réponse négative, un questionnaire papier me sera fourni).

⋆ Oui **⋆ Non**

Étant suffisamment bien informé(e), je donne mon accord pour permettre le recueil, autoriser l'analyse génétique de mes échantillons de salive demandés pour cette recherche.

⋆ Oui **⋆ Non**

J'atteste ne pas être sous sauvegarde de justice, sous tutelle ou sous curatelle.

⋆ Oui **⋆ Non**

Je pourrai à tout moment demander des informations complémentaires au Docteur Marie-Odile Bernier, investigateur principal de l'étude Enfant Scanner, dont les coordonnées figurent ci-dessous.

Fait à…….. ,

le └─┘─┘ └─┘─┘ └─┘─┘─┘─┘

Fait à ……,

Le └─┘─┘ └─┘─┘ └─┘─┘─┘─┘

Signature du participant :

Signature du médecin, investigateur principal :

	Dr Marie-Odile Bernier

Dr Marie-Odile BERNIER
Investigateur principal de l'étude cas-témoins Enfant Scanner
Institut de Radioprotection et de Sûreté Nucléaire (IRSN)
Pôle « Santé Environnement »
Laboratoire d'épidémiologie des rayonnements ionisants (LEPID)
B.P. 17 - 92262 Fontenay-aux-Roses Cedex
Tél : 01 58 35 72 25
Courriel : marie-odile.bernier@irsn.fr

Ce document est à compléter et à signer en <u>3 exemplaires originaux</u>. Le premier est conservé par la personne donnant son consentement ; les deux autres exemplaires sont transmis par courrier (à l'aide de la lettre préaffranchie et pré-adressée à l'IRSN) à l'investigateur principal et au promoteur qui conserveront ces deux exemplaires à l'IRSN.

FORMULAIRE DE CONSENTEMENT (UN DES DEUX PARENTS POUR LE PARTICIPANT MINEUR)

Etude Enfant Scanner

Impact des irradiations médicales sur la santé des enfants et des jeunes adultes

PROMOTEUR DE LA RECHERCHE : **Institut de Radioprotection et de Sureté Nucléaire (IRSN)**
INVESTIGATEUR PRINCIPAL : **Dr Marie-Odile Bernier, Médecin-Chercheur de l'IRSN**

FORMULAIRE DE CONSENTEMENT

Je soussigné(e) …… *(nom, prénom),* père / mère *(rayer la mention inutile)* de l'enfant ……..…….. *(nom, prénom)*, participant à l'étude Enfant Scanner, certifie avoir lu et compris la lettre d'information que j'ai reçue par courrier.

J'ai bien compris les informations décrites sur cette lettre d'information et j'ai eu la possibilité de poser toutes les questions que je souhaitais en contactant l'investigateur principal de l'étude, Dr Marie-Odile Bernier.

J'ai pu lire avec mon enfant la lettre d'information à son intention et je me suis assuré(e) que mon enfant ait bien compris tous les aspects liés à sa participation à cette étude.

Je connais la possibilité qui m'est réservé(e) d'interrompre la participation de mon enfant à cette recherche, à tout moment, sans avoir à justifier ma décision en informant pour cela le Dr Marie-Odile Bernier, dont les coordonnées figurent à la fin de ce document.

L'investigateur principal de l'étude peut décider de l'arrêt de la participation de mon enfant à cette recherche, pour des raisons scientifiques ou pratiques.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes de l'Ile de France X, le ..... et a été autorisée par la Cnil, le …….

Dans le respect des règles de protection des données personnelles et de confidentialité formulées dans la loi n°2004-801 du 6 août 2004 modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, j'accepte que les données collectées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte.

J'accepte que seules les personnes qui collaborent à cette recherche ou qui sont mandatées par le promoteur, ainsi qu'éventuellement le représentant des Autorités de Santé, aient accès aux données collectées dans cette recherche, dans le respect le plus strict de la confidentialité.

J'ai bien noté que, conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, je dispose d'un droit d'accès et de rectification des données concernant mon enfant et moi-même.

Je dispose également d'un droit d'opposition à la transmission des données susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du médecin, investigateur principal de l'étude, Dr Marie-Odile Bernier, qui connait mon identité et celle de mon enfant.

Je peux également accéder à tout moment, au cours ou à l'issue de la recherche, à l'ensemble de de mes données personnelles et celles de mon enfant, en application des dispositions de l'article L1111-7 du code de la santé publique.

Mon consentement ne décharge en rien l'investigateur principal et le promoteur de la recherche de leurs responsabilités à mon égard et à l'égard de mon enfant. Mon enfant et moi conservons tous les droits garantis par la loi.

Conformément à la loi du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé, les résultats globaux de la recherche seront communiqués directement à moi et à mon enfant, si nous le souhaitons.

Ayant disposé(e) d'un temps de réflexion suffisant avant de prendre ma décision, j'accepte librement et volontairement que mon enfant participe à l'étude Enfant Scanner (nom complet : étude cas-témoins Enfant Scanner), dans les conditions établies par la loi et telles que précisées dans les lettres d'information qui ont été remises, à mon enfant et à moi.

⋆ Oui ⋆ Non

Je donne mon accord pour fournir des données personnelles concernant mon enfant et moi-même à travers des questionnaires et une fiche de coordonnées et que ces données puissent faire l'objet d'un traitement informatique, conformément aux recommandations de la loi relative à l'informatique, aux fichiers et aux libertés.

⋆ Oui ⋆ Non

Je souhaite remplir le questionnaire en ligne sur Internet (en cas de réponse négative, un questionnaire papier me sera fourni).

⋆ Oui ⋆ Non

Étant suffisamment bien informé(e), je donne mon accord pour permettre le recueil, autoriser l'analyse génétique des échantillons de salive de mon enfant demandés pour cette recherche.

⋆ Oui ⋆ Non

J'atteste ne pas être sous sauvegarde de justice, sous tutelle ou sous curatelle.

⋆ Oui ⋆ Non

Je pourrai à tout moment demander des informations complémentaires au Docteur Marie-Odile Bernier, investigateur principal de l'étude Enfant Scanner, dont les coordonnées figurent ci-dessous.

Fait à…….. ,

le └─┘─┘ └─┘─┘ └─┘─┘─┘─┘

Fait à ……,

Le └─┘─┘ └─┘─┘ └─┘─┘─┘─┘

Signature du participant :	Signature du médecin, investigateur principal :
	Dr Marie-Odile Bernier

Dr Marie-Odile BERNIER
Investigateur principal de l'étude cas-témoins Enfant Scanner
Institut de Radioprotection et de Sûreté Nucléaire (IRSN)
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Ce document est à compléter et à signer en <u>3 exemplaires originaux</u>. Le premier est conservé par le parent donnant son consentement pour son enfant mineur ; les deux autres exemplaires sont transmis par courrier (à l'aide de la lettre préaffranchie et pré-adressée à l'IRSN) à l'investigateur principal et au promoteur qui conserveront ces deux exemplaires à l'IRSN.

FORMULAIRE DE CONSENTEMENT (PARENT)

Etude Enfant Scanner

Impact des irradiations médicales sur la santé des enfants et des jeunes adultes

PROMOTEUR DE LA RECHERCHE : **Institut de Radioprotection et de Sureté Nucléaire (IRSN)**
INVESTIGATEUR PRINCIPAL : **Dr Marie-Odile Bernier, Médecin-Chercheur de l'IRSN**

FORMULAIRE DE CONSENTEMENT

Je soussigné(e) _____*(nom, prénom)* certifie avoir lu et compris la lettre d'information que j'ai reçue par courrier.

J'ai bien compris les informations décrites sur cette lettre d'information et j'ai eu la possibilité de poser toutes les questions que je souhaitais en contactant l'investigateur principal de l'étude, Dr Marie-Odile Bernier.

Je connais la possibilité qui m'est réservé(e) d'interrompre ma participation à cette recherche, à tout moment, sans avoir à justifier ma décision et cela en informant le Dr Marie-Odile Bernier, dont les coordonnées figurent à la fin de ce document.

L'investigateur principal de l'étude peut décider de l'arrêt de ma participation à cette recherche, pour des raisons scientifiques ou pratiques.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes de l'Ile de France X, le ..... et a été autorisée par la Cnil, le …….

Dans le respect des règles de protection des données personnelles et de confidentialité formulées dans la loi n°2004-801 du 6 août 2004 modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, j'accepte que les données collectées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte.

J'accepte que seules les personnes qui collaborent à cette recherche ou qui sont mandatées par le promoteur, ainsi qu'éventuellement le représentant des Autorités de Santé, aient accès aux données collectées dans cette recherche, dans le respect le plus strict de la confidentialité.

J'ai bien noté que, conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, je dispose d'un droit d'accès et de rectification des données me concernant.

Je dispose également d'un droit d'opposition à la transmission des données susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du médecin, investigateur principal de l'étude, Dr Marie-Odile Bernier, qui connait mon identité.

Je peux également accéder à tout moment, au cours ou à l'issue de la recherche, à l'ensemble de mes données personnelles, en application des dispositions de l'article L1111-7 du code de la santé publique.

Mon consentement ne décharge en rien l'investigateur principal et le promoteur de la recherche de leurs responsabilités à mon égard. Je conserve tous les droits garantis par la loi.

Conformément à la loi du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé, les résultats globaux de la recherche me seront communiqués directement si je le souhaite.

Ayant disposé(e) d'un temps de réflexion suffisant avant de prendre ma décision, j'accepte librement et volontairement de participer à l'étude Enfant Scanner (nom complet : étude cas-témoins Enfant Scanner), dans les conditions établies par la loi et telles que précisées dans la lettre d'information qui m'a été remise.

⋆ Oui **⋆ Non**

Je donne mon accord pour fournir des données personnelles me concernant à travers des questionnaires et une fiche de coordonnées et que ces données puissent faire l'objet d'un traitement informatique, conformément aux recommandations de la loi relative à l'informatique, aux fichiers et aux libertés.

⋆ Oui **⋆ Non**

Je souhaite remplir le questionnaire en ligne sur Internet (en cas de réponse négative, un questionnaire papier me sera fourni).

⋆ Oui **⋆ Non**

J'atteste ne pas être sous sauvegarde de justice, sous tutelle ou sous curatelle.

⋆ Oui **⋆ Non**

Je pourrai à tout moment demander des informations complémentaires au Docteur Marie-Odile Bernier, investigateur principal de l'étude Enfant Scanner, dont les coordonnées figurent ci-dessous.

Fait à…….. ,

le └─┴─┘ └─┴─┘ └─┴─┴─┴─┘

Fait à ……,

Le └─┴─┘ └─┴─┘ └─┴─┴─┴─┘

Signature du participant :	Signature du médecin, investigateur principal :
	Dr Marie-Odile Bernier

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Annex II -List of predisposing conditions of interest

Name of the condition	
Li-Fraumeni syndrome	Tuberous sclerosis
Fanconi Anemia	Von Hippel Lindau
Neurofibromatosis type 1, Neurofibromatosis type 2 and other facomatosis	MEN (multiple endocrine neoplasia) 1 and MEN 2
Primary immunodeficiency	Pheochromocytoma and paraganglioma syndromes
Beckwith Wiedemann syndrome	Familial adenomatous polyposis
WAGR syndrome	Down syndrome
Noonan syndrome	Retinoblastoma
Bloom syndrome	Xeroderma pigmentosum
Ataxia telangiectásica	Klinefelter syndrome
Gorlin syndrome	