Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Projected Future Cancer Risks in Children Treated With Fluoroscopy-Guided Cardiac Catheterization Procedures

BACKGROUND: Children treated with cardiac catheterization procedures have now a long life expectancy and consequently potential long-term radiation-induced risks. We projected lifetime attributable risks (LARs) of cancer incidence from the most frequent procedures in pediatrics: atrial septal defect closure, patent ductus arteriosus occlusion, or pulmonary valvuloplasty.

METHODS AND RESULTS: Organ equivalent doses were estimated for 1251 procedures performed in children aged ≤15 years at 2 reference catheterization centers in France from 2009 to 2013. Sex-specific LARs were projected in lifelong nonsmokers using extended Committee on Biological Effects of Ionizing Radiation VII risk models and considering various sources of risk projection uncertainties and dose variability (Radiation Risk Assessment Tool software). Median LARs ranged between 0.3 and 1.4 (atrial septal defect closure), 0.6 and 5.0 (patent ductus arteriosus occlusion), and 1.0 and 12.0 (pulmonary valvuloplasty) per 1000 procedures, depending on patient sex and age at treatment. These radiation-related risks would represent 0.4% to 6.0% of children's total lifetime cancer risk. For the 10% of procedures (all types combined) with highest exposures, LARs reached 4.2 per 1000 (95% uncertainty interval, 0.8–13.1) in boys and 22.2 per 1000 (95% uncertainty interval, 7.4–45.6) in girls. In boys, lung cancer accounted for 70% to 80% of the projected LARs, whereas in girls it accounted for 20% to 60% and breast cancer for 30% to 80% of the excess risks, depending on the type of procedure and patient age.

CONCLUSIONS: Radiation exposure may lead to substantial radiation doses and increased cancer risks in some cases. This suggests the need for dose reporting to support recommendations for long-term surveillance and prevention strategies when it is necessary.

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WHAT IS KNOWN

- Increased cancer risks are associated with radiation exposures at dose levels that can be received by children undergoing cardiac catheterization procedures.
- Cardiac catheterization procedures in pediatrics are associated with widely variable radiation doses.

WHAT THE STUDY ADDS

- The study projects lifetime risks of cancer incidence subsequent to radiation exposures from atrial septal defect closure, patent ductus arteriosus occlusion, or pulmonary valvuloplasty in children aged ≤15 years.
- Overall, projected lifetime risks would represent 0.4% to 6.0% of children's total lifetime cancer risk, mainly attributable to increased risks of lung and breast cancers.
- The 10% most irradiating procedures are associated with projected lifetime risks of 0.4% in boys and 2% in girls subsequent to cardiac catheterization.

Congenital heart diseases (CHDs) are the most frequent birth defects, accounting for 9 per 1000 live births worldwide.[1,2] Progresses in cardiac catheterization procedures (CCPs) during the past years have considerably increased the range of treatable defects and contributed in reducing infant and child mortality associated with CHDs.[3,4] The longer life expectancy (which was estimated to reach 75 years in Canada in 2005[4]) has thus increased the number of CHD survivors and made long-term disease management and potential adverse effects of treatments an important clinical issue.[5]

Fluoroscopy used during CCPs to obtain hemodynamic images of the circulatory system is typically associated with effective radiation doses ranging from 3 to 15 mSv and can result in organ equivalent doses exceeding 50 mSv for some complex procedures.[6,7] At those dose levels, the risk of radiation-induced effects is to be considered, all the more so because children are particularly sensitive to ionizing radiation[8] and, as mentioned above, many of those born with CHD have now a long life expectancy.[4] The only 2 epidemiological studies to date that have reported cancer risks in patients receiving CCPs found opposite results, but they involved small numbers of cases (n=13 in Canada,[9] 11 in Israel[10]) and had no dosimetry.[9,10] Other cohort studies are currently set-up in France[11] and in the United Kingdom[7] with inclusion of large populations, collection of detailed treatment data, and estimation of individual radiation doses to palliate the limitations of previous studies. Considering that radiation-related cancers may have latency times more than 20 years after exposures[12] and that tumors at the most exposed organs (eg, breasts, lungs and stomach) are mainly diagnosed after the age of 40 years, it is nevertheless unlikely to observe excess risks before decades of follow-up after CCPs in children. In the meanwhile, the use of existent biological and epidemiological knowledge on the effects of radiation exposures allows projecting risks (with numerical simulations) and informing on potential future cancer risks CHD survivors would face in adolescence and adulthood.[13]

The aim of the present article is to report projected lifetime excess cancer risks for children who underwent an atrial septal defect (ASD) closure, a patent ductus arteriosus (PDA) occlusion or a pulmonary valvuloplasty (which are the most common pediatric CCPs), based on estimates of radiation doses to organs located within or outside the irradiation field in routine practice in pediatrics.

METHODS

The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, in compliance with the ethical requirements of this study. The analytic methods may be made available to other researchers on request.

Study Population

The study included all children aged ≤15 years who underwent ASD closure, PDA occlusion, or pulmonary valvuloplasty between 2009 and 2013 in 2 reference pediatric cardiac catheterization centers in France (Necker-Enfants Malades pediatric hospital in Paris and Marie Lannelongue hospital in Le Plessis-Robinson). The included children were all participants of the "Coccinelle" cohort study which aims at investigating the long-term incidence of leukemia and solid cancers among children treated in France with a CCP.[11] Exclusions consisted of children with missing mandatory information to assess radiation doses or belonging to a nonrepresentative exposure scenario group (see below). The study was approved by the French National Agency regulating Data Protection (Commission Nationale Informatique et Liberté; agreement no. 911112, published on December 12, 2011) exempting the study from requiring individual patient's or parent's consent.

Radiation Exposure Scenarios and Equivalent Organ Doses

Exposure scenarios were defined based on individual patient data and radiological parameters routinely used in the participating hospitals. CCPs were performed on a dual-arm Siemens Axiom Artis BC (Siemens, Healthcare Sector, Forchheim, Germany) equipped with 23 cm image intensifiers at Necker hospital, and on a dual-arm Siemens Axiom Artis DBC (Siemens, Healthcare Sector, Forchheim, Germany) equipped with 20 cm flat panels at Marie Lannelongue hospital. From medical records, we extracted the following information: patient's age and weight, type of procedure (ASD, PDA, pulmonary valvuloplasty), and Kerma Area Product (P_{KA};

Table 1). Routine radiological parameters (x-ray beam orientation, field size, tube voltage, additional copper filtration) were collected in each hospital based on the experience of the practicing cardiologists. Exposure scenarios were subsequently defined for common procedures in pediatrics for given procedure types and age groups (Appendix A and Table I in the Data Supplement). Subsequently, ASD occlusion at age <1 year and pulmonary valvuloplasty at age ≥5 years were not considered. For each exposure scenario, we estimated organ equivalent dose per unit P_{KA} (mSv/Gy.cm^2) for each procedure using PCXMC version 2.0 (STUK, Helsinki, Finland). This dosimetry system dedicated to calculation of patient doses in medical x-ray examinations (radiography and fluoroscopy) integrates Monte Carlo particles transport simulation and idealized mathematical human phantoms representing individuals of age (weight) 0 (3.4 kg), 1 (9.2 kg), 5 (19.0 kg), 10 (32.4 kg), and 15 (56.3 kg) years to simulate the absorption of radiation doses within tissues/organs. Organ equivalent doses (used for risk projection) were then calculated for each patient by linear interpolation between the 2 nearest phantoms in terms of weight and multiplication of the conversion factors by the P_{KA} of the procedure. Doses to parallel organs (breasts, lungs) were averaged for the 2 organs. Procedures with missing information on P_{KA} or patient age were excluded. When information on weight was missing (15% of the procedures), a weight category was assigned according to the patient's age (<1 year, 0–6.5 kg; 1–4.9 years, 6.5–14.5 kg; 5–9.9 years, 14.5–25.5 kg; 10–15.9 years, 25.5–43.5 kg).[14] Last, effective doses (provided for comparison with other procedure types and studies) were calculated as sums of organ equivalent doses for 1 procedure multiplied by tissue weighting factors that represent the varying radiosensitivity of the tissues in the human body with respect to risks of stochastic effects[15] (Appendix A and Figure I in the Data Supplement for dose indexes and conversion factors, and Table II in the Data Supplement for dose estimates).

Estimation of Baseline All-Cause Mortality and Cancer Risks in CHD Survivors

Previous studies reported low mortality rates from CHD (in particular, ASD, PDA, and pulmonary artery stenosis) in individuals who survived beyond the age of 1 year.[16,17] We thus assumed a life expectancy comparable to that of the general population in children alive at age 1. Although all-cause mortality, baseline, and radiation-induced cancer risks depend on smoking behaviors, we, nevertheless, had to account for the presumably less frequent smoking history of CHD survivors as compared to the general population. Without information on smoking behaviors in CHD survivors in France, we projected cancer risks for lifelong nonsmokers only. We estimated baseline (ie, in the absence of radiation exposure from CCP) age- and sex-specific survival probabilities in lifelong nonsmokers based on the 2010 to 2012 life tables for the French (mainland) general population published by the National Institute for Demographic Studies,[18] where we deducted the proportion of all-cause deaths attributable to smoking. The attributable fraction of all-cause mortality to smoking was derived from a previous report of tobacco-attributable mortality in France[19] and national statistics of all-causes deaths.[20] Baseline incidence rates of lung cancer in lifelong nonsmokers were extracted from a pooled study of 8 cohorts in European descents.[21] For the other cancer sites, we calculated theoretical incidence rates in never-smokers by deducting the site-specific attributable fraction to smoking from the 2012 incidence rates in the French general population.[22] Attributable fractions of cancer incidence to smoking were derived from age-standardized prevalence of smoking in the general population (Appendix B and Table III in the Data Supplement) and tobacco-related risks published in the literature (Appendix B and Table IV in the Data Supplement).[23] Details of the applied methods and calculated age- and sex-specific incidence rates for lifelong nonsmokers

Table 1. Main Dosimetry Information on Radiation Exposure Scenarios From Pediatric CCPs: Median Values (95th Percentile Intervals)

	Atrial Septal Defect Occlusion			Patent Ductus Arteriosus Occlusion				Pulmonary Valvuloplasty	
	Age at Exposure, y								
	1 to <5	5 to <10	10–15	0 to <1	1 to <5	5 to <10	10–15	0 to <1	1 to <5
Dosimetric Parameters	(n=37)	(n=145)	(n=115)	(n=219)	(n=315)	(n=101)	(n=50)	(n=232)	(n=37)
Weight, kg	15 (10–25)	20 (15–45)	40 (25–65)	5 (5–10)	10 (5–20)	20 (15–35)	45 (25–90)	5 (0–10)	15 (10–20)
Kerma area product, Gy.cm^2	1.0 (0.5–7.5)	1.5 (0.5–10)	3.5 (0.5–28.5)	1.5 (0.5–6)	1.5 (0.5–7)	2.5 (0.5–12)	8.0 (1–47)	1.0 (<0.5–4)	2.0 (0.5–22)
Equivalent doses, mSv									
Oesophagus	2 (1–18)	2 (1–14)	2 (<1–21)	9 (3–42)	6 (2–29)	5 (1–20)	5 (1–34)	8 (2–38)	7 (1–74)
Lungs	3 (1–27)	3 (1–25)	4 (1–41)	11 (3–50)	8 (2–39)	10 (2–45)	17 (3–93)	10 (3–46)	10 (2–104)
Breasts	1 (<1–13)	1 (<1–10)	1 (<1–10)	16 (4–72)	12 (3–61)	9 (2–56)	10 (1–59)	10 (3–50)	10 (2–143)
Stomach	1 (<1–6)	<1 (<1–4)	<1 (<1–4)	2 (1–10)	1 (<1–6)	1 (<1–4)	1 (<1–7)	2 (1–10)	2 (<1–14)
Liver	1 (<1–7)	<1 (<1–5)	1 (<1–5)	5 (2–26)	3 (1–15)	3 (1–11)	4 (1–18)	5 (2–25)	4 (1–49)
Pancreas	1 (<1–12)	1 (<1–7)	1 (<1–8)	3 (1–17)	2 (<1–9)	2 (<1–6)	2 (<1–12)	4 (1–18)	4 (<1–24)
Active bone marrow	1 (<1–5)	1 (<1–5)	1 (<1–8)	1 (<1–5)	1 (<1–3)	1 (<1–3)	1 (<1–7)	1 (<1–6)	1 (<1–10)
Effective dose, mSv*	1 (<1–8)	1 (<1–7)	1 (<1–11)	5 (1–21)	3 (1–16)	3 (1–13)	4 (1–23)	4 (1–17)	4 (1–41)

N denotes number of procedures during the study period. Weight and P_{KA} values are, respectively, rounded at the nearest 5 and 0.5 units. CCPs indicates cardiac catheterization procedures; and ICRP, International Commission on Radiological Protection.

*ICRP 103 tissue weighting factors.

(Table V in the Data Supplement) are provided in Appendix B in the Data Supplement.

Projection of Radiation-Related Cancer Risks From CCPs

Based on estimated organ equivalent doses, we projected future sex-specific cancer risks subsequent to radiation exposure for each CCP and child's weight category, using the Radiation Risk Assessment Tool developed by the National Cancer Institute (Bethesda, MD, United States, public version freely accessible at https://irep.nci.nih.gov/radrat).[24] This risk assessment tool incorporates an extended list of cancer-specific (Committee on Biological Effects of Ionizing Radiation VII, National Research Council, Washington, DC) risk models derived from cohort studies of the survivors of the Hiroshima and Nagasaki atomic bombings and patients exposed to x-rays for benign health conditions.[25] Those models estimate age-specific excess risk (which would occur in addition to baseline risk, that is, here without receiving a CCP) per dose unit depending on age at exposure, time since exposure, and sex. Projected risks at each attained age are accumulated up to age 100 while accounting for sex- and age-specific survival probabilities and risks of developing a cancer without receiving a CCP in childhood (baseline risks), thus providing estimates of lifetime attributable risk (LAR).[26] To incorporate organ doses distributions and baseline mortality and cancer incidence rates for nonsmokers as above described, we used the home version of Radiation Risk Assessment Tool built with Analytica (Lumina Decision Systems, Inc, Los Gatos, CA). Risk projection uncertainties and individual dose variability were propagated through projected LARs by Monte Carlo simulations to produce uncertainty intervals (UIs). Uncertainties in dose-response model parameters, minimum latency period between radiation exposure and cancer occurrence, high-to-low doses risk extrapolation, and population-to-population risk transport were incorporated in Radiation Risk Assessment Tool as it has been detailed in the original publication.[24] For solid cancers, a dose effectiveness factor of 1.5 (95% uncertainty range, 0.95–2.5) is applied to doses of 10 mSv. To account for individual dose variability, we considered a triangular probability distribution for each exposure scenario with minimal, modal, and maximal values defined as the 5th, 50th, and 95th percentiles of the dose distribution in the study population. The results are displayed as median simulated LAR values (per 1000 CCPs) with 95% UI. Because high uncertainties in risks at low doses (<1 mSv), LARs were projected only for cancer sites which received at least 1 mSv, that is, oesophagus, lung, breast (in females only), stomach, liver, pancreas, leukemia except chronic lymphoid leukemia (related to mean whole-body dose to red bone marrow). LARs were then summed over the 7 cancer sites, for each CCP type and age group at the time of the CCP (<1, 1 to <5, 5 to <10, and 10–15 years).

RESULTS

After exclusion of children with missing P_{KA} (n=114), missing age (n=16) or nonrepresentative exposure scenario (ie, age <1 year for ASD closure or ≥5 years for pulmonary valvuloplasty, n=27), the study population consisted of 1175 children (sex-ratio, 1.7 girls/1 boy) who underwent 1251 procedures in 2009 to 2013 (Table 1). Median age at CCP was 8.7 years for ASD closure (n=297), 2.7 years for PDA occlusion (n=685), and 1 month for pulmonary valvuloplasty (n=269).

Radiation exposure was the highest to the lungs and breasts with estimated median equivalent doses ranging, respectively, from 3 to 17 mSv and 1 to 16 mSv, depending on the type of procedure and patient age (Table 1). Median doses were 2 to 9 mSv to the esophagus, 1 to 5 mSv to active bone marrow, stomach, liver, and pancreas median doses, and below 1 mSv to the other organs (Appendix A and Table II in the Data Supplement). A wide individual variability was, nevertheless, estimated, even within age groups. For a given procedure, the 95th percentile intervals of breast and lung doses (ie, ratios between 97.5th/2.5th percentile values of the dose distribution) by age group ranged from 15 to 80 mSv (Table 1).

Pulmonary valvuloplasty was the procedure associated with the highest median projected LARs, ranging from 5 to 12 per 1000 procedures in girls and 1 to 2 per 1000 procedures in boys. For PDA occlusion, median LARs ranged from 4 to 7 per 1000 in girls and 0.5 to 1 per 1000 in boys, depending on the age group (Table 2). For ASD closure, median LARs were about 1 and 0.5 per 1000 in girls and boys, respectively. The 25% of CCPs with highest radiation exposure (ie, effective dose >5 mSv) were associated with LARs of 9 (95% UI, 4–20) per 1000 procedures in girls and 2 (95% UI, 1–6) per 1000 procedures in boys, and the 10% of CCPs with effective dose >10 mSv were associated with LARs of 22 (95% UI, 7–46) per 1000 in girls and 4 (95% UI, 1–13) per 1000 in boys (Table 3).

The projected LARs were highest in the youngest patients, except for pulmonary valvuloplasty (Table 2). In these latter procedures, LAR in children aged <1 year were half those in children aged 1 to 5 years because of a much-reduced P_{KA}. Overall, projected LARs were 3 to 7× higher in girls than in boys (Table 2), mainly due to breast exposure and higher risks of lung cancer in females than males (Appendix C, Table VI in the Data Supplement). In boys, lung cancer accounted for 70% to 80% of the projected CCP-related risks, whereas, in girls, lung cancer accounted for 20% to 60% and breast cancer for 30% to 80%, depending on the procedure type at age at treatment (Appendix C and Figure II in the Data Supplement). Other cancer sites accounted each for <15% of the projected LARs.

To put the projected LARs in the context of baseline risks, we calculated that radiation exposure from a CCP in childhood would account for 0.4% to 0.7% (ASD), 0.8% to 3.7% (PDA occlusion), and 1.5% to 6.0% (pulmonary valvuloplasty) of the total lifetime risk of developing a cancer in children who will never smoke

Table 2. Projected Lifetime Risks of Developing a Tumor (at the Esophagus, Lungs, Breasts, Stomach, Liver, Pancreas, or Leukemia) From Cardiac Catheterization Procedures in Children

Procedure	Patient Age Group, y	Lifetime Attributable Risks Per 1000 Procedures			No. of Procedures That Would Lead to 1 Radiation-Related Cancer		Proportion of Attributable Cancers Among 1000 Children Who Will be Diagnosed With Cancer Over Their Lifetime*	
		Girls	Boys	Ratio Girls/Boys	Girls	Boys	Girls	Boys
Atrial septal defect occlusion	1 to <5	1.4 (0.5–3.5)	0.5 (0.1–2.0)	2.8	730 (285–2215)	2045 (515–9265)	7.3 (2.4–0.18.4)	6.1 (1.4–23.8)
	5 to <10	0.9 (0.2–2.6)	0.3 (0.1–1.2)	2.8	1070 (385–4185)	3020 (810–15 325)	5.0 (1.3–13.7)	4.1 (0.8–15.3)
	10–15	1.0 (0.3–2.9)	0.4 (0.1–1.6)	2.7	1025 (340–4015)	2720 (640–11 010)	5.2 (1.3–15.5)	4.6 (1.1–19.1)
Patent ductus arteriosus occlusion	0 to <1	7.1 (2.2–17.2)	1.2 (0.2–4.8)	5.9	140 (60–460)	825 (210–4715)	36.8 (11.6–84.8)	14.9 (2.7–56.4)
	1 to <5	5.0 (1.4–11.9)	0.7 (0.2–3.2)	7.3	200 (85–720)	1470 (310–6380)	26.0 (7.4–60.2)	8.5 (2.0–38.5)
	5 to <10	3.6 (1.0–9.5)	0.6 (0.1–2.1)	5.7	275 (105–1025)	1585 (470–9115)	19.0 (5.2–48.4)	7.9 (1.4–25.9)
	10–15	4.1 (1.3–10.5)	1.0 (0.2–4.6)	4.1	245 (95–780)	985 (220–6725)	21.7 (6.8–53.6)	12.6 (1.9–54.3)
Pulmonary valvuloplasty	0 to <1	5.0 (1.8–11.8)	1.2 (0.2–3.6)	4.2	200 (85–565)	855 (275–4460)	26.0 (9.4–59.7)	14.5 (2.8–43.2)
	1 to <5	12.0 (2.1–29.5)	2.0 (0.3–8.0)	6.0	85 (35–475)	505 (125–3050)	60.4 (11.2–136.8)	24.3 (4.1–90.9)

Numbers of procedures that would lead to 1 radiation-related cancer are rounded at the nearest 5 units.

*We estimated a total lifetime baseline risk (ie, without receiving a cardiac catheterization procedure) of developing cancer of the esophagus, lungs, breasts, stomach, liver, pancreas, or leukemia of 18.6% in females and 8.0% in males among lifelong nonsmokers in France, in 2010–2012.

during their lifetime, depending on their sex and age at treatment (Table 2). Similar to the trends of incidence rates by age in the general population (Appendix B and Table V in the Data Supplement), radiation-related risks would sharply increase from age 40 for breast cancer, age 50 for lung cancer, and age 70 for liver cancer (Figure).

DISCUSSION

Among children treated in 2009 to 2013 for a CHD in 2 of the largest catheterization centers in France, the projected LARs of cancer incidence ranged from 0.5 to 10 per 1000 procedures, depending on the procedure type, patient's sex and age at treatment (Table 2). Assuming a normal life expectancy and a lifelong nonsmoking history, excess cancer risks subsequent to radiation exposure from a childhood CCP would represent 0.4% to 6.0% of the children's total lifetime cancer risks, with lung and breast cancers accounting for the vast majority of the radiation-related risk.

The LARs of cancer would be higher for pulmonary valvuloplasty and PDA occlusion than for ASD closure. They would also be higher in children treated before age 5 than in older patients and in girls who had 3 to 7× higher LARs than boys due to breast exposure but also higher radiation-related risks of lung cancer per dose unit in females.[24] There was, nevertheless, a large variability in individual radiation doses (and projected subsequent risks), even for a given type of CCP, sex, and age group (Table 1). For the 10% most irradiating procedures, radiation-related cancer risks would account for 5.0% and 10.7% of boys' and girls' total lifetime cancer risk (Table 3).

A large variability in radiation exposures among children undergoing CCPs has already been reported in previous studies.[7,27–29] The survey conducted by Cevallos et al,[28] which collected dosimetry information at 9 US congenital cardiac catheterization center in 2014 to 2015, showed ratios of the 95th percentile to the 50th percentile values of individual P_{KA} distributions ranging from 4 to 12 depending on the age group for ASD closure (n=289), PDA occlusion (n=445), and pulmonary valvuloplasty (n=250). In this survey, P_{KA} was nevertheless higher than in this current study. Other studies have reported a large individual variability in dosimetry indexes (ie, fluoroscopy times, P_{KA}),[27] but relatively few studies have assessed its impact on organ equivalent doses.[7,14,29] The largest one was conducted at 3 hospitals in the UK and achieved dose reconstruction for 10 257 diagnostic and therapeutic CCPs performed between 1994 and 2013[7]. In this study, the interquartile ratios of lung and breast doses ranged between 5 and 14 depending on the weight group, for all procedure types combined.

Previous studies have projected potential subsequent cancer risks from practices in few hospitals in Israel,[30] United States,[31] and United Kingdom,[13] Among 59 children aged 2.8 years on average at the time of a diagnostic or interventional CCP in 2007, Ait-Ali et al[30] projected LARs of 0.6 per 1000 (in boys) and 0.9 per 1000 (in girls) associated with cumulative exposures from CCPs and prior x-ray examinations corresponding to cumulative effective doses of 7 to 9 mSv. Johnson et al[31] projected LARs of 0.06 (UI, 0.04–0.11) per 1000 children undergoing an ASD closure (n=21) and 0.13 (UI, 0.09–0.22) per 1000 children undergoing an atrial switch operation (n=24) for both sexes combined, corresponding to mean cumulative effective doses of 0.2

Table 3. Radiation Exposure and Projected Lifetime Attributable Risks Among Children Who Received Highest Effective Doses

Dosimetric Parameters and Projected Risks	ED >5 mSv (n=369)		ED >10 mSv (n=114)	
	Median Values (95th Percentile Intervals)			
Age, y	1 (0–14)		1 (0–14)	
Weight, kg	8 (3–61)		8 (3–70)	
Dose area-product, Gy.cm^2	3 (1–31)		5 (2–55)	
Effective dose, mSv	7 (5–26)		13 (10–59)	
Equivalent doses, mSv				
Esophagus	15 (8–55)		25 (11–115)	
Lung	20 (13–75)		34 (25–158)	
Breast	24 (10–87)		44 (14–206)	
Stomach	3 (1–13)		6 (2–24)	
Liver	9 (5–38)		14 (7–70)	
Pancreas	6 (2–21)		9 (4–35)	
Active bone marrow	2 (1–10)		3 (2–16)	
Lifetime attributable risk (per 1000 procedures)	Girls	Boys	Girls	Boys
All ages combined*	9.4 (3.5–20.1)	2.0 (0.4–6.4)	22.2 (7.4–45.6)	4.2 (0.8–13.1)
<1 y	10.2 (3.7–22.4)	2.1 (0.4–7.0)	24.6 (8.3–52.1)	4.7 (0.9–14.4)
1 to <5 y	9.6 (3.9–19.8)	2.1 (0.4–6.4)	23.3 (7.6–44.9)	4.3 (0.9–13.8)
5 to <10 y	7.7 (2.8–16.9)	1.6 (0.3–5.0)	18.0 (5.8–38.4)	3.5 (0.6–10.2)
10–15 y	6.0 (2.0–12.5)	1.3 (0.3–4.4)	14.5 (4.7–29.6)	2.7 (0.6–9.5)
Proportion of future attributable cancers (per 1000 children who would be diagnosed with cancer)*	48 (19–98)	24 (5–74)	107 (38–197)	50 (10–141)

Procedures associated with ED >5 mSv are atrial septal defect (n=12; 3.2%), patent ductus arteriosus (n=252; 68.4%), pulmonary valve stenosis (n=105; 28.4%); procedures associated with ED >10 mSv are atrial septal defect occlusion (n=5; 4.4%), patent ductus arteriosus occlusion (n=80; 70.4%), balloon pulmonary valvuloplasty (n=29; 25.2%). ED indicates effective dose.

*Mean risks weighted by the frequency of each age group by procedure types (for ED >5 mSv, <1 y: 49.6%, 1 to <5 y: 30.1%, 5 to <10 y: 12.2%, 10–15 y: 8.1%; for ED>10 mSv, <1 y: 45.6%, 1 to <5 y: 29.8%, 5 to <10 y: 13.2%, 10–15 y: 11.4%).

to 0.6 mSv which included both CCPs and other x-ray examinations received within the first 3 years of life. These 2 single-institution studies had nevertheless limited sample sizes to account for the variability of practices and clinical situations. The use of effective doses, rather than organ equivalent doses, also limited their interpretation. As previously underlined, the concept of effective dose, which is useful to compare radiation exposures from different sources or protocols, is not appropriate for risk projection, especially for children and medical exposures targeting specific body regions.[32,33] The study conducted by Harbron et al[13] used organ equivalent doses from a large sample (2749 CCPs, of which 1641 ASD, PDA occlusion procedures, or pulmonary valvuloplasty). From the supplementary tables provided by the authors, we derived median LARs of cancer incidence for all sites (lung, stomach, liver, thyroid, breast, and leukemia) of 0.4, 0.9, and 1.5 per 1000 procedures for ASD closure, PDA occlusion, and pulmonary valvuloplasty, respectively, in boys and 0.9, 2.7, and 2.6 per 1000 procedures for ASD closure, PDA occlusion, and pulmonary valvuloplasty in girls, at reference ages. The lower median doses for PDA occlusion and pulmonary valvuloplasty in this population as compared to the present study were associated with lower risks in girls but not in males. The assumption the authors made on similar smoking behaviors in CHD survivors than in the UK general population when deriving baseline cancer and mortality risks probably contributed in projecting higher LARs per dose unit in males who are more frequently smokers than females. In this study, the possibility of a reduced life expectancy in CHD survivors was considered by accumulating excess risks up to various attained ages (in a similar manner than it is shown in the Figure) but without reducing the survival probabilities at each prior age, which might have led to overestimate the LARs at intermediate ages for individuals with a reduced early life expectancy.

The present study assumed a normal life expectancy beyond the age of 1 year in CHD survivors undergoing an ASD closure, a PDA occlusion or a pulmonary valvuloplasty, in agreement with results from long time series of mortality rates in similar populations.[16,17] Subsequently, the current risk projections do not apply to specific cases where the cardiac disease or subsequent comorbidities substantially reduce the survival probability after CCP. More generally, those risk projections must not be used for prediction of individual risks,

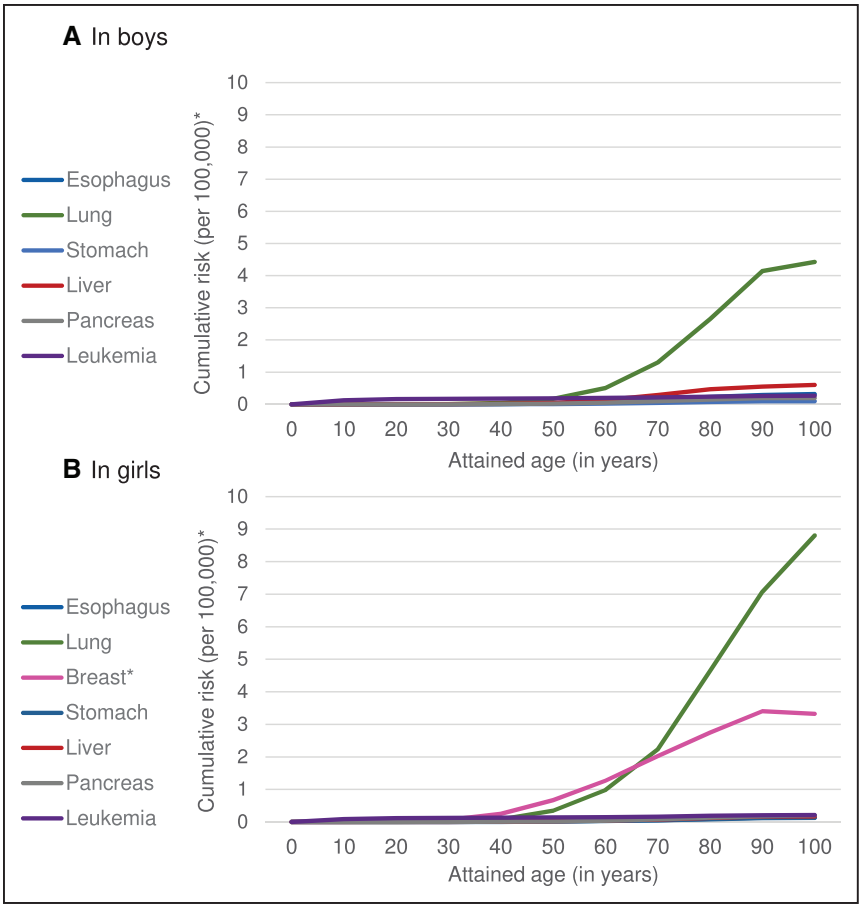

Figure. Projected cumulative excess risks of cancer incidence subsequent to radiation exposures from cardiac catheterization procedures in children—the example of patent ductus arteriosus occlusion.
*For breast cancer, risks are given per 1000 procedures. For other cancer sites, risks are given per 10 000 procedures.

which can be modified by a variety of clinical, genetic, environmental, and lifestyle factors. The usefulness of LAR projection is rather to provide the clinicians with information on the potential cancer burden in the population of CHD survivors that might justify long-term surveillance and prevention strategies for all or in some patient groups. Smoking prevention could be a component of such strategies in view of the existing evidence of higher radiation-related risks of lung cancer among low-to-moderate smokers (1 to 20 cigarettes per day) than in nonsmokers.[34] For other cancer sites, there has been no detailed investigation to our knowledge at low radiation doses, but a multiplicative interaction between radiation exposure and smoking is plausible, as well as is a reduction of LARs because of a shortened lifespan among smokers.

The methodological framework used here to project future cancer risks potentially induced by x-ray exposures from CCPs has been previously applied in various contexts of radiation exposures.[35–37] As it has already been extensively discussed in the literature, this approach is undoubtedly subjected to uncertainties.[25] The main sources of uncertainty are related to the shape of the dose-response relationship, particularly at doses <100 mSv and after childhood exposures, the joint effect of radiation and other risk factors for cancer, and the latency time between radiation exposure and cancer diagnosis. Propagation of uncertainties by Monte Carlo simulations as it is implemented in Radiation Risk Assessment Tool accounts for these uncertainties to provide ranges of possible risk values.[24] However, it only considers 1 set of risk models and does not allow for different modeling of the dose-response relationship and modifying effects for particular cancer sites. Published and ongoing epidemiological studies focusing on radiation exposures, such as computed tomography scans, during childhood, adolescence, and young adulthood are contributing in better characterizing the long-term risks for children medically exposed to ionizing radiations.[38–40] Current evidence is supporting the assumptions we made for risk projection, at least for brain cancer and leukemia.[40] In the future, a long-term follow-up of young patients undergoing CCPs will allow to assess specific risks of radiation-related risks for this population and the validity of current risk projections.[11,41]

Other important sources of uncertainty were the lack of information on beam collimation in the patient medical records and the inability to account for the inhomogeneous radiation exposure to parallel organs/tissues (eg, breasts, lungs) and those partially located within the primary beam (eg, esophagus) with the use of PCXMC software. Based on the current state of knowledge, we considered mean doses to organs (and the 2 sides of parallel organs) assuming that the risk was not modified by a

heterogeneous low-dose distribution, but further investigations could invalidate this assumption. Last, the present study only considered CCPs in CHD management, which represent the largest part of the radiation exposure but do not reflect the total cumulative exposure from diagnostic and therapeutic x-ray procedures.[30,31] Other imaging procedures, such as computed tomography scans, could also increase the long-term cancer risks in children with CHD, in particular, if they are repeated over time.[42] We also acknowledge that the 2 participating hospitals, though treating the largest number of children in France, may not be representative of practices at other cardiac catheterization centers. Last, the current study may not represent the most recent or future practices in interventional cardiology, which can be associated with reduced radiation doses and subsequent cancer risks. Several studies tend to establish that despite the increasing complexity of the procedures, patient dose has decreased during the past decade in interventional cardiology.[43–45] Operators' experience and training, enhanced cooperation between cardiologists and medical physicists, a more effective use of dose reducing techniques, and technological improvements in new fluoroscopy equipment are the main reasons for this tendency.

CONCLUSIONS

In a large population of children who underwent a CCP, this study shows a large variability in patient radiation doses, even for a given age group and procedure type. The potential subsequent cancer risks would also widely vary among children and could reach 2.2% among girls and 0.4% among boys who received the highest doses. In the future, the ongoing Coccinelle cohort study should contribute to better evaluate the potential long-term cancer risks among those children.[11] At the present time, the high degree of individual dose variability and the possible accumulation of radiological exposures for management of CHDs, and their potential subsequent comorbidities suggests the need for systematic dose reporting to support recommendations for long-term surveillance and prevention strategies, particularly for lung and breast cancers.

ARTICLE INFORMATION

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Disclosures

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