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Exposure to low-dose ionizing radiation from cardiac catheterization and risk of cancer: the COCCINELLE study cohort profile

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Abstract

Purpose: The COCCINELLE study is a nationwide retrospective French cohort set up to evaluate the risk of cancer in patients who undergone cardiac catheterization (CC) procedures for diagnosis or treatment of congenital heart disease (CHD) during childhood.

Participants: Children who undergone CC procedures from 01/01/2000 to 31/12/2013, before the age of 16 in one of the 15 pediatric cardiology departments which perform pediatric CC in mainland France were included. The follow-up started at the date of the first recorded CC procedure 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. The cohort was linked to the National Childhood Cancer Registry to identify patients diagnosed with cancer and with the French National Directory for the Identification of Natural Persons to retrieve the patients' vital status.

Findings to date: A total of 17,104 children were included in the cohort and followed for 110,335 person-years, with 22,227 CC procedures collected. Among the patients, 81.6 % received only one procedure. Fifty-nine cancer cases were observed in the cohort. Standardized Incidence Ratios (SIRs) were increased for all-cancer (SIR = 3.8, 95% confidence interval (CI) 2.9, 4.9), leukemia (SIR = 3.3, 95% CI 2.0, 5.4), lymphoma (SIR = 14.9, 95% CI 9.9, 22.5) and solid cancers excluding central nervous system (CNS) tumors (SIR = 3.3, 95% CI 2.0, 5.5) compared with the general population.

Future plans: Dose reconstruction is currently underway to estimate individual cumulative doses absorbed to relevant organs, including red bone marrow and brain for respectively hematologic disorders and CNS tumors risk estimation. A dose-response-analysis will be conducted with consideration to confounding factors such as age at exposure, gender, predisposing factors to cancer and other sources of medical diagnostic low-dose ionizing radiation.

Strengths and limitations of this study

- The study includes a large national sample of children with congenital heart disease who have undergone cardiac catheterization in France.
- Medical information will be collected from medical records and national databases to take into account potential confounding factors such as predisposing conditions to cancer or exposures to other sources of medical diagnostic low-dose ionizing radiation.
- The organ doses due to ionizing radiation will be estimated for each participant.
- Due to the lack of nationwide cancer registry for adults, the evaluation of the quality of the National Health care database to assess the risk of cancer after 18 years of age is underway. The cohort will be matched with the National Health care database and the association between low-doses ionizing radiation exposure and cancer risk beyond the age of 18 years will be assessed.
- The statistical power of the study is limited due to the small size of the study population in view of the low expected cancer risk and the low doses of radiation exposure. The ongoing European Harmonic project, aiming to pool seven national cohorts (Belgium, France, Italy, Germany, Norway, Spain, and UK) will increase the statistical power of the analyses.

Introduction

Great improvements have been made in medical diagnostic and treatment tools in the recent decades, and modalities using low-dose ionizing radiation (LDIR) have been extensively used in medical routine practices. Patients with congenital heart defect (CHD) benefit from better quality of life and longer life expectancy due to improvements in cardiac imaging and therapeutic procedures such as cardiac catheterization (CC). A steady increase in the number of cardiac imaging and therapeutic procedures using LDIR has been observed in patients with CHD from the 1990s [1–3]. Radiation doses associated to CC procedures are low-to-moderate compared to conventional radiology procedures. However, in some pediatric patients such as transplanted patients and patients with complex heart defects, CC procedures cumulative radiation doses can exceed 100 millisievert (mSv) [4–6]. Furthermore, CHD pediatric patients undergo various forms of other medical X-ray examinations in relation to their condition, including computed tomography (CT), nuclear medicine, and conventional radiology procedures [3, 5, 7–9]. For these patients, about 60% of the cumulative radiation dose come from interventional procedures such as CC [5] and about 80 to 95% come from both interventional and CT procedures [5, 7, 8].

A 1.6 to 2 times higher prevalence of cancer has been reported in adult patients with CHD compared to the general population [10]. Potential explanations to this higher cancer rate include shared genetic or environmental factors, immunosuppression drugs [11, 12], and exposure to medical LDIR procedures [13]. If ionizing radiation is a well-known risk factor of cancer for moderate to high doses, the risk is still debated for doses under 100 mSv, level of doses that can be reached in case of several CC procedures or in case of association between CC and other diagnostic procedures. However, some epidemiological studies have reported an increased cancer risk for doses lower than 50 mSv with risk decreasing with increasing age at exposure [14–16]. Exposure to medical procedures using LDIR in children is an issue as they have a long life expectancy (therefore more time to develop cancer after exposure to LDIR) and they present a higher sensitivity to LDIR than adults (due to their less mature tissues and organs) [17–19]. Data on cancer risk among children and adults with CHD who have undergone cardiac procedures are scarce and only few studies have been published [11, 12, 20–23]. Some investigators reported increased risk of cancer among CHD pediatric patients diagnosed and or treated with CC [12, 22], while others did not report any significant findings [23]. Common limitations to these previous studies were their small size, lack of precise dose assessment and short duration of follow-up.

A nationwide cohort of children and young adults who have undergone diagnostic or therapeutic CC for CHD in childhood, the COCCINELLE (French acronym for *COhorte sur le risque de Cancer après Cardiologie INterventionnELLE*) cohort has been established in mainland France. The study aims to assess the risk of cancer in patients with CHD exposed to LDIR during CC procedures. The aim of this study is to describe the cohort and to analyze the cancer occurrence in this population in comparison to the general population.

Cohort description

Study design

COCCINELLE is a multicenter cohort study on the risk of cancer in patients with CHD who underwent CC procedures for diagnosis or treatment during childhood [24]. The study received ethical approval from the French national data protection commission (*Commission Nationale de l'Informatique et des Libertés*). Retrospective data collection was conducted in fifteen hospitals in France based on medical records of CC examinations performed in pediatric cardiology departments.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Subject identification and inclusion

The study participants are patients who underwent their first CC for CHD between 1st January 2000 and 31st December 2013, who were aged <16 years at the time of the examination, and who have not been diagnosed with cancer before the first recorded CC procedure.

Medical records for 18,906 patients and their 25,139 CC procedures were obtained from pediatric cardiology departments. Patients for whom the type of procedure could not be identified from medical records (unknown procedures) and those with unknown gender or those with missing information on dates (birth, death, examination or cancer diagnosis date) were excluded as those with a diagnostic of cancer before the first CC. Then, 17,104 patients with 22,227 procedures were included in the cohort (Figure 1).

Data collection

Collected data from hospitals include the name, the gender, the place and the date of birth, the identification number, the height and the weight of each patient included in the cohort. The characteristics of the CC procedures such as the date, the type of procedure and the technical details including fluoroscopy time and kerma area product (P_{KA}) when available were also collected.

At each participating hospital, the history of the angiographic systems used during the study period including the type and the brand of the system, the type and the size (in centimeters (cm)) of the image detector and the fixed X-ray filtration were collected. In addition, detailed dosimetry reports issued from the system at the end of each CC procedure were collected for a sample of patients. The detailed dosimetry reports include information on primary and secondary angulation, field of view (in cm), source-image distance (in cm), and tube potential (in kilovolt (kV)), as well as air kerma and P_{KA} per acquisition.

In order to assess a potential confounding effect of the patient's health condition, information on underlying diseases or cancer predisposing factors will be retrieved from various sources including hospital discharge databases or from examination of notes fields in procedures' logbooks.

Exposure assessment

To assess the possible link between the exposure to LDIR from CC procedures and the subsequent occurrence of cancer, individual doses to specific relevant organs, including red bone marrow and brain for respectively hematologic disorders (leukemia and lymphoma) and central nervous system (CNS) cancer risk estimation, will be estimated. First of all, the CC procedures were grouped into a common classification defined by an expert group of cardiologists (DB, SMM, SH, SC), in order to define families of procedures that are similar. Twelve and three families of procedures were defined respectively for therapeutic and diagnostic procedures (Supplemental material S1). LDIR exposure scenarios will be defined based on available detailed dosimetry reports for each family of procedures, for different patient age group (0-1, 1-5, 5-10, 10-15, and ≥15 years), and if necessary, for each cardiology department. Based on these exposure scenarios, organ dose computations will be performed with the PCXMC Monte Carlo simulation code (v2.0, STUK, Helsinki, Finland). The organ dose assessment is underway,

consequently at this step of the study, only the number of CC procedures will be considered with regard to the cancer incidence analysis.

Follow-up and outcome

Follow-up started at the date of the first recorded CC procedure until the exit date i.e. the date of death, the date of first cancer diagnosis, the date of the 18th birthday, or the 31st December 2015, whichever occurred first.

Vital status and date of death were obtained through linkage with the French National Directory for the Identification of Natural Persons (RNIPP). Additional information from medical records allowed to complete vital status when the linkage of the cohort with the RNIPP failed to identify a patient (25% of the cohort), as the large majority of the patients were closely followed in the cardiology department for their CHD.

Matching the COCCINELLE cohort with the National Childhood Cancer Registry (*Registre National des Cancers de l'Enfant* (RNCE)) allowed to identify patients who had been diagnosed with cancer and to obtain the recorded date of diagnosis and the type of cancer. The RNCE have been registering all cancer cases in children less than 15 years old in mainland France, since 1990 for hematologic disorders and since 2000 for solid tumors [25]. Since 2011, the coverage perimeter of the RNCE has been extended to adolescents under the age of 18 and to residents of French overseas departments. At the time of the linkage, the cancer registry data were available until 31/12/2015.

Since the distribution of childhood cancers according to the histological type and location might be very different from what is observed in adults, cancers cases are described according to the International Classification of Disease – Oncology, third edition (ICDO- 3) and grouped further using the International Classification of Childhood Cancer – third version (ICCC3) [26]. For patients diagnosed with multiple cancers during the follow-up, only the first occurring cancer was considered, except for non-melanoma skin cancers.

Statistical analysis

The cohort characteristics were described as counts, proportions, means (with the standard deviation (SD)) or median (with the interquartile range (IQR)).

We conducted external comparisons using standardized incidence ratios (SIR) calculated as the ratio of the number of observed cases in the cohort to the number of expected cases based on the national cancer incidence rates provided by the RNCE [25, 27]. The SIRs were standardized by age (0-1, 1-5, 5-10 and 10-15), calendar year (2000-2005, 2005-2010, and 2010-2015), and by gender (male and female). Breslow and Day's approximation [28] was used to estimate 95% confidence intervals (CI) for the SIRs. The SIRs were calculated for five groups of cancer: all-cancer (including all childhood cancer types ICCC3: I - XII), leukemia (ICCC3: Ia, Ib, Id, Ie), lymphoma (ICCC3: IIa–IIc), CNS tumors (ICCC3: IIIb, IIIc, IIIe, IIIf), and solid cancers excluding CNS tumors (ICCC3: IV, VI, VIII – XII).

In order to consider incident cancers possibly associated with CC exposure, we conducted sensitivity analyses in which a minimal exclusion period of two and five years between the first exposure and the cancer onset was applied by excluding respectively, patients who were diagnosed with a cancer within two and five years after the first CC procedure. The SIRs were also computed according to the number of procedure undergone (1, 2, and 3 or more) and a trend test was performed. SIRs analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria) using the package Epi for the person-years computation and the package popEpi [29]. The statistical significance was defined by $p < 0.05$.

Results

Characteristics of the study population

The whole cohort consisted of 17,104 subjects, 51% of whom were males. The median duration of follow-up was 5.9 years (IQR 6.4 years), accounting for a total of 110,335 person-years. Children younger than one year at their first CC represented 38.7% of the whole cohort. The median age at exit from the cohort was 10.8 years (IQR 9.3 years). The characteristics of the study patients are described in Table 1.

A total of 22,227 CC procedures were recorded in the cohort (Table 2). The number of procedures received by the patients ranged from 1 to 14; about 82% of the study subjects received only one procedure. Diagnostic procedures represented 8,931 (40.2%) of all procedures performed whereas therapeutic procedures represented 13,296 (59.8 %) (Table 2). Among therapeutic procedures, the most frequent ones were patent ductus arteriosus closure (13.7%), pulmonary valvuloplasty (9.2%), atrial septal defect closure (7.8%), and pulmonary artery dilatation or stenting (5.9%).

Findings to date

Fifty-nine cancer cases were recorded from 2000 to 2015, among them 34 (57.6%) occurred in males. The median age at cancer diagnosis was 7.4 years (IQR 10.4 years). The cancer types are described in Table 3. The number of procedures per subject was not different between the cancer cases and the non-cancer patients. Thirty-four out of 59 cancers were diagnosed at least two years after the first CC procedures which count 13 (38.2%) lymphomas, 7 (20.6%) leukemia and 14 (41.2%) solid cancers. After a 5-year exclusion period, 15 out of 59 cancer cases were observed with 7 (46.7%) lymphomas, 2 (13.3%) leukemia and 6 (40%) solid cancers.

The results of the analyses comparing cancer incidence in the cohort with that of the general population are presented in Table 4. The SIRs were increased for all-cancer (SIR = 3.8, 95% CI 2.9, 4.9), leukemia (SIR = 3.3, 95% CI 2.0, 5.4), lymphoma (SIR = 14.9, 95% CI 9.9, 22.5) and solid cancers excluding CNS tumors (SIR = 3.3% CI 2.0, 5.5) compared with the general population. In a sensitivity analyses, after exclusion of cases diagnosed within the first 2 years after exposure to the first CC examination, SIRs were increased for all-cancer (SIR = 3.4, 95% CI 2.4, 4.7), leukemia (SIR = 2.3, 95% CI 1.1, 4.9), lymphoma (SIR = 10.8, 95% CI 6.3, 18.7) and solid cancers excluding CNS tumors (SIR = 3.4, 95% CI 1.8, 6.5). When considering a 5-year exclusion period, increased SIRs were observed for all-cancer (SIR = 3.3, 95% CI 2.0, 5.4), lymphoma (SIR = 9.5, 95% CI 4.5, 20.0) and solid cancers excluding CNS tumors (SIR = 4.3, 95% CI 1.8, 10.2). SIRs were increased whatever the number of procedure received (1, 2 and 3 or more) with higher SIR for patients receiving 3 or more procedures (SIR = 6.1, 95% CI 3.0, 12.1) compare to those receiving 1 procedure (SIR = 3.7, 95% CI 2.7, 4.9). However, the p-value for trend in SIRs according to the number of procedures undergone (1, 2 and 3 or more) was not statistically significant, p-value = 0.2 (Table 4).

Discussion

Main findings

This first analysis of the COCCINELLE cohort shows a higher incidence of all-cancer, leukemia, lymphoma, and other solid cancer (excluding CNS tumors) in the cohort compared to the general population. In a sensitivity analysis in which all cases occurring during the first 2- and 5-year were excluded, the SIRs remained significantly increased for all-cancer, lymphoma and solid cancer excluding CNS tumors. The SIRs increased non-significantly with the increasing number of procedures received in childhood.

The results from the current study are consistent with the two previous studies that reported increased cancer incidence following pediatric CC for CHD [12, 22] compared to the general population. Modan et al. [12] observed a SIR of 2.3 (95% CI 1.2, 4.1) based on the follow-up of 674 children between 1950-1970 in Israel and Harbron et al.[22] reported higher incidence rates for all-cancer (SIR = 2.32; 95% CI: 1.65, 3.17), lymphoma (SIR = 8.34; 95% CI 5.22, 12.61), and leukemia (SIR = 2.11; 95% CI 0.82, 4.42) in a cohort of 11,270 children exposed when aged ≤ 22 years. On the contrary, a study based on the follow-up of 4,891 children and young adults exposed to CC before the age of 18 between 1946 and 1968 in Canada did not report any significant increase in cancer incidence, with a SIR of 1.2 (90% CI 0.6, 2.3) [23]. In adult population, an increased SIR for all-cancer was also reported from a study on patients who had undergone CC for CHD at adulthood [30].

CT and CC procedures both deliver X-ray radiation. Recent studies reported radiation doses delivered by CT ranging from 8 to 12 milliGray (mGy) to the red bone marrow [31–34], a range of doses consistent to the mean dose of 8.8 mGy to the red bone marrow reported from a recent CC study [22]. As cumulative doses due to CT in childhood are in the range of those delivered by CC procedures, the estimated SIRs in our cohort can be compared to those from recently published CT studies [32–35]. Findings from the current study are consistent with results from a nationwide retrospective cohort of 168,394 children who received one or more CT in Dutch hospitals between 1979 and 2012, when aged <18 years [36]: the SIRs were 1.47 (95% CI 1.34, 1.61) for all-cancer, 1.39 (95% CI 1.13, 1.70) for hemato-lymphoproliferative disorders, and 2.05 (95%CI 1.48, 2.83) for CNS tumors after applying a 5-year latency period. In a German study on 39,184 children younger than 15 years who received CT between 1980 and 2010, Krille et al. [32, 33] reported significant increased SIRs for all-cancer (SIR = 1.82, 95% CI 1.29, 2.50), and lymphoma (SIR = 2.96, 95% CI 1.42, 5.45).

CHD patients usually require ongoing care to monitor their condition that may result in repeated exposure to LDIR [3, 5, 7–9] and may lead to high cumulative doses. In the current study, the cumulative number of procedure received (1, 2 and ≥ 3 procedures) is used as a surrogate to the cumulative individual doses. A significant increased SIR was observed whatever the number of CC procedures performed, but a slight non-significant positive trend was observed in the SIRs according to the increasing number of procedures received (SIR = 3.7, 95% CI 2.7, 4.9 for one procedure, SIR = 3.2, 95% CI 1.5, 6.8 for 2 procedures and SIR = 6.1, 95% CI 3.0, 12.1 for ≥ 3 procedures; p-value for trends = 0.2). Cohen et al. used the cumulative number of procedure performed to estimate the risk of cancer after

exposure to LDIR in adult patients and shown that the cumulative number of procedures and the cumulative effective dose could lead to similar results [30]. In the current study, however, since no dose assessment and no dose-response analyses are yet available to explain the increased SIRs according to the cumulative number of procedures received, this result should be interpreted with caution. An individual dose reconstruction is currently underway to estimate the cumulative organ doses for each of the cohort members, including the contribution of doses from CTs and other medical diagnostic radiation procedures. A dose-response analysis will then be performed to confirm or not these first results.

Strengths and limitations

The COCCINELLE cohort is the first study in France to assess cancer risk in 17,104 CHD patients who undergone CC in childhood. The study has access to national well-handled registries which have almost an exhaustive coverage of the general population. The sample of CHD patient included in the cohort is representative of the pediatric CHD patients since the major pediatric departments performing CC in mainland France agreed to participate to the study and contributed actively. However, several limitations should be mentioned.

The SIR analyses did not include any information on the dose received during the CC procedures and the results should be interpreted consequently. Doses estimates are currently underway to provide with accurate dosimetry data for each patient in the study and cumulative organ doses will be used in the dose response analyses. In addition, CHD pediatric patients could undergo other diagnostic LDIR procedures such as CT which deliver dose in the same range as CC, nuclear medicines, and conventional radiographies. The more patients have received CC, the more they are susceptible to be exposed to other diagnostic medical LDIR. It is important to consider these various sources of exposure since they can contribute significantly to the overall cumulative organ dose. Further analyses of the cohort will address this issue in the risk estimate models.

The individual dose reconstruction is intended for procedures performed in the cohort, from 2000 to 2013. However single doses delivered per examination are continuously decreasing due to advances in technologies, protocol improvements and awareness of cardiologists. Therefore, the dose estimates will not reflect the current dose reduction practices in cardiology departments and this weakness is inherent to all retrospective epidemiology studies. Nevertheless, epidemiology studies are still relevant for decision making and radioprotection purposes.

Other limitation from the first results of the SIR analyses is the use of the general population as reference group. An increased risk of cancer in CHD patients compared to the general population has already been reported [13]. Common etiologic factors in CHD patients could be suspected [11, 21] as gene mutations in embryogenesis related to birth defects and cancer development [37]. Post-transplants are also known to present higher rate of cancer due to the use of immunosuppression drugs [38]. In the UK study on cancer risk after CC in childhood, 509 out of 11,270 individuals had received a transplanted organ with twenty-six malignancies occurring among these transplanted patients. The authors reported that all of the lymphoma cases observed in the cohort came from transplanted subjects. Furthermore, censoring these transplant subjects decreased the SIR for all-cancer from 2.32 (95% CI 1.65, 3.17) to 0.90 (95% CI 0.49, 1.49) [22]. Transplantation status and any other cancer predisposing factors are not considered in the SIRs analysis and the increased SIRs reported in the present study might be confounded with a potential effect of underlying cancer predisposing factors such as Down syndrome, Noonan syndrome, severe combined immune deficiency, etc.

Indication bias and reverse causation bias can be suspected when cancer predisposing factors or early symptoms of undetected cancer are the indication of the examination. In the COCCINELLE cohort study, reverse causation bias can be ruled out as the indication of CC is always the CHD. However, indication bias should be studied since medical conditions associated with cancer risk predisposition could also be associated with exposure to LDIR diagnostic procedures. Then, it will be crucial to take into account individual information on cancer risk predisposition in the ongoing main analyses. Due to the lack of a national registry on transplantation or genetic syndromes in France, the COCCINELLE cohort will use information from discharge databases, which are complete enough to retrieve patients with predisposing factors to cancer [39]. Additionally, information from the National Health Insurance database will be used for a large part of the studied population. However, the study was not designed to directly assess the effect of factors such as obesity, socio-economic status, and heredity (for inherited cancer predisposing factors) in the risk estimate models since these data could not be retrieved directly from medical record databases.

The death rate in the cohort is currently 6.5% for 803 deaths registered in patients for whom this information is available. Investigators had reported an increased mortality rates among CHD population [40], suggesting that some subjects might die from the underlying condition (i.e. cardiac dysfunction) before developing cancer. Therefore,

competitive risk should be considered in the ongoing analyses to take into account the risk of death before the studied outcome, i.e. cancer. This was observed in the French cohort study on CTs, where the early increased mortality in patients with predisposing factors to cancer leads to decreased risks of radiation associated leukemia and CNS tumor compared to the increased risk observed in patients without predisposing factors to cancer [31].

The number of patients lost to follow-up is currently low in the cohort since children with CHD are closely followed in cardiology departments involved in this study for the monitoring of their conditions. They can be retrieved from medical records or from National health databases after 2006; however, we are not able to follow patients, who have emigrated, been diagnosed, or treated outside France borders. The follow-up of our population is currently limited to the age of 18 years, due to the lack of a nationwide cancer registry for adults. However, the building of a national cohort of cancer patients since 2010 by the French national cancer institute (*Institut National du Cancer*) based on the National Health Insurance data will provide a very useful tool to follow the incidence of cancer in our cohort at adult age [41].

In perspective, further improvements of the cohort data including dosimetry data, exposure to other LDIR, and cancer predisposing factors will be available to provide more insight on the risk of cancer following CC exposure in childhood.

Collaboration

The COCCINELLE study data are not freely available because of ethical and data protection constraints. However, we welcome inputs from researchers on collaborative projects that will involve the study data. Proposals for possible collaborations in further analyses of the data should be addressed to Dr Estelle Rage. Currently, such collaboration have been established in an international collaborative project named Harmonic (Health effects of cArdiac fluoRoscopy and mOdern radIotherapy in paediatriCs)[42], with the aim of gather the few studies on CC already set-up in France and in the UK and to build new ones to provide more insight on the association between low to moderate radiation doses received during childhood and cancer risk.

Contributorship statement

MOB, ER, KL lead the project at national level, raised the funding, established the cohort, and provided intellectual inputs to the manuscript. KDA and TF were involved in data analysis, data presentation and drafted the manuscript. SMM, SH, SD, SC and DB contributed to the implementation of the project and to the conception of this article. CD, SDF, SD, FG, PG, PH, CK, BL, PM, CO, JFP and JBT were the local investigators of the project. They contributed to the study design and critically revised the manuscript for important intellectual content. All authors critically revised the manuscript and approved the final version.

Competing interests

None to declare

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Data sharing statement

All data from the COCCINELLE study are deposited at the Laboratory of Epidemiology at French Institute for Radiological Protection and Nuclear Safety (IRSN), BP 17, 92262 Fontenay-aux-Roses, France. The COCCINELLE study data sharing is subject to ethical and data protection constraints. Interested researchers can approach ER principal investigator (estelle.rage@irsn.fr) for sharing COCCINELLE data as part of collaborative research projects (if not overlapping with ongoing research projects, and subject to a Data Use Agreement).

Ethics approval

The study received ethical approval from the French national data protection commission (*Commission Nationale de l'Informatique et des Libertés*), deliberation N°2016-067 of 13/08/2016.

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Table 1: Description of the COCCINELLE cohort, 2000-2015

	Patients with cancer N=59	**Patients without cancer** N=17,045
Demographics		
Male, N (%)	34 (57.6)	8,702 (51.1)
Median age (in year) at first procedure (IQR)	2.6 (9.9)	2.2 (7.4)
Median age (in year) at exit (IQR)	7.4 (10.4)	10.9 (9.3)
Age at first procedure, N (%)		
< 1 year	24 (40.7)	6,589 (38.7)
1 – 5 years	12 (20.3)	4,206 (24.7)
5 – 10 years	8 (13.6)	3,216 (18.9)
10 – 15 years	15 (25.4)	3,034 (17.8)
Birth period, N (%)		
[1980, 1990]	2 (3.4)	484 (2.8)
]1990, 2000]	20 (33.9)	4,273 (25.1)
]2000, 2010]	31 (52.5)	9,511 (55.8)
]2010, 2013]	6 (10.2)	2,777 (16.3)
Number of procedures received by children, N (%)		
1 procedure	44 (74.6)	13,929 (81.7)
2 procedures	7 (11.9)	2,021 (11.9)
≥ 3 procedures	8 (13.6)	1,095 (6.4)

IQR: Interquartile range

Table 2: Description of the cardiac catheterization procedures received in the COCCINELLE cohort

	Total	(%)
Category of procedures		
Therapeutic	13,296	59,8
Diagnostic	8,931	40.2
Total	22,227	100
Most frequent families of procedures		
Diagnostic cardiac catheterization without angiography[d]	3,868	17.4
Patent ductus arteriosus closure	3,046	13.7
Pulmonary valvuloplasty	2,052	9.2
Atrial septal defect closure	1,741	7.8
Right and left heart angiography[d]	1,466	6.6
Left heart angiography[d]	1,313	5.9
Pulmonary artery dilatation or stenting	1,310	5.9
Atrial septostomy	1,208	5.4
Rythmology	1,165	5.2
Right heart angiography[d]	1,066	4.8
Other procedures	3,992	17.9

d: Diagnostic procedures

Table 3: Description of the cancers that occurred in the COCCINELLE cohort from 2000 - 2015

Cancer type	**All period** N (%)	**After a 2-year exclusion*** N (%)	**After a 5-year exclusion*** N (%)
Leukemia ICCC3: Ia, Ib, Id, Ie	15 (25.4)	7 (20.6)	2 (13.3)
Lymphoma ICCC3: IIa-IIc	23 (39.0)	13 (38.2)	7 (46.7)
Central nervous system ICCC3: IIIb, IIIc, IIIe, IIIf	6 (10.2)	5 (14.7)	1 (6.7)
Neuroblastoma and other peripheral nervous cell tumors ICCC3: IVa, IVb	1 (1.7)	1 (2.9)	1 (6.7)
Renal tumors ICCC3: VIa, VIb	4 (6.8)	3 (8.8)	-
Malignant bone tumors ICCC3: VIII	1 (1.7)	-	-
Soft tissue and other extra osseous sarcomas ICCC3: IXb, IXe	4 (6.8)	2 (5.9)	2 (13.3)
Germ cell tumors ICCC3: X	2 (3.4)	1 (2.9)	-
Other malignant epithelial neoplasms ICCC3: XI	2 (3.4)	1 (2.9)	1 (6.7)
Other and unspecified malignant neoplasms ICCC3: XII	1 (1.7)	1 (2.9)	1 (6.7)
All-cancer	59 (100)	34 (100)	15 (100)

ICCC3: International Classification of Childhood Cancer – third version (ICCC3) [25]
** : 2- and 5-year exclusion: Exclusion of all -cancer cases diagnosed respectively within 2 or 5 years after the first CC procedure.*

Table 4: Standardized incidence ratio (SIR) for cancers in the COCCINELLE cohort

	All-period		After a 2-year exclusion*		After a 5-year exclusion*	
	Number of cases	SIR (95% CI)	Number of cases	SIR (95% CI)	Number of cases	SIR (95% CI)
Type of cancer						
All-cancer	59	3.8 (2.9; 4.9)	34	3.4 (2.4; 4.7)	15	3.3 (2.0; 5.4)
Leukemia	15	3.3 (2.0; 5.4)	7	2.3 (1.1; 4.9)	2	1.6 (0.4; 6.6)
Lymphoma	23	14.9 (9.9; 22.5)	13	10.8 (6.3; 18.7)	7	9.5 (4.5; 20.0)
CNS	6	1.5 (0.7; 3.4)	5	1.9 (0.8; 4.5)	1	0.8 (0.1; 5.5)
Solid cancer**	15	3.3 (2.0; 5.5)	9	3.4 (1.8; 6.5)	5	4.3 (1.8; 10.2)
By gender: Male						
All-cancer	34	3.9 (2.8; 5.5)	21	3.7 (2.4; 5.7)	7	2.7 (1.3; 5.6)
Leukemia	9	3.5 (1.8; 6.7)	7	4.1 (1.9; 8.5)	2	2.8 (0.7; 11.1)
Lymphoma	16	15.3 (9.4; 25.0)	10	12.3 (6.6; 22.9)	4	8.2 (3.1; 21.7)
CNS	4	1.8 (0.7; 4.9)	3	2.0 (0.6; 6.2)	-	-
Solid cancer**	5	2.2 (0.9; 5.2)	1	0.7 (0.1; 5.2)	1	1.7 (0.2; 12.2)
By gender: Female						
All-cancer	25	3.6 (2.5; 5.4)	13	3.0 (1.7; 5.1)	8	4.1 (2.0; 8.1)
Leukemia	6	3.0 (1.4; 6.7)	-	-	-	-
Lymphoma	7	14.2 (6.8; 29.7)	3	7.8 (2.5; 24.1)	3	12.2 (3.9; 37.9)
CNS	2	1.1 (0.3; 4.5)	2	1.7 (0.4; 6.7)	1	1.8 (0.3; 12.6)
Solid cancer**	10	4.6 (2.5; 8.5)	8	6.1 (3.1; 12.2)	4	6.7 (2.5; 17.9)
By age group (all-cancer)						
< 1 year	1	0.9 (0.0; 4.8)	-	-	-	-
1 – 5 years	23	3.7 (2.3; 5.5)	13	3.9 (2.1; 6.7)	-	-
5 – 10 years	12	2.7 (1.4; 4.6)	8	2.1 (0.9; 4.2)	6	2.4 (0.9; 5.3)
10 – 15 years	14	3.9 (2.1; 6.5)	8	2.7 (1.2; 5.3)	6	2.8 (1.0; 6.2)
By calendar period (all-cancer)						
2000 - 2005	8	4.2 (2.1; 8.4)	1	1.6 (0.2; 11.6)	-	-
2005 - 2010	23	4.3 (2.9; 6.5)	13	3.9 (2.3; 6.7)	5	4.5 (1.9; 10.9)
2010 - 2015	28	3.4 (2.3; 4.9)	20	3.3 (2.1; 5.1)	10	2.9 (1.6; 5.4)
Number of the cardiac catheterization procedures received (all-cancer)						
1	44	3.7 (2.7; 4.9)	24	3.1 (2.1; 4.7)	7	2.1 (1; 4.3)

2	7	3.2 (1.5; 6.8)	5	3.4 (1.4; 8.2)	4	5.7 (2.1; 15.2)
3 or more	8	6.1 (3.0; 12.1)	5	5.5 (2.3; 13.1)	4	8.8 (3.3; 23.3)
*p-value***		0.2		0.2		< 0.01

CNS: Central nervous system tumors
SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
***: 2- and 5-year exclusion: Exclusion of all -cancer cases diagnosed respectively within 2 or 5 years after the first CC procedure*
****: Solid cancer excluding central nervous system tumors*
*****: p-value for trends.*

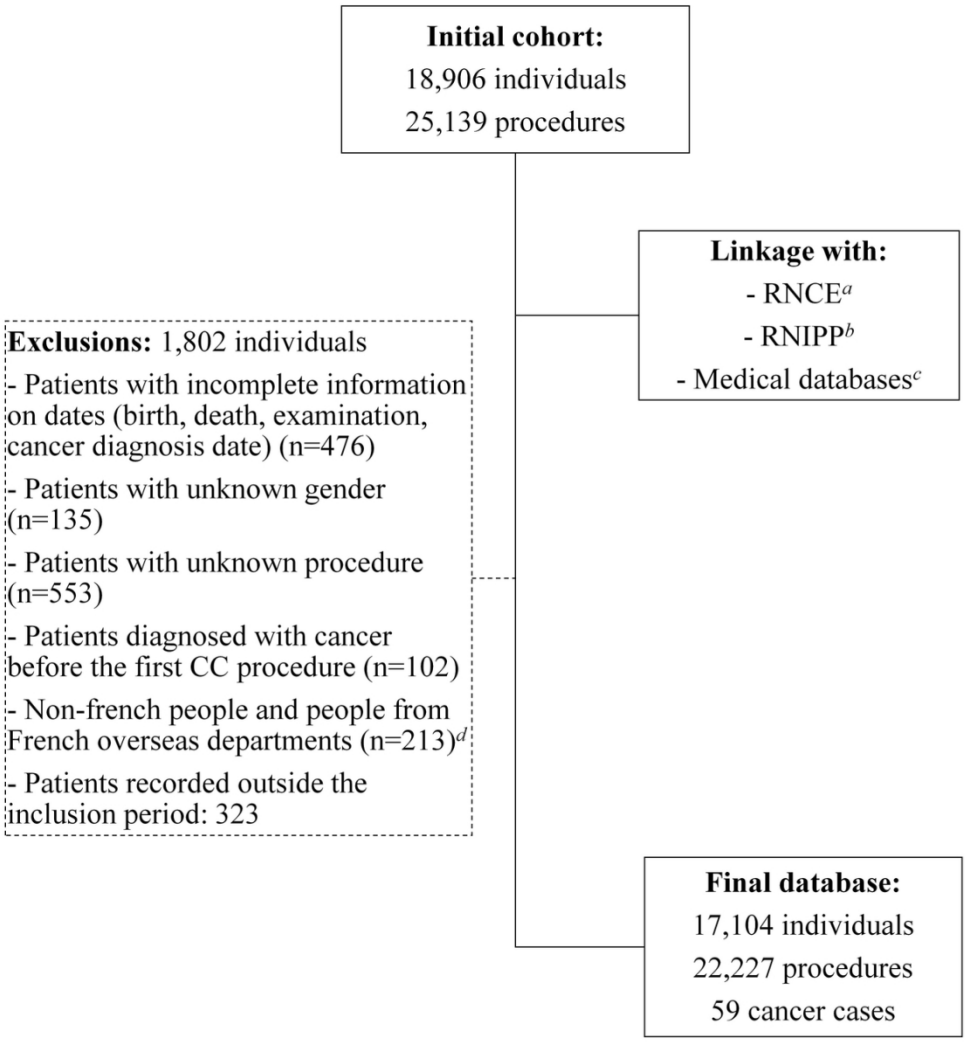

Figure 1: Flow chart of the COCCINELLE cohort constitution

a: RNCE: French National Childhood Cancer Registry (Registre National des Cancers de l'Enfant)
b: RNIPP: French National Directory for the Identification of Natural Persons
c: Medical discharge and reimbursement databases
d: French oversea departments not covered by the RNCE before 2011
CC: Cardiac catheterization

109x118mm (300 x 300 DPI)

Supplemental material

S1: Category and family classification of cardiac catheterization procedures in the COCCINELLE cohort

Category of procedures	Family of procedures	Names of the procedures
Diagnostic procedures	Right heart angiography	- Catheterization right with contrast
	Diagnostic procedures without angiography	- Catheterization right without contrast - Catheterization left without contrast - Catheterization left and right without contrast - Biopsy endo-myocardial Pulmonary arterial hypertension - Pulmonary arterial hypertension with normal heart - Pulmonary arterial hypertension shunt (Eisenmenger)
	Left heart angiography	- Catheterization left with contrast
Therapeutic procedures	Pulmonary valvuloplasty	- Pulmonary valve dilatation - Pulmonary atresia intact ventricular septum, radiofrequency, perforation - Perforation pulmonary valve
	Aortic valvuloplasty	- Aortic valve dilatation
	Rashkind	- Atrial septostomy
	Aortic dilatation / stenting	- Balloon dilatation of coarctation of the aorta - Stenting of aortic coarctation
	Pulmonary artery dilatation / stenting	- Balloon dilatation of pulmonary artery: unique / multiple - Balloon dilatation of pulmonary artery - Balloon dilatation of right ventricle - pulmonary artery conduit - Balloon dilatation of homograft - Balloon dilatation of pulmonary artery banding - Stenting of pulmonary artery branch: unique stent / multiple stents - Stenting of pulmonary artery trunk: unique stent / multiple stents - Stenting of right ventricle - pulmonary artery conduit: unique stent / multiple stents - Percutaneous pulmonary valve implantation - Patent ductus arteriosus dilatation

	Various angiography	- Balloon dilatation of superior vena cava - Superior vena cava stenting - Balloon dilatation of inferior vena cava - Inferior vena cava stenting - Balloon dilatation of pulmonary vena - Pulmonary vein stenting: unique / multiple - Balloon dilatation of coronary artery - Stenting Coronary: unique / multiple - Patent ductus arteriosus stent (non-neotal) - Major aortopulmonary collateral arteries: unique/ multiples - Balloon dilatation of Blalock - Stenting Blalock: unique/ multiples - Thrombo-aspiration, Vertical vein closure, Occlusion femoral artery, stenting iliac artery, Stenting subclavian artery. - Percutaneous removal of a foreign body - Arterio-venous fistula embolization: unique/ multiples - Blalock embolization - Fenestration closure - Sequestration closure: unique / multiple - Coronary fistula closure: unique / multiple - Aorto-pulmonary collaterals embolization: unique / multiple
	Complex neonatal procedures	- Hybrid procedures - Patent ductus arteriosus stenting - Atrial septal defect creation - Atrial septal defect stenting
	Atrial septal defect closure	- Atrial septal defect closure - Patent foramen ovale
	Ventricular Septal Defect (VSD) closure	- Ventricular septal defect closure
	Arterial duct closure	- Patent ductus arteriosus closure: coil / plug
	Rythmology: stimulation	- Pacemaker - Defibrilators - Pacing
	Rythmology: electrophysiology	- Electrophysiology, Flutter, Kent
Other procedures	Other unclassified procedures	- Catheterization left and right with contrast - Biopsy and coronarography - Tricuspid dilatation - Mitral valve dilatation - Aorto-pulmonary window (aorto-pulmonary septal defect)

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Exposure to low-dose ionizing radiation from cardiac catheterization and risk of cancer: the COCCINELLE study cohort profile

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Abstract

Purpose: The COCCINELLE study is a nationwide retrospective French cohort set up to evaluate the risk of cancer in patients who undergone cardiac catheterization (CC) procedures for diagnosis or treatment of congenital heart disease (CHD) during childhood.

Participants: Children who undergone CC procedures from 01/01/2000 to 31/12/2013, before the age of 16 in one of the 15 pediatric cardiology departments which perform pediatric CC in mainland France were included. The follow-up started at the date of the first recorded CC procedure 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. The cohort was linked to the National Childhood Cancer Registry to identify patients diagnosed with cancer and with the French National Directory for the Identification of Natural Persons to retrieve the patients' vital status.

Findings to date: A total of 17,104 children were included in the cohort and followed for 110,335 person-years, with 22,227 CC procedures collected. Among the patients, 81.6 % received only one procedure. Fifty-nine cancer cases were observed in the cohort. Standardized Incidence Ratios (SIRs) were increased for all-cancer (SIR = 3.8, 95% confidence interval (CI) 2.9, 4.9), leukemia (SIR = 3.3, 95% CI 2.0, 5.4), lymphoma (SIR = 14.9, 95% CI 9.9, 22.5) and solid cancers excluding central nervous system (CNS) tumors (SIR = 3.3, 95% CI 2.0, 5.5) compared with the general population.

Future plans: Dose reconstruction is currently underway to estimate individual cumulative doses absorbed to relevant organs, including red bone marrow and brain for respectively hematologic disorders and CNS tumors risk estimation. A dose-response-analysis will be conducted with consideration to confounding factors such as age at exposure, gender, predisposing factors to cancer and other sources of medical diagnostic low-dose ionizing radiation.

Strengths and limitations of this study

- The study includes a large national sample of children with congenital heart disease who have undergone cardiac catheterization in France.
- Medical information will be collected from medical records and from the National Health Data System to take into account potential confounding factors such as predisposing conditions to cancer or exposures to other sources of medical diagnostic low-dose ionizing radiation.
- The organ doses due to ionizing radiation will be estimated for each participant.
- Due to the lack of a nationwide cancer registry for adults in France, the cohort will be matched with the National Cancer Institute database built since 2011, to retrieve cancer cases occurring in adulthood in order to assess the association between low-doses ionizing radiation exposure and cancer risk throughout the lifetime of the patient.
- The statistical power of the study is limited due to the small size of the study population in view of the low expected cancer risk, however, the ongoing European HARMONIC project, aiming to pool seven national cohorts (Belgium, France, Italy, Germany, Norway, Spain, and UK) will increase the statistical power of the analyses.

Introduction

Great improvements have been made in medical diagnostic and treatment tools in the recent decades, and modalities using low-dose ionizing radiation (LDIR) have been extensively used in medical routine practices. Patients with congenital heart defect (CHD) benefit from better quality of life and longer life expectancy due to improvements in cardiac imaging and therapeutic procedures such as cardiac catheterization (CC). A steady increase in the number of cardiac imaging and therapeutic procedures using LDIR has been observed in patients with CHD from the 1990s [1–3]. Radiation doses associated to CC procedures are low-to-moderate compared to conventional radiology procedures. However, in some pediatric patients such as transplanted patients and patients with complex heart defects, CC procedures cumulative radiation doses can exceed 100 millisievert (mSv) [4–6]. Furthermore, CHD pediatric patients undergo various forms of other medical X-ray examinations in relation to their condition, including computed tomography (CT), nuclear medicine, and conventional radiology procedures [3, 5, 7–9]. For these patients, about 60% of the cumulative radiation dose come from interventional procedures such as CC [5] and about 80 to 95% come from both interventional and CT procedures [5, 7, 8].

A 1.6 to 2 times higher prevalence of cancer has been reported in adult patients with CHD compared to the general population [10]. Potential explanations to this higher cancer rate include shared genetic or environmental factors, immunosuppression drugs [11, 12], and exposure to medical LDIR procedures [13]. If ionizing radiation is a well-known risk factor of cancer for moderate to high doses, the risk is still debated for doses under 100 mSv, level of doses that can be reached in case of several CC procedures or in case of association between CC and other diagnostic procedures. However, some epidemiological studies have reported an increased cancer risk for doses lower than 50 mSv with risk decreasing with increasing age at exposure [14–16]. Exposure to medical procedures using LDIR in children is an issue as they have a long life expectancy (therefore more time to develop cancer after exposure to LDIR) and they present a higher sensitivity to LDIR than adults (due to their less mature tissues and organs) [17–19]. Data on cancer risk among children and adults with CHD who have undergone cardiac procedures are scarce and only few studies have been published [11, 12, 20–23]. Some investigators reported increased risk of cancer among CHD pediatric patients diagnosed and or treated with CC [12, 22], while others did not report any significant findings [23]. Common limitations to these previous studies were their small size, lack of precise dose assessment and short duration of follow-up.

A nationwide cohort of children and young adults who have undergone diagnostic or therapeutic CC for CHD in childhood, the COCCINELLE (French acronym for *COhorte sur le risque de Cancer après Cardiologie INterventionnELLE*) cohort has been established in mainland France. The study aims to assess the risk of cancer in patients with CHD exposed to LDIR during CC procedures. The aim of this study is to describe the cohort and to analyze the cancer occurrence in this population in comparison to the general population.

Cohort description

Study design

COCCINELLE is a multicenter cohort study on the risk of cancer in patients with CHD who underwent CC procedures for diagnosis or treatment during childhood [24]. The study received ethical approval from the French national data protection commission (*Commission Nationale de l'Informatique et des Libertés*). Retrospective data collection was conducted in fifteen hospitals in France based on medical records of CC examinations performed in pediatric cardiology departments.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Subject identification and inclusion

The study participants are patients who underwent their first CC for CHD between 1st January 2000 and 31st December 2013, who were aged <16 years at the time of the examination, and who have not been diagnosed with cancer before the first recorded CC procedure.

Medical records for 18,906 patients and their 25,139 CC procedures were obtained from pediatric cardiology departments. Patients for whom the type of procedure could not be identified from medical records (unknown procedures) and those with unknown gender or those with missing information on dates (birth, death, examination or cancer diagnosis date) were excluded as those with a diagnostic of cancer before the first CC. Then, 17,104 patients with 22,227 procedures were included in the cohort (Figure 1).

Data collection

Collected data from hospitals include the name, the gender, the place and the date of birth, the identification number, the height and the weight of each patient included in the cohort. The characteristics of the CC procedures such as the date, the type of procedure and the technical details including fluoroscopy time and kerma area product (P_{KA}) when available were also collected.

At each participating hospital, the history of the angiographic systems used during the study period including the type and the brand of the system, the type and the size (in centimeters (cm)) of the image detector and the fixed X-ray filtration were collected. In addition, detailed dosimetry reports issued from the system at the end of each CC procedure were collected for a sample of patients. The detailed dosimetry reports include information on primary and secondary angulation, field of view (in cm), source-image distance (in cm), and tube potential (in kilovolt (kV)), as well as air kerma and P_{KA} per acquisition.

In order to assess a potential confounding effect of the patient's health condition, information on underlying diseases or cancer predisposing factors will be retrieved from various sources including the National Health Data System (*Système National des Données de Santé* (SNDS)) or from examination of notes fields in procedures' logbooks.

Exposure assessment

To assess the possible link between the exposure to LDIR from CC procedures and the subsequent occurrence of cancer, individual doses to specific relevant organs, including red bone marrow and brain for respectively hematologic disorders (leukemia and lymphoma) and central nervous system (CNS) cancer risk estimation, will be estimated. First of all, the CC procedures were grouped into a common classification defined by an expert group of cardiologists (DB, SMM, SH, SC), in order to define families of procedures that are similar. Twelve and three families of procedures were defined respectively for therapeutic and diagnostic procedures (Supplemental material S1). LDIR exposure scenarios will be defined based on available detailed dosimetry reports for each family of procedures, for different patient age group (0-1, 1-5, 5-10, 10-15, and ≥15 years), and if necessary, for each cardiology department. Based on these exposure scenarios, organ dose computations will be performed with the PCXMC Monte Carlo simulation code (v2.0, STUK, Helsinki, Finland). The organ dose assessment is underway,

consequently at this step of the study, only the number of CC procedures will be considered with regard to the cancer incidence analysis.

Follow-up and outcome

Follow-up started at the date of the first recorded CC procedure until the exit date i.e. the date of death, the date of first cancer diagnosis, the date of the 18th birthday, or the 31st December 2015, whichever occurred first.

Vital status and date of death were obtained through linkage with the French National Directory for the Identification of Natural Persons (RNIPP). Additional information from medical records allowed to complete vital status when the linkage of the cohort with the RNIPP failed to identify a patient (25% of the cohort), as the large majority of the patients were closely followed in the cardiology department for their CHD.

Matching the COCCINELLE cohort with the National Childhood Cancer Registry (*Registre National des Cancers de l'Enfant* (RNCE)) allowed to identify patients who had been diagnosed with cancer and to obtain the recorded date of diagnosis and the type of cancer. The RNCE has been registering all cancer cases in children less than 15 years old in mainland France, since 1990 for hematologic disorders and since 2000 for solid tumors [25]. Since 2011, the coverage perimeter of the RNCE has been extended to adolescents under the age of 18 and to residents of French overseas departments. At the time of the linkage, the cancer registry data were available until 31/12/2015.

Since the distribution of childhood cancers according to the histological type and location might be very different from what is observed in adults, cancers cases are described according to the International

Classification of Disease – Oncology, third edition (ICDO- 3) and grouped further using the International Classification of Childhood Cancer – third version (ICCC3) [26]. For patients diagnosed with multiple cancers during the follow-up, only the first occurring cancer was considered, except for non-melanoma skin cancers.

Statistical analysis

The cohort characteristics were described as counts, proportions, means (with the standard deviation (SD)) or median (with the interquartile range (IQR)).

We conducted external comparisons using standardized incidence ratios (SIR) calculated as the ratio of the number of observed cases in the cohort to the number of expected cases based on the national cancer incidence rates provided by the RNCE [25, 27]. The SIRs were standardized by age (0-1, 1-5, 5-10 and 10-15), calendar year (2000-2005, 2005-2010, and 2010-2015), and by gender (male and female). Breslow and Day's approximation [28] was used to estimate 95% confidence intervals (CI) for the SIRs. The SIRs were calculated for five groups of cancer: all-cancer (including all childhood cancer types ICCC3: I - XII), leukemia (ICCC3: Ia, Ib, Id, Ie), lymphoma (ICCC3: IIa–IIc), CNS tumors (ICCC3: IIIb, IIIc, IIIe, IIIf), and solid cancers excluding CNS tumors (ICCC3: IV, VI, VIII – XII).

In order to consider incident cancers possibly associated with CC exposure, we conducted sensitivity analyses in which a minimal exclusion period of two and five years between the first exposure and the cancer onset was applied by excluding respectively, patients who were diagnosed with a cancer within two and five years after the first CC procedure. The SIRs were also computed according to the number of procedure undergone (1, 2, and 3 or more) and a trend test was performed. SIRs analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria) using the package Epi for the person-years computation and the package popEpi [29]. The statistical significance was defined by $p < 0.05$.

Results

Characteristics of the study population

The whole cohort consisted of 17,104 subjects, 51% of whom were males. The median duration of follow-up was 5.9 years (IQR 6.4 years), accounting for a total of 110,335 person-years. Children younger than one year at their first CC represented 38.7% of the whole cohort. The median age at exit from the cohort was 10.8 years (IQR 9.3 years). The characteristics of the study patients are described in Table 1.

A total of 22,227 CC procedures were recorded in the cohort (Table 2). The number of procedures received by the patients ranged from 1 to 14; about 82% of the study subjects received only one procedure. Diagnostic procedures represented 8,931 (40.2%) of all procedures performed whereas therapeutic procedures represented 13,296 (59.8 %) (Table 2). Among therapeutic procedures, the most frequent ones were patent ductus arteriosus closure (13.7%), pulmonary valvuloplasty (9.2%), atrial septal defect closure (7.8%), and pulmonary artery dilatation or stenting (5.9%).

Findings to date

Fifty-nine cancer cases were recorded from 2000 to 2015, among them 34 (57.6%) occurred in males. The median age at cancer diagnosis was 7.4 years (IQR 10.4 years). The cancer types are described in Table 3. The number of procedures per subject was not different between the cancer cases and the non-cancer patients. Thirty-four out of 59 cancers were diagnosed at least two years after the first CC procedures which count 13 (38.2%) lymphomas, 7 (20.6%) leukemia and 14 (41.2%) solid cancers. After a 5-year exclusion period, 15 out of 59 cancer cases were observed with 7 (46.7%) lymphomas, 2 (13.3%) leukemia and 6 (40%) solid cancers.

The results of the analyses comparing cancer incidence in the cohort with that of the general population are presented in Table 4. The SIRs were increased for all-cancer (SIR = 3.8, 95% CI 2.9, 4.9), leukemia (SIR = 3.3, 95% CI 2.0, 5.4), lymphoma (SIR = 14.9, 95% CI 9.9, 22.5) and solid cancers excluding CNS tumors (SIR = 3.3% CI 2.0, 5.5) compared with the general population. In sensitivity analyses, after exclusion of cases diagnosed within the first 2 years after exposure to the first CC examination, SIRs were increased for all-cancer (SIR = 3.4, 95% CI 2.4, 4.7), leukemia (SIR = 2.3, 95% CI 1.1, 4.9), lymphoma (SIR = 10.8, 95% CI 6.3, 18.7) and solid cancers excluding CNS tumors (SIR = 3.4, 95% CI 1.8, 6.5). When considering a 5-year exclusion period, increased SIRs were observed for all-cancer (SIR = 3.3, 95% CI 2.0, 5.4), lymphoma (SIR = 9.5, 95% CI 4.5, 20.0) and solid cancers excluding CNS tumors (SIR = 4.3, 95% CI 1.8, 10.2). SIRs were increased whatever the number of procedure received (1, 2 and 3 or more) with higher SIR for patients receiving 3 or more procedures (SIR = 6.1, 95% CI 3.0, 12.1) compare to those receiving 1 procedure (SIR = 3.7, 95% CI 2.7, 4.9). However, the p-value for trend in SIRs according to the number of procedures undergone (1, 2 and 3 or more) was not statistically significant, p-value = 0.2 (Table 4).

Discussion

Main findings

This first analysis of the COCCINELLE cohort shows a higher incidence of all-cancer, leukemia, lymphoma, and other solid cancer (excluding CNS tumors) in the cohort compared to the general population. The SIRs increased non-significantly with the increasing number of procedures received in childhood. In a sensitivity analysis in which all cases occurring during the first 2- and 5-year were excluded, the SIRs remained significantly increased for all-cancer, lymphoma and solid cancer excluding CNS tumors. As about 82% of the cohort received only one procedure,

these exclusion periods were used as a surrogate to the latency period, i.e. the minimal delay between exposure and cancer incidence to be considered.

The results from the current study are consistent with the two previous studies that reported increased cancer incidence following pediatric CC for CHD [12, 22] compared to the general population. Modan et al. [12] observed a SIR of 2.3 (95% CI 1.2, 4.1) based on the follow-up of 674 children between 1950-1970 in Israel and Harbron et al.[22] reported higher incidence rates for all-cancer (SIR = 2.32; 95% CI: 1.65, 3.17), lymphoma (SIR = 8.34; 95% CI 5.22, 12.61), and leukemia (SIR = 2.11; 95% CI 0.82, 4.42) in a cohort of 11,270 children exposed when aged ≤ 22 years. On the contrary, a study based on the follow-up of 4,891 children and young adults exposed to CC before the age of 18 between 1946 and 1968 in Canada did not report any significant increase in cancer incidence, with a SIR of 1.2 (90% CI 0.6, 2.3) [23]. In adult population, an increased SIR for all-cancer was also reported from a study on patients who had undergone CC for CHD at adulthood [30].

CT and CC procedures both deliver X-ray radiation. Recent studies reported radiation doses delivered by CT ranging from 8 to 12 milliGray (mGy) to the red bone marrow [31–34], a range of doses consistent to the mean dose of 8.8 mGy to the red bone marrow reported from a recent CC study [22]. As cumulative doses due to CT in childhood are in the range of those delivered by CC procedures, the estimated SIRs in our cohort can be compared to those from recently published CT studies [32–35]. Findings from the current study are consistent with results from a nationwide retrospective cohort of 168,394 children who received one or more CT in Dutch hospitals between 1979 and 2012, when aged <18 years [36]: the SIRs were 1.47 (95% CI 1.34, 1.61) for all-cancer, 1.39 (95% CI 1.13, 1.70) for hemato-lymphoproliferative disorders, and 2.05 (95%CI 1.48, 2.83) for CNS tumors after applying a 5-year latency period. In a German study on 39,184 children younger than 15 years who received CT between 1980 and 2010, Krille et al. [32, 33] reported significant increased SIRs for all-cancer (SIR = 1.82, 95% CI 1.29, 2.50), and lymphoma (SIR = 2.96, 95% CI 1.42, 5.45).

CHD patients usually require ongoing care to monitor their condition that may result in repeated exposure to LDIR [3, 5, 7–9] and may lead to high cumulative doses. In the current study, the cumulative number of procedure received (1, 2 and ≥ 3 procedures) is used as a surrogate to the cumulative individual doses. A significant increased SIR was observed whatever the number of CC procedures performed, but a slight non-significant positive trend was observed in the SIRs according to the increasing number of procedures received (SIR = 3.7, 95% CI 2.7, 4.9 for one

procedure, SIR = 3.2, 95% CI 1.5, 6.8 for 2 procedures and SIR = 6.1, 95% CI 3.0, 12.1 for ≥ 3 procedures; p-value for trends = 0.2). Cohen et al. used the cumulative number of procedure performed to estimate the risk of cancer after exposure to LDIR in adult patients and shown that the cumulative number of procedures and the cumulative effective dose could lead to similar results [30]. In the current study, however, since no dose assessment and no dose-response analyses are yet available to explain the increased SIRs according to the cumulative number of procedures received, this result should be interpreted with caution. An individual dose reconstruction is currently underway to estimate the cumulative organ doses for each of the cohort members, including the contribution of doses from CTs and other medical diagnostic radiation procedures. A dose-response analysis will then be performed to confirm or not these first results.

Strengths and limitations

The COCCINELLE cohort is the first study in France to assess cancer risk in 17,104 CHD patients who undergone CC in childhood. The study has access to national well-handled registries which have almost an exhaustive coverage of the general population. The sample of CHD patient included in the cohort is representative of the pediatric CHD patients since the major pediatric departments performing CC in mainland France agreed to participate to the study and contributed actively. However, several limitations should be mentioned.

The SIR analyses did not include any information on the dose received during the CC procedures and the results should be interpreted consequently. Doses estimates are currently underway to provide with accurate dosimetry data for each patient in the study and cumulative organ doses will be used in the dose response analyses. In addition, CHD pediatric patients could undergo other diagnostic LDIR procedures such as CT which deliver dose in the same range as CC, nuclear medicines, and conventional radiographies. The more patients have received CC, the more they are susceptible to be exposed to other diagnostic medical LDIR. It is important to consider these various sources of exposure since they can contribute significantly to the overall cumulative organ dose. This additional information on other medical exposure would be retrieved from the National Health Data System. Further analyses in the cohort will include doses from CC and other medical diagnosis procedures in the dose-response analyses.

The individual dose reconstruction is intended for procedures performed in the cohort, from 2000 to 2013. However single doses delivered per examination are continuously decreasing due to advances in technologies, protocol improvements and awareness of cardiologists. Therefore, the dose estimates will not reflect the current dose reduction practices in cardiology departments and this weakness is inherent to all retrospective epidemiology studies. Nevertheless, epidemiology studies are still relevant for decision making and radioprotection purposes.

Other limitation from the first results of the SIR analyses is the use of the general population as reference group. An increased risk of cancer in CHD patients compared to the general population has already been reported [13]. Common etiologic factors in CHD patients could be suspected [11, 21] as gene mutations in embryogenesis related to birth defects and cancer development [37]. Post-transplants are also known to present higher rate of cancer due to the use of immunosuppression drugs [38]. In the UK study on cancer risk after CC in childhood, 509 out of 11,270 individuals had received a transplanted organ with twenty-six malignancies occurring among these transplanted patients. The authors reported that all of the lymphoma cases observed in the cohort came from transplanted subjects. Furthermore, censoring these transplant subjects decreased the SIR for all-cancer from 2.32 (95% CI 1.65, 3.17) to 0.90 (95% CI 0.49, 1.49) [22]. Transplantation status and any other cancer predisposing factors are not considered in the SIRs analysis and the increased SIRs reported in the present study might be confounded with a potential effect of underlying cancer predisposing factors such as Down syndrome, Noonan syndrome, severe combined immune deficiency, etc.

Indication bias and reverse causation bias can be suspected when cancer predisposing factors or early symptoms of undetected cancer are the indication of the examination. In the COCCINELLE cohort study, reverse causation bias can be ruled out as the indication of CC is always the CHD. However, indication bias should be studied since medical conditions associated with cancer risk predisposition could also be associated with exposure to LDIR diagnostic procedures. Then, it will be crucial to take into account individual information on cancer risk predisposition in the ongoing main analyses. Due to the lack of a national registry on transplantation or genetic

syndromes in France, the COCCINELLE cohort will use information from the National Health Data System, which are complete enough to retrieve patients with predisposing factors to cancer [39].

The study took into account as much as possible the main factors that could be associated with the studied outcome, as the genetic or hereditary disorders and immunodeficiency factors associated with cancer. In addition, children with history of cancer prior to the CC examination were excluded from the cohort to avoid potential effect of radiotherapy or chemotherapy on a subsequent cancer. However, our study was not designed to directly assess the effect of factors such as obesity, socio-economic status, lifestyle, and environmental factors in the risk estimate models since these data could not be retrieved directly from medical record databases. However, major known factors associated with cancer risks such as smoking and/or alcohol consumption are unlikely to impact the risk estimates as the studied population includes only children with a follow-up limited to 18 years in this analysis. A strength of the study is to be able to take into account some other cancer risk factors such as exposure to other medical diagnostic LDIR such as computed tomography, nuclear medicine, and conventional radiography that will be retrieved from the National Health Data System.

The death rate in the cohort is currently 6.5% for 803 deaths registered in patients for whom this information is available. Investigators had reported an increased mortality rates among CHD population [40], suggesting that some subjects might die from the underlying condition (i.e. cardiac dysfunction) before developing cancer. Therefore, competitive risk should be considered in the ongoing analyses to take into account the risk of death before the studied outcome, i.e. cancer. This was observed in the French cohort study on CTs, where the early increased mortality in patients with predisposing factors to cancer leads to decreased risks of radiation associated leukemia and CNS tumor compared to the increased risk observed in patients without predisposing factors to cancer [31].
The number of patients lost to follow-up is currently low in the cohort since children with CHD are closely followed in cardiology departments involved in this study for the monitoring of their conditions. They can be retrieved from medical records or from the National Health Data System after 2006; however, we are not able to follow patients,

who have emigrated, been diagnosed, or treated outside France borders. The follow-up of our population is currently limited to the age of 18 years, due to the lack of a nationwide cancer registry for adults. However, the building of a national cohort of cancer patients since 2011 by the French National Cancer Institute (*Institut National du Cancer*) based on the National Health Data System will provide a very useful tool to follow the incidence of cancer in our cohort at adult age [41].

Perspectives and collaboration

Overall, the future plans for the cohort analysis include an individual dose reconstruction and the assessment of the dose-response relationship in regard of the cumulative radiation dose received by each patient. Furthermore, potential impact of confounding factors such as age at exposure, gender, and attained age will be assessed. The assessment of potential bias as cancer predisposing factors or additional doses from other medical diagnostic procedure will be possible thanks to the information retrieved from the National Health Data System. We plan also to link our cohort with the ongoing national cohort of cancer cases set up by the French National Cancer Institute since 2011, based on data from the National Health Data System [41], which will allow the follow-up of the cohort patients beyond the age of 18 years old.

The number of cancer cases reported in the current study is small, due to a short duration of follow-up and low cancer incidence rates. A way to overcome this limitation and increase the statistical power of the study is to conduct combined analyses of several similar studies. The COCCINELLE cohort is contributing to the HARMONIC (for Health effects of cArdiac fluoRoscopy and MOderN radIotherapy in paediatrICs) project [42] that pools together seven large national European cohorts (Belgium, France, Italy, Germany, Norway, Spain, and UK), to increase the statistical power of the analyses. In a few years, HARMONIC will provide information on the risk of cancer associated with exposure to diagnostic radiation received during childhood with a precision that could not be achieved with individual national studies.

The COCCINELLE study data are not freely available because of ethical and data protection constraints. However, we welcome inputs from researchers on collaborative projects that will involve the study data. Proposals for possible collaborations in further analyses of the data should be addressed to Dr Estelle Rage.

Contributorship statement

MOB, ER, KL lead the project at national level, raised the funding, established the cohort, and provided intellectual inputs to the manuscript. KDA and TF were involved in data analysis, data presentation and drafted the manuscript. SMM, SH, SD, SC and DB contributed to the implementation of the project and to the conception of this article. CD, SDF, SD, FG, PG, PH, CK, BL, PM, CO, JFP and JBT were the local investigators of the project. They contributed to the study design and critically revised the manuscript for important intellectual content. All authors critically revised the manuscript and approved the final version.

Competing interests

None to declare

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Data sharing statement

All data from the COCCINELLE study are deposited at the Laboratory of Epidemiology at French Institute for Radiological Protection and Nuclear Safety (IRSN), BP 17, 92262 Fontenay-aux-Roses, France. The COCCINELLE study data sharing is subject to ethical and data protection constraints. Interested researchers can approach ER principal investigator (estelle.rage@irsn.fr) for sharing COCCINELLE data as part of collaborative research projects (if not overlapping with ongoing research projects, and subject to a Data Use Agreement).

Ethics approval

The study received ethical approval from the French national data protection commission (*Commission Nationale de l'Informatique et des Libertés*), deliberation N°2016-067 of 13/08/2016.

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Table 1: Description of the COCCINELLE cohort, 2000-2015

	Patients with cancer N=59	**Patients without cancer** N=17,045
Demographics		
Male, N (%)	34 (57.6)	8,702 (51.1)
Median age (in year) at first procedure (IQR)	2.6 (9.9)	2.2 (7.4)
Median age (in year) at exit (IQR)	7.4 (10.4)	10.9 (9.3)
Age at first procedure, N (%)		
< 1 year	24 (40.7)	6,589 (38.7)
1 – 5 years	12 (20.3)	4,206 (24.7)
5 – 10 years	8 (13.6)	3,216 (18.9)
10 – 15 years	15 (25.4)	3,034 (17.8)
Birth period, N (%)		
[1980, 1990]	2 (3.4)	484 (2.8)
]1990, 2000]	20 (33.9)	4,273 (25.1)
]2000, 2010]	31 (52.5)	9,511 (55.8)
]2010, 2013]	6 (10.2)	2,777 (16.3)
Number of procedures received by children, N (%)		
1 procedure	44 (74.6)	13,929 (81.7)
2 procedures	7 (11.9)	2,021 (11.9)
≥ 3 procedures	8 (13.6)	1,095 (6.4)

IQR: Interquartile range

Table 2: Description of the cardiac catheterization procedures received in the COCCINELLE cohort

	Total	**(%)**
Category of procedures		
Therapeutic	13,296	59,8
Diagnostic	8,931	40.2
Total	22,227	100
Most frequent families of procedures		
Diagnostic cardiac catheterization without angiography[d]	3,868	17.4
Patent ductus arteriosus closure	3,046	13.7
Pulmonary valvuloplasty	2,052	9.2
Atrial septal defect closure	1,741	7.8
Right and left heart angiography[d]	1,466	6.6
Left heart angiography[d]	1,313	5.9
Pulmonary artery dilatation or stenting	1,310	5.9
Atrial septostomy	1,208	5.4
Electrophysiology procedures	1,165	5.2
Right heart angiography[d]	1,066	4.8
Other procedures	3,992	17.9

d: Diagnostic procedures

Table 3: Description of the cancers that occurred in the COCCINELLE cohort from 2000 - 2015

Cancer type	**All period** N (%)	**After a 2-year exclusion*** N (%)	**After a 5-year exclusion*** N (%)
Leukemia ICCC3: Ia, Ib, Id, Ie	15 (25.4)	7 (20.6)	2 (13.3)
Lymphoma ICCC3: IIa-IIc	23 (39.0)	13 (38.2)	7 (46.7)
Central nervous system ICCC3: IIIb, IIIc, IIIe, IIIf	6 (10.2)	5 (14.7)	1 (6.7)
Neuroblastoma and other peripheral nervous cell tumors ICCC3: IVa, IVb	1 (1.7)	1 (2.9)	1 (6.7)
Renal tumors ICCC3: VIa, VIb	4 (6.8)	3 (8.8)	-
Malignant bone tumors ICCC3: VIII	1 (1.7)	-	-
Soft tissue and other extra osseous sarcomas ICCC3: IXb, IXe	4 (6.8)	2 (5.9)	2 (13.3)
Germ cell tumors ICCC3: X	2 (3.4)	1 (2.9)	-
Other malignant epithelial neoplasms ICCC3: XI	2 (3.4)	1 (2.9)	1 (6.7)
Other and unspecified malignant neoplasms ICCC3: XII	1 (1.7)	1 (2.9)	1 (6.7)
All-cancer	59 (100)	34 (100)	15 (100)

ICCC3: International Classification of Childhood Cancer – third version (ICCC3) [25]
** : 2- and 5-year exclusion: Exclusion of all -cancer cases diagnosed respectively within 2 or 5 years after the first CC procedure.*

Table 4: Standardized incidence ratio (SIR) for cancers in the COCCINELLE cohort

	All-period		After a 2-year exclusion*		After a 5-year exclusion*	
	Number of cases	SIR (95% CI)	Number of cases	SIR (95% CI)	Number of cases	SIR (95% CI)
Type of cancer						
All-cancer	59	3.8 (2.9; 4.9)	34	3.4 (2.4; 4.7)	15	3.3 (2.0; 5.4)
Leukemia	15	3.3 (2.0; 5.4)	7	2.3 (1.1; 4.9)	2	1.6 (0.4; 6.6)
Lymphoma	23	14.9 (9.9; 22.5)	13	10.8 (6.3; 18.7)	7	9.5 (4.5; 20.0)
CNS	6	1.5 (0.7; 3.4)	5	1.9 (0.8; 4.5)	1	0.8 (0.1; 5.5)
Solid cancer**	15	3.3 (2.0; 5.5)	9	3.4 (1.8; 6.5)	5	4.3 (1.8; 10.2)
By gender: Male						
All-cancer	34	3.9 (2.8; 5.5)	21	3.7 (2.4; 5.7)	7	2.7 (1.3; 5.6)
Leukemia	9	3.5 (1.8; 6.7)	7	4.1 (1.9; 8.5)	2	2.8 (0.7; 11.1)
Lymphoma	16	15.3 (9.4; 25.0)	10	12.3 (6.6; 22.9)	4	8.2 (3.1; 21.7)
CNS	4	1.8 (0.7; 4.9)	3	2.0 (0.6; 6.2)	-	-
Solid cancer**	5	2.2 (0.9; 5.2)	1	0.7 (0.1; 5.2)	1	1.7 (0.2; 12.2)
By gender: Female						
All-cancer	25	3.6 (2.5; 5.4)	13	3.0 (1.7; 5.1)	8	4.1 (2.0; 8.1)
Leukemia	6	3.0 (1.4; 6.7)	-	-	-	-
Lymphoma	7	14.2 (6.8; 29.7)	3	7.8 (2.5; 24.1)	3	12.2 (3.9; 37.9)
CNS	2	1.1 (0.3; 4.5)	2	1.7 (0.4; 6.7)	1	1.8 (0.3; 12.6)
Solid cancer**	10	4.6 (2.5; 8.5)	8	6.1 (3.1; 12.2)	4	6.7 (2.5; 17.9)
By age group (all-cancer)						
< 1 year	1	0.9 (0.0; 4.8)	-	-	-	-
1 – 5 years	23	3.7 (2.3; 5.5)	13	3.9 (2.1; 6.7)	-	-
5 – 10 years	12	2.7 (1.4; 4.6)	8	2.1 (0.9; 4.2)	6	2.4 (0.9; 5.3)
10 – 15 years	14	3.9 (2.1; 6.5)	8	2.7 (1.2; 5.3)	6	2.8 (1.0; 6.2)
By calendar period (all-cancer)						
2000 - 2005	8	4.2 (2.1; 8.4)	1	1.6 (0.2; 11.6)	-	-
2005 - 2010	23	4.3 (2.9; 6.5)	13	3.9 (2.3; 6.7)	5	4.5 (1.9; 10.9)
2010 - 2015	28	3.4 (2.3; 4.9)	20	3.3 (2.1; 5.1)	10	2.9 (1.6; 5.4)
Number of the cardiac catheterization procedures received (all-cancer)						
1	44	3.7 (2.7; 4.9)	24	3.1 (2.1; 4.7)	7	2.1 (1; 4.3)

2	7	3.2 (1.5; 6.8)	5	3.4 (1.4; 8.2)	4	5.7 (2.1; 15.2)
3 or more	8	6.1 (3.0; 12.1)	5	5.5 (2.3; 13.1)	4	8.8 (3.3; 23.3)
*p-value***		0.2		0.2		< 0.01

CNS: Central nervous system tumors
SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
**: 2- and 5-year exclusion: Exclusion of all -cancer cases diagnosed respectively within 2 or 5 years after the first CC procedure*
***: Solid cancer excluding central nervous system tumors*
****: p-value for trends.*

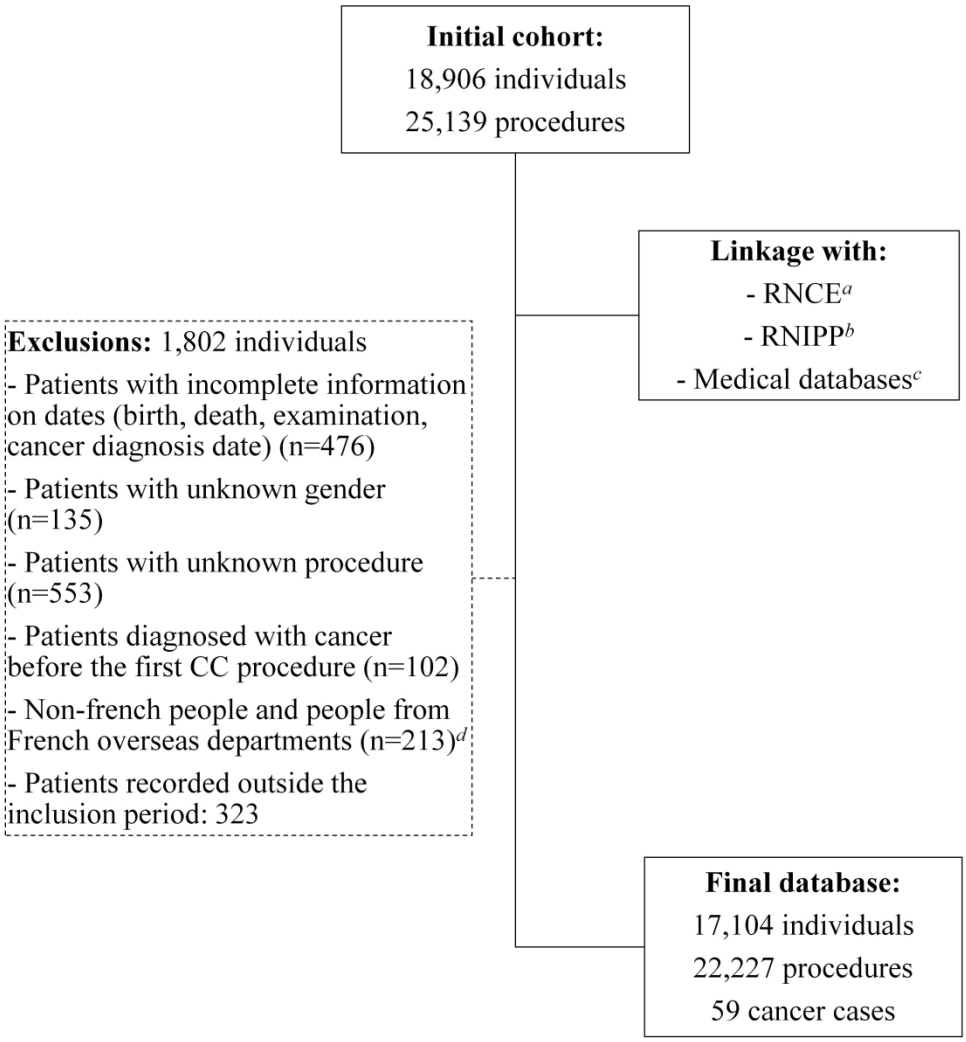

Figure 1: Flow chart of the COCCINELLE cohort constitutiona: RNCE: French National Childhood Cancer Registry (Registre National des Cancers de l'Enfant)b: RNIPP: French National Directory for the Identification of Natural Personsc: Medical discharge and reimbursement databasesd: French oversea departments not covered by the RNCE before 2011 CC: Cardiac catheterization

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Supplemental material

S1: Category and family classification of cardiac catheterization procedures in the COCCINELLE cohort

Category of procedures	Family of procedures	Names of the procedures
Diagnostic procedures	Right heart angiography	- Catheterization right with contrast
	Diagnostic procedures without angiography	- Catheterization right without contrast - Catheterization left without contrast - Catheterization left and right without contrast - Biopsy endo-myocardial Pulmonary arterial hypertension - Pulmonary arterial hypertension with normal heart - Pulmonary arterial hypertension shunt (Eisenmenger)
	Left heart angiography	- Catheterization left with contrast
Therapeutic procedures	Pulmonary valvuloplasty	- Pulmonary valve dilatation - Pulmonary atresia intact ventricular septum, radiofrequency, perforation - Perforation pulmonary valve
	Aortic valvuloplasty	- Aortic valve dilatation
	Rashkind	- Atrial septostomy
	Aortic dilatation / stenting	- Balloon dilatation of coarctation of the aorta - Stenting of aortic coarctation
	Pulmonary artery dilatation / stenting	- Balloon dilatation of pulmonary artery: unique / multiple - Balloon dilatation of pulmonary artery - Balloon dilatation of right ventricle - pulmonary artery conduit - Balloon dilatation of homograft - Balloon dilatation of pulmonary artery banding - Stenting of pulmonary artery branch: unique stent / multiple stents - Stenting of pulmonary artery trunk: unique stent / multiple stents - Stenting of right ventricle - pulmonary artery conduit: unique stent / multiple stents - Percutaneous pulmonary valve implantation - Patent ductus arteriosus dilatation

	Various angiography	- Balloon dilatation of superior vena cava - Superior vena cava stenting - Balloon dilatation of inferior vena cava - Inferior vena cava stenting - Balloon dilatation of pulmonary vena - Pulmonary vein stenting: unique / multiple - Balloon dilatation of coronary artery - Stenting Coronary: unique / multiple - Patent ductus arteriosus stent (non-neotal) - Major aortopulmonary collateral arteries: unique/ multiples - Balloon dilatation of Blalock - Stenting Blalock: unique/ multiples - Thrombo-aspiration, Vertical vein closure, Occlusion femoral artery, stenting iliac artery, Stenting subclavian artery. - Percutaneous removal of a foreign body - Arterio-venous fistula embolization: unique/ multiples - Blalock embolization - Fenestration closure - Sequestration closure: unique / multiple - Coronary fistula closure: unique / multiple - Aorto-pulmonary collaterals embolization: unique / multiple
	Complex neonatal procedures	- Hybrid procedures - Patent ductus arteriosus stenting - Atrial septal defect creation - Atrial septal defect stenting
	Atrial septal defect closure	- Atrial septal defect closure - Patent foramen ovale
	Ventricular Septal Defect (VSD) closure	- Ventricular septal defect closure
	Arterial duct closure	- Patent ductus arteriosus closure: coil / plug
	Rythmology: stimulation	- Pacemaker - Defibrilators - Pacing
	Rythmology: electrophysiology	- Electrophysiology, Flutter, Kent
Other procedures	Other unclassified procedures	- Catheterization left and right with contrast - Biopsy and coronarography - Tricuspid dilatation - Mitral valve dilatation - Aorto-pulmonary window (aorto-pulmonary septal defect)