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Childhood cancer risks estimates following CT scans: an update of the French CT cohort study

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Abstract

Objectives: Increased risks of central nervous system (CNS) tumors and leukemia associated with computed tomography (CT) exposure during childhood have been reported in recent epidemiological studies. However, no evidence of increased risks was suggested in a previous analysis of the French CT cohort. This study benefits from an updated cohort with a longer follow-up and a larger sample size of patients.

Methods: The patients were followed from the date of their first CT (between 2000 and 2011) until their date of cohort exit defined as the earliest among the following: 31st December 2016, date of death, date of first cancer diagnosis or date of their 18th birthday. Cancer incidence, vital status, cancer predisposing factors (PFs) and additional CT scans were collected via external national databases. Hazard ratios (HRs) associated to cumulative organ doses and sex were estimated from Cox models.

Results: At the end of follow-up, mean cumulative doses were 27.7 and 10.3 mGy for the brain and the red bone marrow (RBM), respectively. In patients without PFs, an HR per 10 mGy of 1.05 (95% CI: 1.01 – 1.09) for CNS tumors, 1.17 (95% CI: 1.09 – 1.26) for leukemia and 0.96 (95% CI: 0.63 – 1.45) for lymphoma was estimated. These estimates were not modified by the inclusion of CT scans performed outside the participating hospitals or after the inclusion period.

Conclusions: This study shows statistically significant dose-response relationships for CNS tumors and leukemia for patients without PFs.

Keywords: Computed tomography – Neoplasms – Child – Cohort studies – Ionizing radiation

Key points:

- Computed tomography is the most important contributor to the collective dose for diagnostic imaging to the French population.
- Concerns have been raised about possible cancer risks, particularly after exposure to CT in childhood, due to the greater radiation sensitivity of children and to their longer life expectancy.
- Analysis of the updated French CT cohort shows statistically significant dose-response relationships for CNS tumors and leukemia.

Abbreviations:

- CT: computed tomography
- IR: ionizing radiation
- CNS: central nervous system
- UK: United Kingdom
- SNDS: Système national des données de santé (National Health Data System)
- RBM : red bone marrow
- ICD-10 classification: International Classification of Diseases, 10th revision
- PF: cancer predisposing factor
- HR: hazard ratio
- CI: confidence interval
- SD: standard deviation
- LSS: Life Span Study
- RIS: radiology information systems
- MRI: magnetic resonance imaging

Introduction

Computed tomography (CT) delivers higher doses of ionizing radiation (IR) than conventional X-rays procedures [1] and is the most important contributor to the collective dose for diagnostic imaging (74.2%) to the French population [2]. However, concerns have been raised about possible cancer risks, particularly after exposure to CT in childhood, due to the greater radiation sensitivity of children for at least 25% of cancer sites [3] and to their longer life expectancy allowing to develop radiation associated late health effects. Significant increased risks of central nervous system (CNS) tumors associated with CT scans exposure during childhood have been reported in the United Kingdom (UK), Australia, Taiwan, Germany and the Netherlands [4–9]. Additionally, some studies pointed out a statistically significant positive association between the incidence of leukemia and CT scans exposure [4, 5, 10] while others found a non-significant one [7–9]. This was particularly the case in the French CT cohort study [11] for which a previous analysis of almost 60,000 patients did not highlight any significant increased risk of both leukemia and CNS tumors. This could be explained by a lack of statistical power due to the restricted sample size of this cohort, the small number of incident cancer cases and the limited follow-up of children. Another limitation of this previous study [11] is the potential underestimation of cumulative organ doses received by patients, since some of them may have undergone additional CTs outside the hospitals participating in the study. The aim of this new study is to present updated risk estimates of CNS tumors, leukemia and lymphoma, from a longer follow-up of the French CT cohort, according to improved doses estimations. About 40,000 new patients were included as well as 5 additional years of follow-up. The cohort was linked with the National Health Data System (Système national des données de santé, SNDS), that provides outpatient and hospital discharge data (reimbursed drugs dispensation, medical and paramedical acts) [12], to collect CTs performed during the follow-up and outside the participating hospitals.

Materials and methods

Inclusion of patients. The original French CT cohort has been described elsewhere [13]. Briefly, this retrospective cohort includes patients born after 1994 who received at least one CT before the age of 10 years, between 2000 and 2011, in one of the 21 participating university hospitals. Patients with personal history of cancer prior to the first CT were excluded.

Exposure assessment. All examinations carried out between 2000 and 2011 in the 21 participating hospitals were included in the current study. CT acquisition parameters were retrieved from radiological protocols implemented in each radiological department according to the period considered, the CT machine and the age group. Cumulative absorbed doses to the brain and the red bone marrow (RBM) were estimated using NCICT version 1.2 software [14]. The linkage of the cohort with the SNDS provided information between 2006 and 2016 for 76.5% of the population. For additional CTs retrieved from the SNDS, organ doses were estimated using NCICT software. As the technical parameters for these CTs were not available, the dose estimation was based on published French parameters values: French diagnostic reference levels [15] until 2011 and radiology protocols used between 2010 and 2013 in the participant hospitals [16] after 2011 (Supplementary Figure 1).

Follow-up. The patients were followed from the date of their first CT until their exit date, which was the earliest among the following: 31st December 2016, date of death, date of first cancer diagnosis, or date of their 18th birthday. Information on vital status was obtained via a national registry. The whole cohort includes a subsample of 40,000 additional patients who were not included in the previous analysis [11] because of the earlier non-availability of their birthplace. A decree in the Council of State was obtained in 2016 to allow the identification of the birthplaces from another source.

Cancer cases ascertainment. Until the 31st December 2016, all incident cancer cases were retrieved from the French national registry of childhood cancers. This pediatric cancer registry records all diagnoses of both hematological malignancies, including lymphomas, since 1990, and solid tumors since 2000. It relates to all the patients living in metropolitan France younger than 15 years until 2011, while living in overseas departments and younger than 18 years after 2011 [17]. Cancer diagnoses were coded according to the ICD-10 classification (International Classification of Diseases, 10th revision). The topography codes used for CNS tumors (benign and malignant) as well as the morphology codes used for leukemia and lymphoma are detailed in Supplementary Table 1.

Cancer-predisposing conditions. The patients with cancer predisposing conditions (PF) were identified by the information available through the medical discharge databases of the hospitals before 2006 and from the SNDS since 2006. The PFs considered are detailed in the Supplementary Table 2.

Data analysis. The statistical analyses were restricted to the most frequent pediatric cancer sites: CNS tumors, leukemia and lymphoma [17]. To evaluate the relationship between cumulative X-ray absorbed doses to the brain (for CNS tumors) and to the RBM (for leukemia and lymphoma) and cancer incidence, a Cox model [18] was adopted for each cancer:

$$\lambda_i(t) = \lambda_0(t)\exp(\beta X_i^{cum}(t) + \gamma Z_i)$$

Attained age was chosen as time scale [19]. In the above semi-parametric survival model, $\lambda_i(t)$ denotes the instantaneous hazard rate of cancer incidence of patient i at age t , $\lambda_0(t)$ corresponds to the baseline instantaneous hazard rate at age t . $X_i^{cum}(t)$ is a time-dependent covariate representing the cumulative X-ray absorbed organ dose of patient i at time t . $\exp(\beta)$ is the instantaneous hazard ratio (HR) associated with the cumulative absorbed dose. Models were adjusted on sex, with Z_i the sex of patient i and $\exp(\gamma)$ the associated HR.

The loglinear assumption of the model was checked with martingale residuals. The proportional hazard assumption was checked through the weighted and scaled Schoenfeld residuals [20]. All the HRs were estimated by the maximum partial likelihood method and Wald-based 95% confidence intervals (CIs) were computed, using the R software [21] (version 3.6.2) “survival” package [22].

To address the possibility of reverse causation, patients with an exit (31st December 2016, date of death, date of first cancer diagnosis, or date of their 18th birthday) within the 2 years after the entry in the cohort were excluded. A latency period was also applied to consider the minimal latency period expected between the exposure and the studied outcome [23]. The cumulative X-ray absorbed organ dose $X_i^{cum}(t)$ is then lagged by 5 years for CNS tumors and 2 years for leukemia and lymphoma [4, 24]. To address the potential issue of bias by indication (i.e. the indication of the CT might be related to underlying PFs that may also increase the risk of developing a cancer), the model was fitted to the cohort and then to the restricted sub-cohorts of patients with PFs and without PFs respectively. Sensitivity analyses considered different lagging and exclusion time periods. The impact on the risks estimates of additional CT doses was also assessed.

Results

Study population. The updated French CT cohort includes 103,015 patients followed for 9.3 years in average. Patients' characteristics are presented in Table 1. The mean age at inclusion and age at the end of follow-up were 3.4 years and 12.6 years respectively. Among the 3,230 (3.1%) patients with PFs, 716 (0.7%) were identified at increased risk of CNS cancer, 2,206 (2.1%) at increased risk of leukemia and 1,787 (1.7%) at increased risk of lymphoma.

CT scan exposure. Two different periods were considered: the inclusion period from 2000 to 2011 and the follow-up period from 2012 to 2016. In total, 159,621 CT scans were eligible including 6,009 (3.8%) additional CTs performed during the inclusion period for 4,816 (4.7%) patients and 13,291 (8.3%) examinations performed during the follow-up period for 8,622 (8.4%) patients, all retrieved from the SNDS. Among the patients who had CTs performed outside the participating hospitals between 2006 and 2011, 83.3% had only one additional CT. Among the patients who had CTs after 2011, 72.5%, 16.4% and 11.1% had one, two and more than two additional CT scans respectively between 2012 and 2016 compared to the original inclusion period. On the whole period from 2000 to 2016, the estimated mean individual cumulative absorbed dose was 27.7 mGy (standard deviation (SD): 39.2) to the brain and 10.3 (SD: 12.8) to the RBM. 73.4% of patients had only one CT and 26.6% had two or more CTs (median, first and third quartiles and maximum number of CT scans per child were 1, 1, 2 and 52 respectively) but those with PFs received more CTs: 2.8 CTs in average for patients with PFs vs 1.5 for patients without PFs (p-value < 0.01).

CNS tumors, leukemia and lymphoma HR estimates. A total sample of 100,560 patients was analyzed (exclusion period of 2 years). Between 2000 and 2016, 75 cases of CNS tumors, 39 cases of leukemia and 41 cases of lymphoma were diagnosed. In the whole cohort, the HR per 10 mGy were 1.06 (95% CI: 1.02 – 1.09), 1.16 (95% CI: 1.07 – 1.29) and 0.89 (95% CI: 0.61 – 1.30) for CNS tumors, leukemia and lymphoma respectively. When considering only patients without cancer PFs, the risks of developing CNS tumors or leukemia significantly increased with increasing cumulative organ doses, with an HR per 10 mGy of 1.05 (95% CI: 1.01 – 1.09) for CNS tumors (50 cases) and 1.17 (95% CI: 1.09 – 1.26) for leukemia (35 cases). On the other hand, there is no evidence of an increased risk of developing lymphoma with increasing cumulative RBM dose: HR per 10 mGy of 0.96 (95% CI: 0.63 – 1.45) (26 cases). There is also no evidence of association between the cumulative organ doses and the incidence of CNS tumors, leukemia and lymphoma in patients with cancer PFs (Table 2). Finally, there is no evidence of association between sex and the incidence of CNS tumors, leukemia and lymphoma (Table 2). Increasing the exclusion period from 2 to 5 years did not substantially affect cancer risks estimates (Supplementary Table 3). HR estimates per 10 mGy associated to CNS tumors became non-significantly higher than 1 with a lagging period of 10 years (24 remaining cases of cancer with dose superior to 0, Supplementary Table 4). Inclusion of additional CTs registered in

the SNDS after 2011 did not impact the HR estimates (Supplementary Table 5). Likewise, considering exposure until 2011, the HR estimates were similar with and without inclusion of CTs performed outside the participating hospitals (Supplementary Table 5).

Discussion

This study is a nationwide, population-based, retrospective cohort study of 103,015 patients who received at least one CT scan in a French participating hospital between 2000 and 2011 before the age of 10 years. For patients without PFs, increased risks of CNS tumors (HR per 10 mGy: 1.05, 95% CI: 1.01 – 1.09) and leukemia (HR per 10 mGy: 1.17, 95% CI: 1.09 – 1.26) were observed with increasing cumulative organ doses, given the 50 and 35 observed cases of CNS tumors and leukemia respectively. However, there was no evidence of association between the cumulative RBM dose and the incidence of lymphoma, given the 26 observed cases (HR per 10 mGy: 0.96, 95% CI: 0.63 – 1.45). These risks estimates were consistent with the results provided by large cohort studies such as the Life Span Study (LSS) [3] that highlighted increased risks of leukemia and solid cancers, like brain tumors after exposure to IR during childhood but available data did not indicate an association between lymphoma and IR. Likewise, by analyzing nine pooled cohort studies, Little et al. (2018, 2021) [25, 26] highlighted significant increased risks of leukemia but non-significant increased risks of lymphoma after exposure to IR at young age. Some CT cohort studies observed significant positive association between radiation dose from CTs and brain tumors [4–9]. Similar results were found for leukemia for some CT cohort studies [4, 5, 10] while others observed non-significant increased risks for this cancer [7–9]. Several CT cohort studies [5, 7, 8] do not show any evidence of an association between CTs exposure and the incidence of lymphoma except for Hodgkin's lymphoma in the Australian study [5]. Finally, in this study of the updated French CT cohort, the HRs estimates associated to absorbed organ doses and reported for patients without PFs are compatible with the ones obtained in the analysis of the original French CT cohort [11]: an HR per 10 mGy of 1.07 (95% CI: 0.99 – 1.10) and 1.16 (95% CI: 0.77 – 1.27) were previously estimated for CNS tumors and leukemia respectively. However, as might be expected, the 95% CI shrank in the new analysis compared to the previous one, leading to statistically significant HRs for CNS tumors and leukemia. This is mainly due to an extended follow-up and a larger sample size of the updated French CT cohort which allow increasing the statistical power of the study.

95% CIs of the HR per 10 mGy were clearly larger for patients with PFs than for patients without PFs. This could be explained by the small sample size of the sub-cohort of patients with PFs compared to the sub-cohort without PFs and the higher premature mortality in patients with PFs, decreasing the number of patients at risk of later radiation associated cancer.

The estimated HRs in patients without PFs were in the range of those observed in the entire cohort. We observed statistically significant increased HRs for CNS tumors and leukemia in these groups of patients. On the other hand, there was no evidence of association between the incidence of CNS tumors and leukemia and CT doses in patients with PFs. Thus, PFs do not appear to largely confound dose-response association but rather modify the dose-response

relationship. Given that these two groups of patients have different baseline hazard rates, they should be analyzed separately [27].

Other published works focused on potential confounding bias by indication. Based on assumptions about CT use among patients with PFs, Meulepas et al. (2016) [28] showed that the existence of PFs were unlikely to cause meaningful confounding on risks estimates for leukemia and CNS tumors after CTs as they were too rare and the CTs frequency was only moderately elevated among these subjects. Similar conclusions were drawn after exclusion of patients with PFs in the UK cohort [29], using information from the radiology information systems (RIS) and death certificates for about 40% of the cohort, and in the German cohort [8], despite limited available medical information. A strength of the French study was the opportunity to link the cohort with the SNDS which allowed to collect medical information on PFs for 76.5% of the cohort. Furthermore, it has been previously shown that the diagnoses of PFs were identified in the SNDS with excellent sensitivity and specificity [30].

In this study, radiation exposure assessment was then completed thanks to the SNDS which provided information on CT scans performed between 2006 and 2011 (initial inclusion period) outside the participating hospitals and after 2011 for both participating and non-participating hospitals. This is an additional strength of the current study, given that the CTs performed outside the participating hospitals are only scarcely available in the other published CT cohorts. The identification of these CTs allowed us to test the impact of these additional doses on the risks estimates. Nevertheless, 60% of the CT scans registered in the cohort between 2006 and 2011 were not traced in the SNDS. Indeed, some medical procedures, such as CTs, were not always individualized in the first years of the implementation of the SNDS since they did not influence the fee related to the stay [12]. The completeness of the SNDS increased with time. HRs estimates do not appear biased by underestimated doses since the estimation of new dose values between 2006 and 2011 did not impact our results. Only 4.7% of patients had CTs not previously collected during this period and 83.3% of them had only one missing examination. Likewise, only 8.4% of patients received CT scans after the inclusion period; HRs estimates were not impacted by the inclusion of the additional examinations performed between 2012 and 2016. Nevertheless, one limitation of our study is the uncertainty associated with the dose reconstruction given the fact that the technique parameters used at each image acquisition may vary from the protocol and were extrapolated over some periods for the National Health Data System, because current modulation was not available in NCICT version 1.2 and since the morphology of the patient might differ from the anthropomorphic phantom.

Like other CT cohorts, this study lacks information regarding the clinical indications for CTs. However, the existence of reverse causation bias in HRs estimates (due to the fact that the tumor is causing symptoms explaining the need for CT scans but the tumor is not detected immediately after the examination) is prevented by applying exclusion and lagging periods at the entry in the

cohort. Extending the exclusion period from 2 to 5 years did not decrease our HRs estimates, suggesting that reverse causation did not substantially bias them. Similar conclusions were made after extending the lagging period from 2 to 5 years for leukemia and lymphoma. HR estimates per 10 mGy associated to CNS tumors became non-significantly higher than 1 with a lagging period of 10 years. However, even if such a long lagging period is recommended in the literature for CNS tumors, this assumption is not the best one here given the short follow-up time (only 9.3 years in average) in the current French CT cohort study.

In our study, the cancer diagnoses were only available until the 18th birthday because of the lack of national cancer registry at adult age. Given the long-expected latency period for most of the radiation-related cancers, the follow-up at adult age is required. The building of a national cohort of all the patients treated for a cancer in France since 2011 based on data retrieved from the SNDS might help to deal with this issue [31].

Childhood cancers are rare diseases and the risks associated with low doses of IR are expected to be small [1]. Large-scale studies are required to have enough statistical power to highlight, if they exist, statistically significant increased risks. The EPI-CT study, a multinational collaborative study, has been designed to achieve this goal by including almost one million patients, pooling nine European pediatric CT cohorts [32, 33].

In conclusion, the French pediatric CT study showed evidence that CT-related radiation exposure produced small statistically significant increased risks of CNS tumors and leukemia with increasing absorbed doses for patients without cancer PFs. However, no evidence of association was observed for patients with PFs. Furthermore, HRs estimates were not impacted by the inclusion of CT scans collected in the SNDS and performed outside the participating hospitals during the inclusion period or after this period. These results should help to balance the risk of detrimental health effects against the clinical benefits of CT. They reinforce the usefulness of radiation protection for children exposed to CT, which implies not only to justify CT examinations compared to other imaging modalities that do not use IR (e.g., ultrasound or magnetic resonance imaging (MRI)) but also to optimize the delivered doses.

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Tables and Figures legends

Table 1: Characteristics of the patients and CT scan exposure according to the presence of clinical factors predisposing to cancer (PFs) in the updated French CT cohort.

Table 2: Hazard-Ratios (HR) and Wald-based 95% confidence interval (95% CI) for CNS tumors, leukemia and lymphoma, for the whole cohort and the sub-cohorts of patients with and without PFs (assuming an exclusion period of 2 years and a lagging period of 5 years for CNS tumors and 2 years for leukemia and lymphoma).