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Abstract

Pediatric patients with congenital heart disease (CHD) often undergo low dose ionizing radiation (LDIR) from cardiac catheterization (CC) for the diagnosis and/or treatment of their disease. Although radiation doses from a single CC are usually low, less is known about the long-term radiation associated cancer risks. We aimed to assess the risk of lympho-hematopoietic malignancies in pediatric CHD patients diagnosed or treated with CC. A French cohort of 17,104 children free of cancer who had undergone a first CC from 01/01/2000 to 31/12/2013, before the age of 16 was set up. The follow-up started at the date of the first recorded CC until the exit date, i.e., the date of death, the date of first cancer diagnosis, the date of the 18th birthday, or the 31/12/2015, whichever occurred first. Poisson regression was used to estimate the LDIR associated cancer risk. The median follow-up was 5.9 years, with 110,335 person-years. There were 22,227 CC procedures, yielding an individual active bone marrow (ABM) mean cumulative dose of 3.0 milligray (mGy). Thirty-eight incident lympho-hematopoietic malignancies were observed. When adjusting for attained age, gender and predisposing factors to cancer status, no increased risk was observed for lympho-hematopoietic malignancies $RR_{/mGy}$ = 1.00 (95% CI: 0.88; 1.10). In summary, the risk of lympho-hematopoietic malignancies and lymphoma was not associated to LDIR in pediatric patients with CHD who undergo CC. Further epidemiological studies with greater statistical power are needed to improve the assessment of the dose-risk relationship.

Keywords Cardiac catheterization · Ionizing radiation · Childhood · Lympho-hematopoietic malignancies

Introduction

Exposures to high dose of ionizing radiation are known to be associated with cancer occurrence [1–3]. However, the risk is still debated for doses lower than 100 milligray (mGy) which are generally considered to be low doses of ionizing radiation (LDIR) [3]. The impact on health of exposure to LDIR has been subject to several investigations [1–5]. Recent studies and reviews reported excess risks of cancer in relation to external exposure to LDIR [6–9]. The follow-up since 1950 of the Japanese atomic bomb survivors cohort, a pioneering study in radiation epidemiology, reported a decreasing risk of cancer with the increasing age at exposure suggesting greater radiation associated risks for children and adolescents than for adults [10]. Less mature tissues and organs with elevated rates of cell division may partly explain the increased sensitivity of children to radiation-induced effects. Moreover, children have a long-life expectancy allowing the development of long-term radiation-induced cancers. Therefore, childhood exposure to LDIR is a public health concern that needs to be investigated.

During the past fifty years, developed countries experienced an increasing use of man-made LDIR mainly for medical diagnostic and therapeutic purposes [11–13], although a downturn in the trend has been observed recently [14]. Patients with congenital heart disease (CHD) have benefited from progress in device development leading to less invasive procedures than surgery such as cardiac catheterization

(CC) for the management of their diseases. These CC contribute to the improvement of the survival and the quality of life of patients with CHD, as CC use had reduced the number of invasive procedures, unnecessary hospital admissions, and the length of hospital stays [15]. A single examination using LDIR implies a very low exposure to radiation and then only carries theoretically a very small cancer risk. This potential long-term risk is negligible compared to the immediate clinical benefit. However, CHD patients may be subjected to several CC during their life, which would increase the overall radiation exposure of these patients. Furthermore, the increased long-life expectancy in the CHD population brings new challenges since these patients have the possibility of developing long-term LDIR-related diseases such as cancer. Hence, a better knowledge of the long-term effects of LDIR used during CC examinations in childhood is important to assess possible modifications in radiological procedures for these patients.

Until now, few studies have focused on childhood exposure to CC and they have led to controversial conclusions [16–19]. However, two epidemiological studies have reported an increased risk of cancer following exposure to LDIR from CC during adulthood [20, 21]. Furthermore, apart from the British study [19] none of these studies assessed the potential impact of cancer predisposing factors (PF) among patients receiving CC procedures and additional dose of radiation linked to other LDIR medical diagnostic procedures, mostly computerized tomography (CT) scans, on the risk estimates.

As CC procedures could be associated with doses in the range of those associated with CT scans, results of epidemiological studies focusing on CT exposure during childhood are important to consider. Several cohorts on CT scan exposure in childhood and radiation associated risks of cancer [22–25] and recent systematic reviews of the literature [7–9] reported increased risks of leukemia and central nervous system (CNS) tumors. However, criticisms have been made on the possibility of reverse causation bias in CT studies since early symptoms of undetected cancer can prompt the indication of the CT scan [26], although a simulation study did not suggest that this was a problem in practice [27]. CC procedures are unlikely to be subject to this kind of bias since the indication is linked to CHD diagnosis and/or treatment. However, confounding bias linked to underlying disease, for example cancer PFs, that could be associated with both the studied outcome and the level of exposure to LDIR could not be ruled out and should be considered. Furthermore, children exposed to CC are likely to be also exposed to CT. It is then important to take into account doses linked to other radiological procedures, mostly the CTs as they are associated with much higher doses than conventional radiology, in the assessment of the relationship between exposure to CC during childhood and subsequent cancer risks.

The aim of this study is to assess lympho-hematopoietic malignancies risk in the COCCINELLE cohort of children exposed to LDIR from CC procedures, by considering potential confounding effect of cancer PFs and additional exposure to radiation from CT scans.

Materials and methods

Study design

The COCCINELLE study is a multicenter cohort study in mainland France, aiming to assess the risk of cancer in patients with CHD who underwent CC procedures for diagnosis or treatment during childhood, based on medical records of CC procedures performed in fifteen pediatric cardiology departments. The cohort's set up and constitution has been described elsewhere [28, 29]. Briefly, all patients from one of the participating centers, who underwent their first CC procedure between 1st January 2000 and 31st December 2013, while aged under 16 years at the time of the examination, and who have not been diagnosed with cancer before the first recorded CC procedure, were included.

The cohort was linked with the RNIPP (French National Directory for the Identification of Natural Persons) to obtain the vital status of each participant and with the RNCE (National Childhood Cancer Registry or *Registre National des Cancers de l'Enfant* in French) to identify the cancer cases that occurred during the follow-up. The RNCE records cancer in children and young adults until 18 years old. Recorded data were available until the 31st December 2015 at the time of the linkage. Then, patients were followed from the date of the first CC procedure until the exit date that is, the date of death, the date of first cancer diagnosis, the date of the 18th birthday, or the 31st December 2015, whichever occurred first.

The outcomes investigated were leukemia including myelodysplastic syndrome (international classification of childhood cancer – third version (ICCC3) Ia, Ib, Ic, Id and Ie, International Classification of Diseases for Oncology – third version (ICD-O3) 98,363, 98,373, 99,893, 98,733, 98,743, 98,613, 98,263), lymphoma (ICCC3: IIa, IIb, IIc, IId and IIe, ICD-O3 95,913, 96,873, 97,143, 97,293, 96,633, 96,513, 96,653, 99,701, 97,543) and all lympho-hematopoietic malignancies (leukemia and lymphoma combined).

The PFs to lymphoma, leukemia, and lympho-hematopoietic malignancies were retrieved from medical discharge database of the participating hospitals from the PMSI (French acronym for *Programme de médicalisation*

des systèmes d'information) from 2000. Data on PFs were also collected from the National Health Database or SNDS (French acronym for *Système National des Données de Santé*), a large database of all health care consumption which covers almost the entire French population since 2006. The list of the PFs was defined, based on experts' knowledge and review of literature [23, 30, 31]. The PFs were defined using the international classification of diseases (ICD-10th version) codes.

The study received ethical approval from the French national data protection commission (Commission Nationale de l'Informatique et des Libertés), n° 911,112 of 12th December 2011 and deliberation N°2016-067 of 13 August 2016.

Organ doses reconstruction from CC

The characteristics of the CC procedures such as the date and the type of procedure, were collected from the cardiology departments, where the CC were performed, as well as the technical details including, when available, fluoroscopy time and dose area product (DAP). DAP represents the dose in air measured at a given distance from the X-ray tube multiplied by the area of the x-ray at that distance [29].

Detailed dose reports available for 1,139 CC procedures performed between 2010 and 2013 in one participating center of the study were used to reconstruct patient's individual doses for the study participants. The dose reports contained detailed dosimetry parameters such as primary and secondary angulations, field of view (in cm), source-image distance (in cm), and tube potential (in kilovolt (kV)), as well as DAP per acquisition for each procedure. These parameters were used to estimate dose coefficients by procedure type using a dosimetry system based on Monte Carlo computer simulations. The PCXMC software calculates organ doses using phantoms that are assigned to different age categories where patients aged [0-1month[were assigned to newborn phantom, patients aged [1 month-1 year] were assigned to a 1-year old phantom, patients aged]1–5] years were assigned to a 5-year old phantom, patients aged]5–10] years were assigned to a 10-year old phantom, patients aged]10–15] years were assigned to a 15-year old phantom, and patients aged more than 15 years old were assigned to an adult phantom (PCXMC V2.0, STUK, Helsinki, Finland) [32]. For procedures with detailed dose reports available, an individual organ dose was computed using values from the reports. For CC procedures without detailed dose report, estimated doses were calculated by multiplying the recorded DAP by the estimated dose coefficients. Finally, for CC procedures with no detailed dose report and no DAP available, organ doses were imputed using the median values of doses estimated with detailed dose reports, considering the procedure type and the age category. The K-Nearest Neighbors (KNN) imputation algorithm was used to fill in missing data. Detailed information on the dose imputation process is given in the Appendix A.

Organ doses reconstruction from computerized tomography (CT) scan

Among the other IR medical diagnostic procedures received by patients with CHD, CT scan is the major contributor to the total cumulative dose [33–35]. We then collected CT scan examinations received by the patients from the SNDS database for the period 2006–2013 and from the French CT Cohort (*Cohorte Enfant Scanner*), a national level multicenter study that includes 93,640 pediatric patients who had undergone at least one CT examination between 2000 and 2010 in France [23, 36].

CT cumulative organ doses were calculated for each CT using CT scans parameters derived from the French national diagnostic reference levels, supplemented with literature published survey data [37]. Scanning parameters (CT scan model, spiral/sequential mode, tube current and voltage, pitch, total collimation, and scan length), gender and patient age categories (0–1, 1–4, 5–9, 10–15, >15 years) allowed to calculate organ doses for each CT performed using the NCICT software, which combines a series of pediatric and adult computational human phantoms coupled with a Monte Carlo transport simulation of a reference CT scan model (NCICT, National Cancer Institute, Bethesda, MD, USA) version 1.0 in batch mode [38].

Statistical analysis

The cohort characteristics were described as counts, proportions, means with the standard deviation (SD) or median with the interquartile range (IQR). Difference in means between two groups was tested using an independent sample Student's t-test (or anova test) where the frequency distribution of nominal variables was tested with a Pearson Chi-square test (or Fisher exact test). When the normal distribution assumption for continuous variable was not met and sample size less than 30, non-parametric (Wilcoxon signed rank or Kruskal-Wallis) tests were used instead.

The cumulative doses to the target organs were expressed in mGy and were calculated for each patient as the cumulative sum of each individual dose received during the follow-up. It was assumed that at least two years are needed for radiation-related lympho-hematopoietic malignancies to develop [1]. Therefore, we lagged the cumulative organ doses by two years for all outcomes, with the assumption that cancers that might occur during the two years after a CC procedure would unlikely be related to this CC procedure

dose. The application of the two-year lagged dose also supposed that all malignant cases occurring during the first two years were considered as unexposed, with a dose of 0 mGy.

Primary analyses were conducted using the active bone marrow (ABM) as target organ in the analyses of lymphoma, leukemia, and lympho-hematopoietic malignancies risks. Since recent studies [39–42] pointed that the ABM may not be the optimal target organ in the dose-response analysis of radiation and lymphoma risk, secondary analyses for lymphoma risk were performed using computed dose to lymphocytes and lymphatic organs as target organs. Summarized dose to lymphatic organ (spleen, small intestine, thymus, and lymph nodes) and to lymphocytes were obtained as previously published by Lee et al. [43]. Lymphocytes and lymphatic organs were further used as target organs for the dose-response analysis of radiation and lymphoma risk. Details on the lymphocyte and lymphatic organ doses computation are provided in the Appendix B.

Dose-response models were fitted by Poisson regression fitted via maximum likelihood to estimate the relative risk (RR) of lympho-hematopoietic malignancies, lymphoma and leukemia. Under the assumption of linearity in the relationship between the cumulative dose and the risk estimate, an excess relative risk (ERR) model was fitted, in which the expected number of cases is given by:

$$\lambda(a, g, pf, d) = \lambda(a, g, pf)(1 + \beta d) \quad (1)$$

where d is the mean two-year lagged cumulative organ dose (in mGy), and β denotes the ERR per mGy. The factor $\lambda(a, g, pf)$ represents the background rate, which was modelled as a parametric function of sex g, attained age a (< 5, 5–10, ≥ 10 years), and covariates pf (coded yes, no, and unknown) representing alternatively PFs to lymphoma, to leukemia or to lympho-hematopoietic malignancies. This function was assumed given by:

$$\lambda(a, g, pf) = PY * e^{\alpha_0 + \alpha_1 * a + \alpha_2 * g + \alpha_3 * pf} \quad (2)$$

Where PY (the number of persons-years) represents an additive offset term to the linear predictors and $\alpha_{0,1,2,and3}$ are the parameters to be estimated.

RR were also estimated according to four categories of ABM doses defined as: ≤ 1 mGy, 1–2 mGy, 2–4 mGy and > 4 mGy. To assess dose effect modification by PFs, the RR models were further stratified according to the PFs levels (yes, no, unknown) and the p-value for heterogeneity was estimated based on the likelihood ratio test (LRT). All significance tests were computed based on the LRT. 95% confidence intervals (CIs) on the maximum likelihood estimate (MLE) were based on the profile likelihood [44]. When the statistical models failed to produce convergent profile likelihood bounds, a Wald-based (Fisher information-based) confidence bound was used instead. All statistical tests are two-sided with $p < 0.05$ regarded as significant. Person-years table and statistical models were computed using the DATAB and AMFIT modules of EPICURE [45], and other descriptive analyses were performed using R [46].

Results

Characteristics of the study population

Overall, 17 104 patients were included in the study. A total of 110 335 person-years was recorded for a median follow-up of 5.9 years (IQR = 6.4 years). Table 1 presents the distribution of the cohort subjects according to various variables. The mean age at first cardiac catheterization was 4.5 years (SD = 4.8 years, median (IQR) = 2.6 (9.9) years) and males accounted for 51% of the study population. Linking the cohort with the SNDS and medical discharge databases identified 10 912 flagged patients (63.8% of the whole cohort) with 718 subjects carrying at least one cancer PF (all cancer types), representing a PF prevalence of 65.8 per 1000 patients. Among the PFs identified, Down syndrome, organ transplantation, and Noonan syndrome accounted for 44.3%, 30.6% and 16.2%, respectively, representing 91.1% of all PFs. The detailed distribution of the PFs in the studied population is presented in the Table 2.

A total of 22 227 CC procedures were recorded in the cohort ranging from 1 to 14 procedures per subject (mean = 1.3) and accounting for a total mean cumulative dose of 3.0 mGy (SD = 6.5 mGy) to the ABM (Table 3). Doses were the highest for the heart (mean = 18.5 mGy, SD = 45.3 mGy) and the lungs (mean = 21.4 mGy, SD = 51.2) (Appendix C Table C1). Ventricular septal defect closure, right ventricular outflow tract interventions, or various angioplasties were among the procedures with higher mean dose (Appendix C Table C2). 7192 CTs were reported in 3567 subjects (mean per subject 2.01, range 1 to 22 CT scans). Most of the anatomical areas explored by CTs were the abdomen, thorax, and pelvis (73.6%). The head and the neck represented 16.9% of the CTs performed (Appendix C Table C3). When accounting for both CC and CTs, the cumulative mean ABM dose was 4.2 mGy (SD = 8.4 mGy). Most of the patients (90%) received CC + CT ABM dose ≤ 10 mGy. Patients diagnosed with lymphoma and those with PFs to lympho-hematopoietic malignancies, lymphoma, and leukemia received in average higher CC + CT ABM doses ($p < 0.01$) than the other patients (Table 3). Figure 1 presents the distribution of CC + CT doses to the ABM in the cohort.

Table 1 Description of the study population according to the age at first exposure, the birth period, and the presence of predisposing factors (PF) to leukemia and/or lymphoma

	Total	Person-years	PF yes	PF No	PF Unknown	*p value* *
Overall	N = 17 104	110 336.8	N = 686	N = 10 226	N = 6 192	
Male, N (%)	8736 (51.1)	53 179.6 (48.2)	355 (51.7)	5187 (50.7)	3194 (51.6)	0.30
Mean age at first CC in years (SD)	4.5 (4.8)		5.2 (5.3)	4.5 (4.8)	4.4 (4.7)	0.07
Mean attained age in years (SD)	10.7 (5.4)		10.7 (5.6)	10.4 (5.2)	11.2 (5.6)	< 0.01
Mean age at cancer diagnosis in years (SD)	9.1 (5.7)		8.9 (5.5)	10.4 (5.7)	8.1 (6.1)	0.50
Age et first CC, N (%)						
< 5 years	11 139 (65.1)	69 884.2 (63.3)	425 (62.0)	6693 (65.5)	4021 (64.9)	
5–10 years	3103 (18.1)	26 727.5 (24.2)	112 (16.3)	1796 (17.6)	1195 (19.3)	< 0.01
> 10 years	2862 (16.7)	13 725.2 (12.4)	149 (21.7)	1737 (17.0)	976 (15.8)	
Birth cohort, N (%)						
< 2000	4776 (27.9)	35 097.8 (31.8)	224 (32.7)	2491 (24.4)	2061 (33.3)	< 0.01
From 2000	12 328 (72.1)	75 239 (68.2)	462 (67.3)	7735 (75.6)	4131 (66.7)	
Cancer types						
Lympho-hematopoietic malignancies, N (%)	38 (64.4)	20 777.1	15 (39.5)	11 (28.9)	12 (31.6)	> 0.50
Leukemia, N (%)	15 (25.4)	11 402.6	8 (53.3)	3 (20.0)	4 (26.7))	> 0.50
Lymphoma, N (%)	23 (39.0)	9374.5	7 (30.4)	8 (34.8)	8 (34.8)	> 0.50

CC: Cardiac Catheterization, SD: Standard deviation, CNS: Central Nervous System, PF: Predisposing factors, *: p value comparing patients for whom data are available on predisposing factors (PF yes/no) to those for whom predisposing factors data are unavailable (PF Unknown)

Table 2 Description of predisposing factor (PF) to cancer type and frequency, and prevalence of different types of predisposing factors

	Predisposing factor to:					
	Leukemia	Lymphoma	Lympho-hematopoietic malignancy	CNS tumors	Frequency of different types of PF (%)*	Prevalence of PF in the cohort (per 1000 patients)
Down syndrome	x		x		318 (44.29)	29.14
Organ transplantation	x	x	x		220 (30.64)	20.16
Noonan syndrome	x		x		116 (16.16)	10.63
Phacomatosis**				x	23 (3.20)	2.11
Severe combined immunodeficiency	x	x	x		11 (1.53)	1.01
Klinefelter's syndrome		x	x		10 (1.39)	0.92
Fanconi Anemia	x		x		9 (1.25)	0.82
Common variable immunodeficiency	x	x	x		9 (1.25)	0.82
Bloom's syndrome	x	x	x		8 (1.11)	0.73
Retinocytoma (RB1)				x	8 (1.11)	0.73
Xeroderma pigmentosum	x		x	x	7 (0.97)	0.64
HIV/AIDS		x	x		6 (0.84)	0.55
Multiple endocrine neoplasia (type 1)				x	1 (0.14)	0.09
Familial adenomatous polyposis				x	1 (0.14)	0.09
Ataxia telangiectasia	x	x	x		1 (0.14)	0.09
Wiskott-Aldrich syndrome	x	x	x		1 (0.14)	0.09
Total					**718 (100)**	**65.80*** **

CNS: Central nervous system, *: A patient can have one or more factors at the same time, **: Phacomatoses including neurofibromatosis (type 1 and 2), ***: Prevalence calculated based on 10 912 patients correctly found in the National Health Database (SNDS) or in the medical discharge databases of the participating cardiology departments

Table 3 Mean with standard deviation (SD) and median with interquartile range (IQR) of cumulative active bone marrow (ABM) dose (in mGy) in the cohort according to cardiac catheterization and both cardiac catheterization plus computed tomography procedures

		ABM (CC)		ABM (CC + CT)		*p value**
	Subjects	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Whole cohort	17 104	3.0 (6.5)	1.4 (2.1)	4.2 (8.4)	1.7 (3.3)	
Patients with lympho-hematopoietic malignancies						
No	17 066	3.0 (6.5)	1.4 (2.1)	4.2 (8.4)	1.7 (3.3)	0.2
Yes	38	4.4 (5.2)	1.9 (4.2)	5.7 (6.9)	2.5 (5.4)	
Patients with leukemia						
No	17 089	3.0 (6.5)	1.4 (2.1)	4.2 (8.4)	1.7 (3.3)	0.13
Yes	15	1.4 (0.9)	1.3 (0.9)	2.3 (4.2)	1.3 (0.9)	
Acute lymphoblastic leukemia	8	0.9 (0.4)	0.8 (0.6)	0.9 (0.4)	0.8 (0.6)	
Myelodysplastic syndrome	3	2.2 (0.8)	1.7 (0.7)	6.9 (9.0)	1.7 (7.8)	
Acute myeloid leukemia	3	1.9 (1.4)	1.6 (1.4)	1.9 (1.4)	1.6 (1.4)	
Burkitt cell leukemia	1	1.6 (--)	1.6 (--)	1.6 (--)	1.6 (--)	
Patients with lymphoma						
No	17 081	3.0 (6.5)	1.4 (2.1)	4.2 (8.4)	1.7 (3.3)	< 0.01
Yes	23	6.4 (5.9)	5.2 (6.4)	7.9 (7.5)	5.4 (8.6)	
Non-Hodgkin's lymphoma	9	6.6 (5.7)	5.4 (3.5)	9.1 (7.2)	6.9 (6.6)	
Hodgkin's lymphoma	7	5.0 (6.3)	2.5 (2.6)	5.0 (6.3)	2.5 (2.6)	
Lymphoproliferative syndrome	6	8..3 (6.7)	8.1 (11.0)	10.4 (9.5)	8.1 (10.1)	
Langerhans histiocytosis	1	2.6 (--)	2.6 (--)	2.6 (--)	2.6 (--)	
Patients with predisposing factors to lympho-hematopoietic malignancies						
No	10 226	2.9 (6.4)	1.4 (2.1)	4.5 (8.3)	1.7 (3.9)	< 0.01
Yes	686	3.9 (6.5)	1.6 (3.4)	7.3 (11.2)	2.6 (8.4)	
Unknown	6192	2.9 (6.7)	1.5 (2.1)	3.5 (8.2)	1.6 (2.4)	
Patients with predisposing factors to leukemia						
No	10 235	2.9 (6.4)	1.4 (2.1)	4.5 (8.3)	1.7 (3.9)	< 0.01
Yes	677**	3.9 (6.5)	1.6 (3.4)	7.4 (11.3)	2.6 (8.5)	
Unknown	6192	2.9 (6.7)	1.5 (2.1)	3.5 (8.2)	1.6 (2.4)	
Patients with predisposing factors to lymphoma						
No	10 659	2.9 (6.3)	1.4 (2.1)	4.4 (8.2)	1.7 (3.8)	< 0.01
Yes	253**	6.8 (9.1)	3.2 (8.0)	13.5 (15.2)	8.5 (14.4)	
Unknown	6192	2.9 (6.7)	1.5 (2.1)	3.5 (8.2)	1.6 (2.4)	

ABM: Active bone marrow, SD: Standard deviation, IQR: Interquartile range, CC: Cardiac catheterization, CT: Computed tomography, *: P value comparing CC + CT dose in the different modalities of each variable, **: A patient could have one or several PFs at a time

Dose-response analyses

Among the 17 104 patients, 38 lympho-hematopoietic malignancies were observed with 15 leukemia and 23 lymphomas. The distribution of AMB doses among the population and the lympho-hematopoietic malignancies, lymphoma and leukemia cases, as well as among their subtypes is described in Table 3. Overall, no statistical difference was observed in lympho-hematopoietic malignancies risk between males and females: The risk of lympho-hematopoietic malignancies was significantly higher in patients with PFs compared to those without PFs, $RR_{PF\ Yes} = 20.25$ (95% CI: 9.34; 45.30), whereas the risk was not significantly different between those with no PF and those with missing information on PFs. The number of cases and the RR per 2-years lag ABM dose categories were presented in Table 4. Most of leukemia cases were distributed in the reference group (the lowest ABM dose category) and the model could not converge for assessing leukemia risks. No significant increased risk was observed among any dose category for all lympho-hematopoietic malignancies or lymphoma. We observed a non-significant association between lympho-hematopoietic malignancies and the CC ABM dose, crude RR = 1.03 (95% CI: 0.90; 1.14) per mGy. The crude risk of lymphoma was of borderline significance, crude RR = 1.12 (95% CI: 0.99; 1.20) per mGy of ABM dose. The model could not converge to estimate the risk for leukemia (Table 5). When adjusting for attained age, gender and PFs, the risk decreased to RR = 1.00 (95% CI: 0.88; 1.10) and to RR = 1.03 (95% CI: 0.90; 1.14) per mGy of ABM

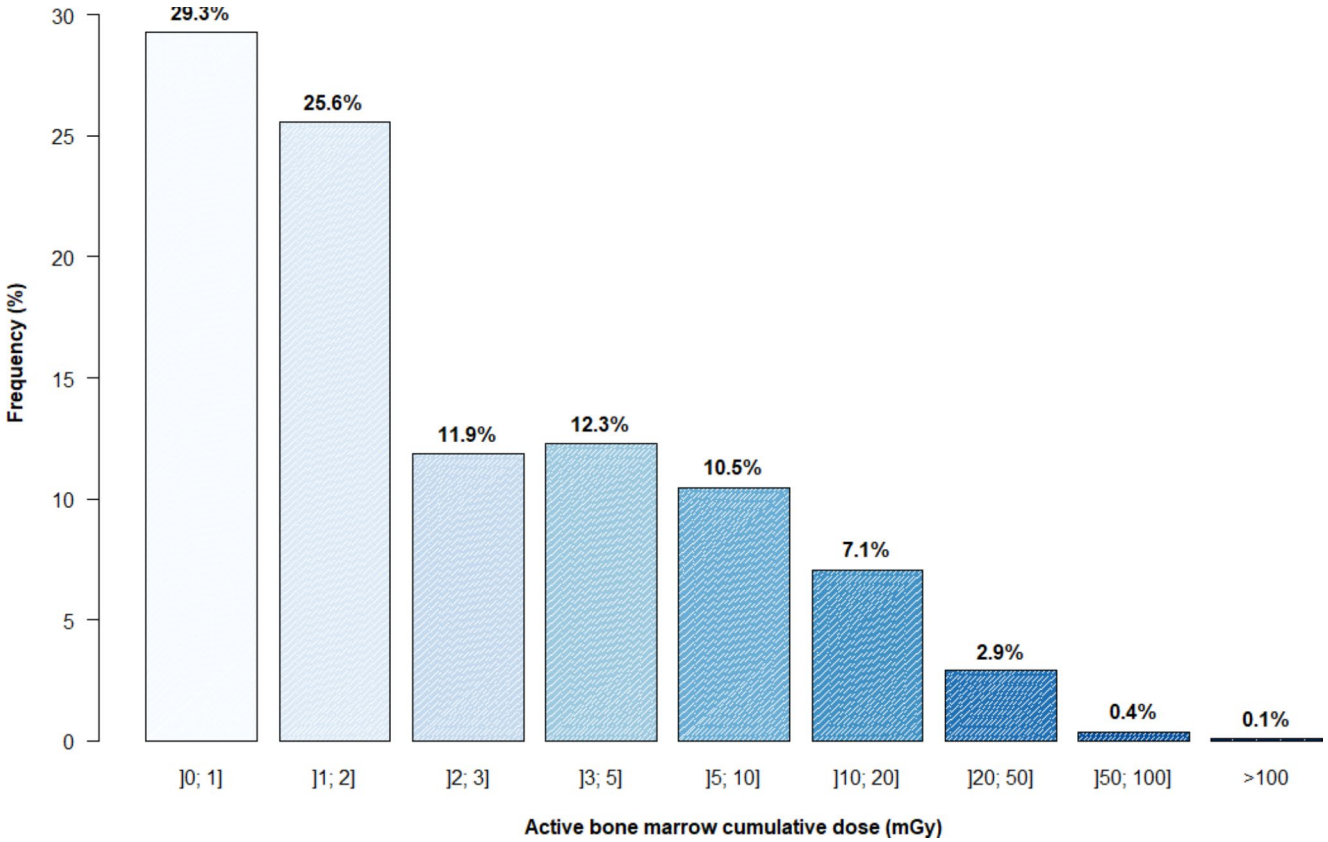

Fig. 1 Distribution of the study population according to cardiac catheterization plus computed tomography according to active bone marrow cumulative dose categories (in mGy)

Table 4 Distribution of lympho-hematopoietic malignancies according to active bone marrow dose categories

	Lympho-hematopoietic malignancies		Lymphoma		Leukemia	
	N	RR [95% CI]	N	RR [95% CI]	N	RR [95% CI]
ABM dose due to CC (in mGy)	**38**		**23**		**15**	
<= 1	20	reference	10	reference	10	reference
]1–2]	9	0.68 (0.29; 1.45)	4	0.60 (0.17; 1.81)	5	--
]2–4]	4	0.59 (0.17; 1.57)	4	1.19 (0.33; 3.55)	0	--
≥4	5	1.23 (0.41; 3.04)	5	2.47 (0.77; 6.94)	0	--
ABM dose due to CC + CT (in mGy)	**38**		**23**		**15**	
<= 1	20	reference	10	reference	10	reference
]1–2]	8	0.64 (0.27; 1.41)	3	0.48 (0.11; 1.58)	5	--
]2–4]	5	0.68 (0.23; 1.69)	5	1.37 (0.43; 3.85)	0	--
≥4	5	0.76 (0.25; 1.89)	5	1.53 (0.48; 4.30)	0	--

ABM: Active bone marrow, CC: Cardiac catheterization, CT: Computed tomography, RR: Relative Risk; 95% CI: 95% Confidence Interval; --: not estimated

dose respectively for lympho-hematopoietic malignancies and for lymphoma. For leukemia risk, the statistical model did not converge after the maximum iterations, preventing the estimation of risks for this outcome. Considering both CC + CT doses to the ABM did not modify the overall risks estimates RR = 0.96 (95% CI: 0.87; 1.03) per mGy for lympho-hematopoietic malignancies, and RR = 0.98 (95% CI: 0.89; 1.04) per mGy for lymphoma. There were no significant effect modification of the dose risk estimates whatever the PF considered and/or the outcome studied (Appendix C, Table C4). The risk of lymphoma was similar when considering the cumulative dose to lymphocytes RR = 1.01 (95% CI: 0.93; 1.04) per mGy or to lymphatic organs RR = 1.02 (95% CI: 0.76; 1.12) per mGy. Relative risks for lympho-hematopoietic malignancies and lymphoma are graphically presented in Fig. 2 according to CC cumulative dose categories. There was no linear trend in the dose response risks estimated for lympho-hematopoietic malignancies

Table 5 Crude and adjusted relative risks (RR) with their 95% confidence interval (95% CI) of lympho-hematopoietic malignancies and lymphoma according to the cumulative active bone marrow dose (in mGy) and different patient characteristics

	Lympho-hematopoietic malignancies			Lymphoma		
	Cases (N)	Crude RR (95% CI)	Adjusted RR (95% CI) *	Cases (N)	Crude RR (95% CI)	Adjusted RR (95% CI) *
Dose	38	1.03 (0.90; 1.14) **	1.00 (0.88; 1.10) **	23	1.12 (0.99; 1.20) **	1.03 (0.90; 1.14) **
Gender						
Male	25	Reference	Reference	16	Reference	Reference
Female	13	0.56 (0.28; 1.07)	0.56 (0.28; 1.08)	7	0.47 (0.18; 1.10)	0.48 (0.19; 1.14)
Attained age						
< 5 years	14	Reference	Reference	3	Reference	Reference
5–10 years	5	0.35 (0.11; 0.91)	0.36 (0.11; 0.93)	2	0.65 (0.09; 3.92)	0.61 (0.08; 3.71)
≥ 10 years	19	1.30 (0.66; 2.65)	1.24 (0.61; 2.57)	18	5.77 (1.95; 24.62)	4.60 (1.52; 19.94)
Predisposing factors[$]						
No	11	Reference	Reference	8	Reference	Reference
Yes	15	21.07 (9.73; 47.06)	20.25 (9.34; 45.30)	7	28.97 (9.71; 80.34)	18.81 (6.08; 54.13)
Unknown	12	1.59 (0.7; 3.67)	1.58 (0.69; 3.64)	8	1.35 (0.51; 3.54)	1.24 (0.46; 3.25)

RR: Relative risk, CI: profile-based confidence interval, *: Adjusted on gender, attained age, and predisposing factors, **: RR per mGy of ABM dose, $: Predisposing factors for the outcome studied. The individual cumulative ABM doses were lagged by two years

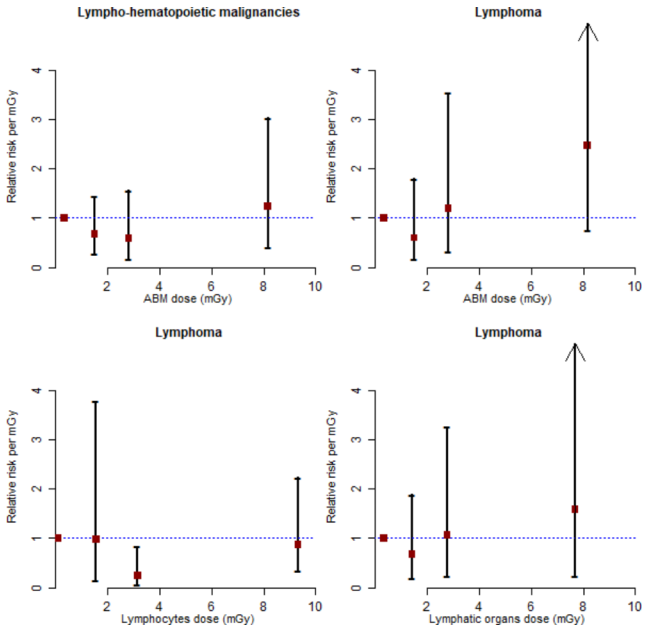

Fig. 2 Estimates of relative risk and profile-base 95% confidence interval (95%CI) per mGy of cardiac catheterization cumulative dose from a univariate log-linear Poisson model across dose categories. Red squares represent the observed relative risk with the vertical solid lines, the 95% CIs. The horizontal dotted blue line gives the relative risk = 1. Dose categories: ≤ 1 mGy, 1–2 mGy, 2–4 mGy and > 4 mGy. The individual cumulative doses were lagged by two years

and lymphoma. Non-significant increased ERR per mGy of lymphoma ($ERR_{/mGy}$ =0.079 (95% CI: -0.152; 0.310)) and lympho-hematopoietic malignancies ($ERR_{/mGy}$ =0.011 (95% CI:-0.119; 0.141)) were observed in relation to ABM dose. ERR per mGy for lymphoma were 0.036 (95% CI: -0.258; 0.329) and 0.009 (95% CI:-0.070; 0.088) in relation to dose to lymphatic organs and to lymphocytes respectively. When the latency period was extended beyond 2 years, ERR for lympho-hematopoietic malignancies and lymphoma tended to decrease, and the uncertainties also markedly increased (Appendix C, Figure C1). Considering the dose-risk relationship for the different subtypes of leukemia or lymphoma cases was not possible due to the low number of cases, nevertheless excluding the three myelodysplastic syndromes (MDS) cases from the main analysis did not result in any substantial change in the reported RR for lympho-hematopoietic malignancies (results not shown).

Discussion

The results of the first dose-response analysis of cancer risk after LDIR exposure from CC during childhood in the COCCINELLE cohort suggest non-significant increased risk of lympho-hematopoietic malignancies and lymphoma after a median follow-up of 5.9 years, whereas no risk could be estimated for leukemia. Taking into account PFs to lympho-hematopoietic malignancy and lymphoma, as well as taking into account for CT doses did not change the overall risk estimations.

The findings from our study are consistent with the unique study to date that assessed excess risk of lympho-hematopoietic malignancies in CHD pediatric and young adult patients after exposure to LDIR from CC and CT [19]. Harbron et al. studied 11 270 children exposed to LDIR from CC aged ≤ 22 years at exposure and followed for 8.4 years in average. The reported ERR/mGy based on 36 malignant and borderline malignant lympho-hematopoietic neoplasia from a total of 74 405 person-years was 0.018 (95% CI: -0.002; 0.096) adjusted on transplant status which is comparable to the $ERR_{/mGy}$ = 0.011 (95% CI: -0.119 ; 0.141) observed in our study.

The most frequent cancer observed in our study population was lymphoma (23 cases, of which 9 Non-Hodgkin's lymphoma, representing 39% of the observed cancers, Table 1). The results from the present study are consistent with those reported earlier, showing limited evidence of radiation-associated lymphoma following exposure to LDIR [47, 48]. Results from the LSS cohort of Japanese atomic bomb survivors showed no evidence of a significant dose-response in the risk of Hodgkin and non-Hodgkin lymphoma [49]. In a recent pooled study of nine cohorts of subjects first exposed to external radiation when aged < 21 years, followed in average for 42.1 years, with a mean ABM dose of 0.14 Gy (ranging from 0 to 5.95 Gy) and with 593 lymphoma cases, there was no significant ERR reported for lymphoma whatever the target tissue/organ considered: $ERR_{/Gy} = -0.031$ (95% CI: −0.237; 0.251) when considering ABM cumulative dose, $ERR_{/Gy}$ = 0.135 (95% CI: −0.205; 0.621), considering lymphocyte dose, and $ERR_{/Gy}$ = 0.492 (95% CI: −0.067; 1.332) when considering lymphatic organ dose [42]. These are demonstrably consistent with risks given here.

In previous published epidemiological studies on medical LDIR exposures and lympho-hematopoietic malignancies risk (leukemia and lymphoma), the target organ used in the dose-response analyses was the ABM [19, 22, 23]. However, the ABM represent only a small fraction (3–7%) of the lymphocyte distribution throughout the body [50, 51]. Biological evidence suggested that the optimal target tissue particularly for lymphoma risk assessment related to LDIR might be the lymphatic tissue or the body of circulating lymphocytes [39–42]. The lymphoma ERRs using respectively ABM, lymphatic organs and lymphocytes doses were all non-significantly increased, whatever the target organ considered. The absence of discrepancies in risk estimates when considering lymphocyte dose and lymphatic organs dose were previously reported [42].

We could not assess the relationship between CC dose and leukemia despite the fact that leukemia cases represented the second most frequent cancer localization in our study. The lack of individual risk estimate for leukemia is a limitation and the combined risk estimates for lympho-hematopoietic malignancies (leukemia and lymphoma) should be read with caution since different patterns in radiation-induced effect had been observed for leukemia and lymphoma. Due to the low number of leukemia cases associated with a specific distribution of cases according to ABM dose categories, models could not fit and it was not possible to assess the dose-risk relationship for leukemia cases only. In the British large study on pediatric CHD patients treated with catheterization [19], the authors had provided an estimate of the excess risk only for lympho-hematopoietic malignancies despite the follow-up of the study pediatric and adolescent population up to adulthood. Nevertheless they conducted a sensibility analysis by excluding all transplanted patients, leading to the exclusion of all lymphoma cases; they observed a borderline significant increased risk (ERR = 0.149 mGy^{-1} [0.001; 0.564]) reflecting risk for leukemia and for borderline malignant hematologic diseases together. These results also highlight the shared limitation of epidemiology studies of radiation exposure which generally require a larger study population with a longer follow-up period. Larger studies conducted in the framework of international collaboration will allow to get a higher number of cases and a better distribution of cases according to the dose categories. The small number of cases for the other cancer sites did not allow analysis of these endpoints. Due to the anatomic zone exposed during CC procedures, breast, lung, liver, and thyroid cancers would be the expected cancer sites associated with the received doses. However, the rather small size of our population, taking into account the small expected risk and the low expected incidence for these cancers because of the young age of the study population at the end of the follow-up (limited to 18 years of age due to the absence of a national adult cancer registry in France), rendered unlikely the observation of any excess of these cancers, which are rare before the age of 35 years [52] and may occur only several decades after exposure [53].

A recent publication on the COCCINELLE cohort reported an increased incidence of all cancer, leukemia, lymphoma, and solid cancers (except for CNS tumors), compared to the French general population after standardization on age, gender and calendar year, without considering the dose received [29]. Mandalenakis et al. assessed the risk of cancer among children and young adults with CHD in a prospective large registry-based cohort [54]. Comparing the cohort with healthy controls, the authors reported a hazard ratio of 2.24 (95% CI: 2.01; 2.48) for all cancer [54]. It is unlikely that exposure to LDIR from CC might explain the large increased risk observed. Other risk factors may include lower physical activity, obesity, socio-economic status, smoking, reduced oxygen uptake and PFs. In our study population of children exposed before 16 years old, the impact of such factors is likely limited due to the long time before the related cancers onset except for PFs. In fact, PFs appear to be the most plausible interpretation for the high risk of cancers among CHD patients. In previous published studies on radiation associated cancers risk after childhood CC, the effect of PFs was not studied [16, 17] or only partially for organ transplantation investigated in the British study [19]. In this last study, the significantly increased estimated risk ($ERR_{/mGy}$=0.542 (95% CI: 0.104; 1.807)) decreased and became non-significant ($ERR_{/mGy}$ =0.018 (95% CI: – 0.002; 0.096)), after adjusting for transplant status. In the present study, the prevalence of PFs was

very high compared to the general population, 65.8 per 1000 patients. However, the lower prevalence of transplanted patients in our study (30.6 per 1000 patients) compared to the prevalence reported in the British study (45.1 per 1000 patients) [19] may explain the small impact of adjustment on PF status on our risk compared to the impact of adjustment on transplant status in the British study. Further analyses did not reveal any significant heterogeneity in the risks across the categories of PFs (Appendix C Table C4). These findings suggest a likely rather small effect of confounding by indication of PFs on the association between radiation and lympho-hematopoietic malignancies or lymphoma risk in our study. A limitation of our study was the absence of information on PF status for about 40% of the cohort. However, the risks estimated for patients without PF and for those with no information on PF were not statistically different, ruling out a large difference between the populations of children with or without available information on PFs.

A strength of our large multicenter study was the individual assessment of CT doses. Recent studies reported that CHD pediatric patients undergo various forms of other medical X-ray examinations in relation to their disease, including CT, nuclear medicine, and conventional radiology procedures [33, 34]. Among the wide range of X-ray examinations that pediatric CHD patients could undergo, about 80 to 95% of the cumulative radiation dose come from both CC and CT procedures [33–35]. We observed that accounting for CT dose in the risk models did not significantly change the radiation-associated lympho-hematopoietic malignancies and lymphoma estimated risks. It had been reported from the past two decades a significant association between CT scan and cancer risk, mainly for leukemia and central nervous system tumors [22, 24, 25, 55, 56]. Reverse causation bias suspected in CTs studies, [26, 27] could be ruled out in our study since CC is always indicated for a cardiac disease, and not for a suspicion of cancer diagnosis. We restricted the dose reconstruction to CTs even if conventional X rays and nuclear medicine procedures were also available, as CTs and CC procedures represent the largest part of the exposure of the patients with CHD [33, 34]. Furthermore, doses from conventional X rays and nuclear medicine examinations would have been associated with large uncertainties in dose reconstruction.

Detailed dosimetry reports were available for 1139 CC procedures between 2010 and 2013 from the largest provider of patients in our cohort. These dosimetry reports allowed for calculation of precise dose estimates per procedure type, allowing an individual dose estimate when the DAP was available. For procedures with missing DAP, imputations based on the median values had been used across age groups and procedure types. Because of the great variability in parameters for each procedure as observed in the detailed dose reports, resulting in a wide variability in dose between similar procedures, future work on the cohort will attempt to better quantify these uncertainties, allowing them to be incorporated into risk estimates.

The quality of the childhood cancer registry (RNCE) is a strength of the study, with its national coverage of pediatric cancers. However, the limitation of the follow-up to the age of 18th is an issue as most of the cancer incidence would be expected at adulthood. Prolonged follow-up of the cohort above 18th based on SNDS database is a great opportunity for further analyses. As the expected risk is small, the statistical power of our study is quite limited, even if the size of our cohort is much higher than in previous published studies [16–19]. The Harmonic (Health effects of cArdiac fluoRoscopy and MOderN radIotherapy in paediatriCs) project, funded by the European commission and launched in 2019, which plans to gather a cohort of 100 000 patients from 7 European countries, will help to better assess the risk linked to CC procedures during childhood [57].

Conclusion

Although pediatric CHD patients exposed to LDIR from CC experienced low levels of radiation exposure, the potential long-term excess risk of radiation-induced cancers is important to assess in particularly among patients that might be subject to several procedures and other LDIR diagnostic imaging. In this study we did not find any statistically significant increased risk of lympho-hematopoietic malignancies and lymphoma in children with CHD diagnosed or treated with CC procedures, and we were not able to assess leukemia risk. Potential confounding factors linked to additional doses linked to CTs and/or underlying disease predisposing to cancers did not modify greatly the risk estimates. However, to increase the statistical power of our analyses, further larger studies at international level are needed to better assess the risks associated with LDIR exposure in the CHD patients. Nevertheless, practitioners should keep in mind the main principles of radiation protection rules, i.e. justification of examinations and optimization of doses, to avoid unnecessary radiation exposure.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-023-01010-7.

Acknowledgments We gratefully thank all the staff members of the participating centers for their contribution to this project, in particular we warmly thank Pr Jérôme Petit (Cardiology department, Hôpital Marie Lannelongue, Le Plessis Robinson), Dr Isabelle Pin, Dr Julia Rousseau and Mrs Caroline Tournegros (Cardiopédiatrie, hôpital couple enfant, CHU Grenoble Alpes), Dr Nadir Benbrik, Dr Bénédicte Romefort, Dr Laurianne Le Gloan and Dr Karine Warin Fresse (CHU Nantes, Clinique Cardiologique et des Maladies Vasculaires, Nantes),

Dr Zakaria Jalal and Dr Xavier Iriart (Department of Paediatric and Adult Congenital Cardiology, Bordeaux University Hospital (CHU), Pessac), Dr Julie Haesebaert (Hospices Civils de Lyon, Pôle de Santé Publique – Service de Recherche et d'Epidémiologie Cliniques, Lyon), Pr Alain Chantepie (Institut des Cardiopathies Congénitales, CHRU Tours), Dr Céline Gronier (Institut cardiovasculaire de Strasbourg - Clinique Rhena), Mrs Brigitte Girodon (M3C-Necker, Hôpital universitaire Necker-Enfants malades), Pr Philippe Acar (Pediatric and Congenital Cardiology, Children's Hospital, University of Toulouse), Pr Jean-René Lusson, Mr Pierre-Emmanuel Dine, Mr Joël Guersen and Mr Florian Magnier (Pôle Imagerie Diagnostique et Radiologie Interventionnelle, CHU Clermont Ferrand), Dr Ali Houeijeh and Mr Jean-Benoît Baudelet (Service de Cardiologie Infantile et Congénitale, Institut Cœur Poumon, Lille), Dr Angelo Livolsi, Dr Selim Saad (Unit of Cardiopediatrics, University Hospital of Strasbourg, Strasbourg), Mrs Christiane Leleu (Unité de cardiologie pédiatrique et congénitale, American Memorial Hospital, CHU de Reims). This report makes use of data obtained from the French national childhood cancer registry and we acknowledge Dr Brigitte Lacour for her help and her support.

Author contributions KDA, SMM, SH, CDa, SDF, SDo, FG, PG, PH, CK, BL, PM, CO, JFP, JBT, DB, MOB, and ER contributed to the study conception and design. SMM, SH, HB, IB, SC, ClDa, SDF, SDo, FG, PG, PH, CK, BL, PM, CO, JFP, JBT, DB extracted and/or provided data. SDr and CeDa worked on the dosimetric aspects. Analyses were performed by KDA, TF, CL, MPL. The first draft of the manuscript was written by KDA, MOB, and ER and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work had received funding from La Ligue contre le cancer (GB/MA/CD/BC 11264), the French National Cancer Institute (INCa) (CFB/SZ-07/06–020) and the Harmonic project with the European Union's Horizon 2020 research and innovation program (grant number 801229).

Declarations

Disclosure of potential conflicts of interest All authors declare no conflict of interest.

Ethics approval The study received ethical approval from the French national data protection commission (*Commission Nationale de l'Informatique et des Libertés*), Agreement number 911112 of 12 December 2011 and Decree in State Council deliberation N°2016-067 of 13/08/2016.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Consent to participate and published This study is a retrospective study and an information letter had been posted in the participating centers.

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