



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

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1 Potential long term cancer risks in children treated with fluoroscopy-guided cardiac
2 catheterization procedures

3 Running title: Lifetime cancer risks after cardiac catheterization procedures in childhood

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ABSTRACT

Background: Cardiac catheterization procedures (CCPs) are increasingly performed in children with congenital heart diseases who have now a long life expectancy and consequently potential long term radiation-induced risks. We evaluated organ equivalent radiation doses and projected Lifetime Attributable Risks (LARs) of cancer incidence from the most frequent procedures in pediatrics: atrial septal defect (ASD) closure, patent ductus arteriosus (PDA) occlusion or pulmonary valvuloplasty.

Methods: Organ equivalent doses were individually estimated for 1251 procedures performed in children aged ≤ 15 years at two reference catheterization centers in France in 2009-2013, based on medical records and exposure scenarios. Gender-specific LARs were projected using the RadRAT software which incorporates extended BEIR VII risk models, various sources of risk projection uncertainties and dose variability. Survival probabilities and baseline cancer risks were those of lifelong non-smokers with no reduced life expectancy due to congenital cardiac diseases.

Results: Median equivalent doses were 1-4 mSv (ASD closure), 8-17 mSv (PDA occlusion), and 10 mSv (pulmonary valvuloplasty) to both the lungs and breasts depending on patient age, and ≤ 10 mSv to other organs. There was a large individual variability, even for a given CCP type and patient age group. Median LARs ranged between 0.3 and 1.4 (ASD closure), 0.6 and 5.0 (PDA occlusion), and 1.0 and 12.0 (pulmonary valvuloplasty) per 1000 procedures, depending on patient gender and age at treatment. These excess risks from CCP radiation exposure would represent 0.4% to 6.0% of children' total lifetime cancer risk. For the 10% of procedures (all

types combined) with highest exposures, LARs reached 4.2 per 1000 [95% Uncertainty Interval (UI): 0.8-13.1] in boys and 22.2 per 1000 (95% UI: 7.4-45.6) in girls. In boys, lung cancer accounted for 70-80% of the projected LARs whereas in girls it accounted for 20-60% and breast cancer for 30-80% of the excess risks, depending on the CCP type and patient age.

Conclusion: There was a large individual variability in radiation exposure which may lead to substantial organ equivalent doses and increased cancer risks in some cases. This suggests the need for dose reporting in clinical practice to support recommendations for long term surveillance and prevention strategies.

INTRODUCTION

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) over 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 2005⁴) has thus increased the number of CHD survivors and made long-term disease management and potential adverse effects of treatments an important clinical issue⁵.

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 radiation⁸ and, as mentioned above, many of those born with CHD have now a long life expectancy⁴. The only two epidemiological studies to date that have reported cancer risks in patients receiving CCPs found opposite results, but they involved very small numbers of cases (N=13 in Canada⁹, 11 in Israel¹⁰) and had no dosimetry^{9,10}. Other cohort studies are currently set-up in France¹¹ and in the United Kingdom (UK)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 up to 20-25 years after exposures¹² and that tumors at the most exposed organs (e.g. 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 adulthood¹³.

The aim of the article is to project 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

Study population

The study included all children aged 15 years or less who underwent ASD closure, PDA occlusion or pulmonary valvuloplasty between 2009 and 2013 in two reference pediatric cardiac catheterization centers in France (APHP-Necker 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 CCP¹¹. Exclusions consisted in children with missing mandatory information to assess radiation doses or belonging to a non-representative exposure scenario group (see below). The study was approved by the French National Agency regulating Data Protection [Commission Nationale Informatique et Liberté] (CNIL agreement no. 911112, published on 12 December 2011).

Radiation exposure scenarios and equivalent organ doses

101 Exposure scenarios were defined based on individual patient data and radiological parameters
 102 routinely used in the participating hospitals. From medical records, we extracted the following
 103 information: patient's age and weight, type of procedure (ASD, PDA, pulmonary valvuloplasty)
 104 and Kerma Area Product (P_{KA}) (Table 1). Routine radiological parameters (x-ray beam
 105 orientation, field size, tube voltage, additional copper filtration) were collected in each hospital
 106 based on direct observation of practices in the hospitals and the experience of the cardiologists.
 107 Exposure scenarios were subsequently defined for each patient weight group, type of procedure
 108 and hospital, as shown in Appendix A (Table S1). CCPs were performed on a dual-arm Siemens
 109 Axiom Artis BC equipped with 23 cm image intensifiers at Necker hospital, and on a dual-arm
 110 Siemens Axiom Artis DBC equipped with 20 cm flat panels at Marie-Lannelongue hospital. For
 111 each exposure scenario, we estimated organ equivalent dose per unit P_{KA} (mSv/Gy.cm²) for each
 112 procedure using PCXMC 2.0 (©STUK 2008, Finland). This dosimetry system dedicated to
 113 calculation of patient doses in medical x-ray examinations (radiography and fluoroscopy)
 114 integrates Monte Carlo particles transport simulation and idealized mathematical human
 115 phantoms representing individuals of age (weight) 0 (3.4 kg), 1 (9.2 kg), 5 (19.0 kg), 10 (32.4
 116 kg) and 15 (56.3 kg) years. Organ equivalent and effective doses were then calculated for each
 117 patient by linear interpolation between the two nearest phantoms in terms of weight and
 118 multiplication of the conversion factors by the P_{KA} of the procedure. Doses to parallel organs
 119 (breasts, lungs) were averaged for the two organs. Procedures with missing information on P_{KA}
 120 or patient age were excluded. When information on weight was missing (15% of the procedures),
 121 a weight category was assigned according to the patient's age (<1 year: 0 to 6.5 kg, 1-4.9 years:
 122 >6.5 to 14.5 kg, 5 to 9.9 years: >14.5 to 25.5 kg, 10 to 15.9 years: >25.5 to 43.5 kg)¹⁴. Exposure

scenarios were defined only for common procedures in pediatrics. Subsequently, ASD occlusion at age <1 year and pulmonary valvuloplasty at age ≥ 5 years were not considered.

Estimation of baseline all-cause mortality and cancer risks in CHD survivors

Previous studies reported very low mortality rates from CHD (in particular, ASD, PDA and pulmonary artery stenosis) in individuals who survived beyond the age of 1 year^{15, 16}. We thus assumed a life expectancy comparable to that of the general population in children alive at age 1. While all-cause mortality, baseline and radiation-induced cancer risks depends 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 non-smokers only. We estimated baseline (i.e. in the absence of radiation exposure from CCP) age- and gender-specific survival probabilities in lifelong non-smokers based on the 2010-2012 life tables for the French (mainland) general population published by the National Institute for Demographic Studies¹⁷, 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 France¹⁸ and national statistics of all-causes deaths¹⁹. Baseline incidence rates of lung cancer in lifelong non-smokers were extracted from a pooled study of eight cohorts in European descents²⁰. 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 population²¹. Attributable fractions of cancer incidence to smoking were derived from tobacco-related risks published in the literature and age-standardized prevalence of smoking in the general population. Details of the applied methods

and estimated age- and gender-specific incidence rates for lifelong non-smokers are provided in Appendix B.

Projection of radiation-related cancer risks from CCPs

For each CCP and child's weight category, we projected future gender-specific cancer risks subsequent to radiation exposure from CCP using RadRAT (National Cancer Institute, Bethesda, MD, United States, freely accessible at <https://irep.nci.nih.gov/radtrat>)²². This risk assessment tool incorporates an extended list of cancer-specific BEIR VII (Committee on Biological Effects of Ionizing Radiation VII, National Research Council, Washington, DC, United States) 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 conditions²³. Those models estimate age-specific excess risk (which would occur in addition to baseline risk, i.e. here without receiving a CCP) per dose unit depending on age at exposure, time since exposure and gender. Projected risks at each attained age are accumulated up to age 100 while accounting for gender- 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)²⁴. To incorporate organ doses distributions and baseline mortality and cancer incidence rates for non-smokers as above described, we used the home version of RadRAT built with Analytica® (Lumina Decision Systems, Inc., Los Gatos, CA, USA). 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 RadRAT as it has been detailed in the original publication²². To account for individual organ 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. Due to very high uncertainties in risks at very low doses (<1 mSv), LARs were projected only for cancer sites which received at least 1 mSv, i.e. 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 seven cancer sites, for each CCP type and age group at the time of the CCP (<1 year, 1 to <5 years, 5 to <10 years, 10 to 15 years).

RESULTS

After exclusion of children with missing P_{KA} ($n=114$), missing age ($n=16$) or non-representative exposure scenario (i.e. age < 1 year for ASD closure or ≥ 5 years for pulmonary valvuloplasty, $n=27$), the study population consisted in 1175 children (sex-ratio: 1.7 girls/1 boy) who underwent 1251 procedures in 2009-2013 (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 2-9 mSv to the esophagus, 1-5 mSv to active bone marrow, stomach, liver and pancreas median doses, and below 1 mSv to the other organs (Appendix A - Table S2). A wide individual variability was nevertheless estimated, even within age groups. For a given procedure, the 95th percentile intervals of breast and lung doses

(i.e. 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 (i.e. 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 less than 1 year were half those in children aged 1-5 years due to a much reduced P_{KA} . Overall, projected LARs were 3 to 7 times 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 S6). In boys, lung cancer accounted for 70-80% of the projected CCP-related risks whereas, in girls, lung cancer accounted for 20-60% and breast cancer for 30-80%, depending on the procedure type at age at treatment (Appendix C - Figure S1). Other cancer sites accounted each for less than 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 0.4-0.7% (ASD), 0.8-3.7% (PDA occlusion), and 1.5-6.0% (pulmonary valvuloplasty) of the total lifetime risk of developing a cancer in children

who will never smoke during their lifetime, depending on their gender and age at treatment (Table 2). Similar to the trends of incidence rates by age in the general population (Appendix B, Table S5), radiation-related risks would sharply increase from age 40 for breast cancer, age 50 for lung cancer and age 70 for liver cancer (Figure 1).

DISCUSSION

Among children treated in 2009-2013 for a CHD in two of the largest catheterization centers in France, the projected LARs of cancer incidence ranged from 0.3 to 12.0 per 1000 procedures, depending on the procedure type, patient's gender and age at treatment (Table 2). Assuming a normal life expectancy and a lifelong non-smoking 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 times higher LARs than boys due to breast exposure but also higher radiation-related risks of lung cancer per dose unit in females²². There was nevertheless a very large variability in individual radiation doses (and projected subsequent risks), even for a given type of CCP, gender 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 risks (Table 3).

A large variability in radiation exposures among children undergoing CCPs has already been reported in previous studies^{7, 25-27}. The survey conducted by Cevallos et al, which collected dosimetry information at nine US congenital cardiac catheterization center in 2014-2015, 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)²⁶. Other studies have also reported a large individual variability in dosimetry indexes (i.e. fluoroscopy times, P_{KA})²⁵, but relatively few studies have assessed its impact on organ equivalent doses^{7, 14, 27}. The largest one was conducted at three hospitals in the UK and achieved dose reconstruction for 10,257 diagnostic and therapeutic CCPs performed between 1994 and 2013⁷. 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 Israel²⁸, US²⁹, and UK¹³. Among 59 children aged 2.8 years on average at the time of a diagnostic or interventional CCP in 2007, Ait-Ali et al 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 7-9 mSv²⁸. Johnson et al 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 genders combined, corresponding to mean cumulative effective doses of 0.2-0.6 mSv which included both CCPs and other x-ray examinations received within the first 3 years of life²⁹. These two 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 regions³⁰.³¹. The study conducted by Harbron et al used organ equivalent doses from a large sample (2749 CCPs, of which 1641 ASD, PDA occlusion procedures or pulmonary valvuloplasty)¹³. 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 Figure 1) 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^{15, 16}. 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, 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 (1-20 cigarettes per day) than in non-smokers³². 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 due to a shortened life span among smokers.

The methodology applied to project future cancer risks potentially induced by x-ray exposures from CCPs is undoubtedly subjected to uncertainties. As it has been extensively discussed in the literature^{23, 33}, the main sources of uncertainty are related to the shape of the dose-response relationship, particularly at doses below 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 RadRAT accounts for these uncertainties to provide ranges of possible risk values²². However, it only considers one set of risk models and does not allow for different modelling 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 (CT) scans, during childhood, adolescence and young adulthood are contributing in better characterizing the long-term risks for children medically exposed to ionizing radiations³⁴⁻³⁶.

Current evidence is supporting the assumptions we made for risk projection, at least for brain cancer and leukemia³⁶.

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 (e.g. breasts, lungs) and those partially located within the primary beam (e.g. esophagus) with the use of PCXMC software. Based on the current state of knowledge, we considered mean doses to organs (and the two 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 accounts for the largest part of the radiation exposure but do not reflect the total cumulative exposure from diagnostic and therapeutic x-ray procedures^{28, 29}. Other imaging procedures, such as CT scans, could also increase the long-term cancer risks in children with CHD, in particular if they are repeated over time³⁷.

Conclusion

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 children¹¹. 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

321 comorbidities suggests the need for systematic dose reporting to support recommendations for
322 long term surveillance and prevention strategies, particularly for lung and breast cancers.

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331 **CONFLICT OF INTEREST**

332 The authors declare no conflict of interest.

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449 Table 1. Number of children and procedures involved and main dosimetry information

450 Table 2. Effective and equivalent doses to organs or tissues of interest (in mSv), median values
451 (95th percentile intervals)

452 Table 3. Projected lifetime risks of developing a tumor (at the esophagus, lungs, breasts,
453 stomach, liver, pancreas, or leukemia) from cardiac catheterization procedures in children

454 Table 4. Radiation exposure and projected lifetime attributable risks among children who
455 received highest effective doses

456 Figure 1. Projected cumulative excess risks of cancer incidence subsequent to radiation
457 exposures from cardiac catheterization procedures in children --the example of Patent Ductus
458 Arteriosus occlusion

459 Supplementary material:

460 Appendix A – Detailed information on the radiation exposure scenarios

461 Appendix B – Estimation of age- and gender-specific incidence rates in lifelong non-smokers

462 Appendix C – Supplementary results

463 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 (in years)								
	1-<5 (N=37)	5-<10 (N=145)	10-15 (N=115)	0-<1 (N=219)	1-<5 (N=315)	5-<10 (N=101)	10-15 (N=50)	0-<1 (N=232)	1-<5 (N=37)
Weight (in 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 (in Gy.cm2)	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 (in 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 (in 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: Number of procedures during the study period *International Commission on Radiological Protection (ICRP 103) tissue weighting factors. Weight and P_{KA} values are respectively rounded at the nearest 5 and 0.5 unit.

466 Table 2. Projected lifetime risks of developing a tumor (at the esophagus, lungs, breasts, stomach, liver, pancreas, or leukemia) from cardiac
467 catheterization procedures in children

Procedure	Patient age group (in years)	Lifetime attributable risks per 1000 procedures			Number of procedures that would lead to one 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
ASD occlusion	1-<5	1.4 (0.5,3.5)	0.5 (0.1,2.0)	2,8	730 (285,2215)	2045 (515,9265)	7.3 (2.4,0.2)	6.1 (1.4,0.2)
	5-<10	0.9 (0.2,2.6)	0.3 (0.1,1.2)	2,8	1070 (385,4185)	3020 (810,15325)	5.0 (1.3,0.1)	4.1 (0.8,0.2)
	10-15	1.0 (0.3,2.9)	0.4 (0.1,1.6)	2,7	1025 (340,4015)	2720 (640,11010)	5.2 (1.3,0.2)	4.6 (1.1,0.2)
PDA occlusion	0-<1	7.1 (2.2,17.2)	1.2 (0.2,4.8)	5,9	140 (60,460)	825 (210,4715)	36.8 (11.6,0.9)	14.9 (2.7,0.6)
	1-<5	5.0 (1.4,11.9)	0.7 (0.2,3.2)	7,3	200 (85,720)	1470 (310,6380)	26.0 (7.4,0.6)	8.5 (2.0,0.4)
	5-<10	3.6 (1.0,9.5)	0.6 (0.1,2.1)	5,7	275 (105,1025)	1585 (470,9115)	19.0 (5.2,0.5)	7.9 (1.4,0.3)
Pulmonary valvuloplasty	10-15	4.1 (1.3,10.5)	1.0 (0.2,4.6)	4,1	245 (95,780)	985 (220,6725)	21.7 (6.8,0.6)	12.6 (1.9,0.6)
	0-<1	5.0 (1.8,11.8)	1.2 (0.2,3.6)	4,2	200 (85,565)	855 (275,4460)	26.0 (9.4,0.6)	14.5 (2.8,0.5)
	1-<5	12.0 (2.1,29.5)	2.0 (0.3,8.0)	6,0	85 (35,475)	505 (125,3050)	60.4 (11.2,1.6)	24.3 (4.1,1)

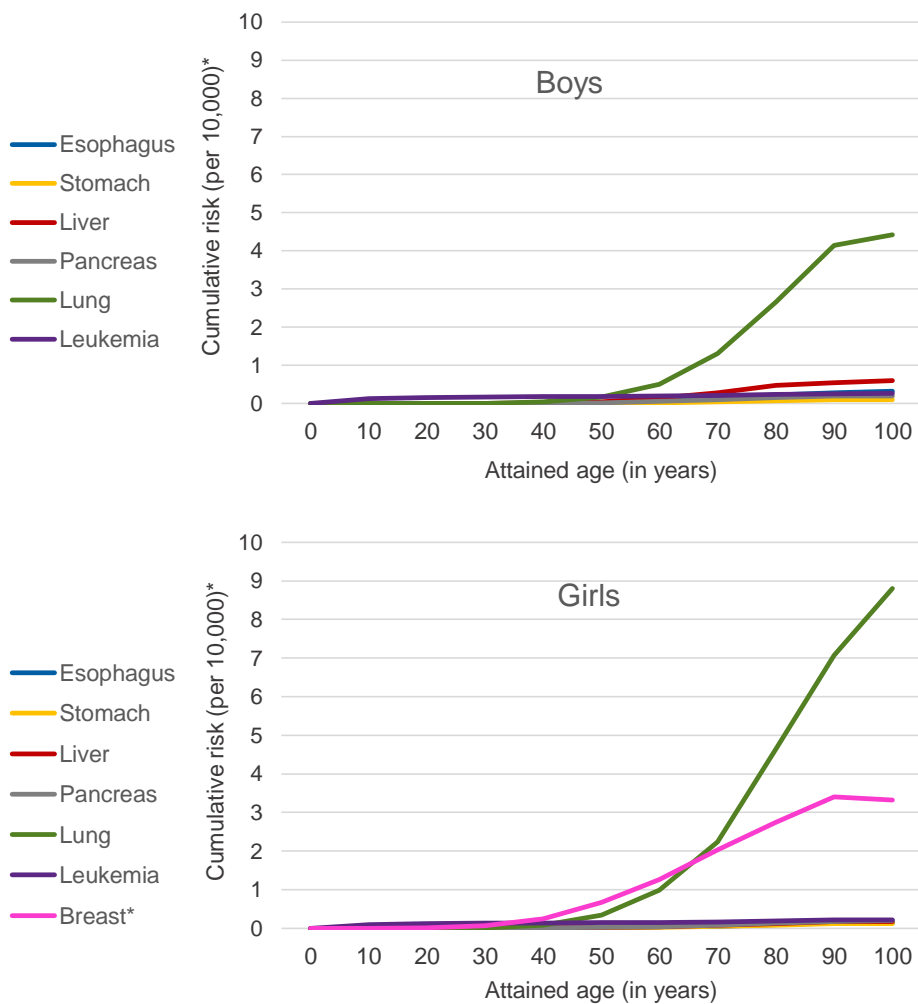
ASD: Atrial septal defect; PDA: Patent ductus arteriosus.

*We estimated a total lifetime baseline risk (i.e. without receiving a cardiac catheterization procedure) of developing a cancer of the esophagus, lungs, breasts, stomach, liver, pancreas, or a leukemia of 18.6% in females and 8.0% in males among lifelong non-smokers in France, in 2010-2012. NB: Number of procedures that would lead to one radiation-related cancer are rounded at the nearest 5 unit.

Table 3. Radiation exposure and projected lifetime attributable risks among children who received highest effective doses

	ED> 5mSv (N=369)		ED >10 mSv (N=114)	
	Median values (95th percentile intervals)			
Age (in years)	1 (0,14)		1 (0,14)	
Weight (in kg)	8 (3,61)		8 (3,70)	
Dose Area-Product (in Gy.cm2)	3 (1,31)		5 (2,55)	
Effective dose (in mSv)	7 (5,26)		13 (10,59)	
Equivalent doses (in mSv)				
Esophagus	15 (8,55)		25 (11,115)	
Stomach	3 (1,13)		6 (2,24)	
Liver	9 (5,38)		14 (7,70)	
Pancreas	6 (2,21)		9 (4,35)	
Lung	20 (13,75)		34 (25,158)	
Breast	24 (10,87)		44 (14,206)	
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 year	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-<5 years	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-<10 years	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 years	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)

ED: Effective dose; †Mean risks weighted by the frequency of each age group by procedure types (for ED >5 mSv, <1 year: 49.6%, 1-<5 years: 30.1%, 5-<10 years: 12.2%, 10-15 years: 8.1%; for ED>10 mSv, <1 year: 45.6%, 1-<5 years: 29.8%, 5-<10 years: 13.2%, 10-15 years: 11.4%). NB: 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%)



*Risks of breast cancer are given per 1,000 procedures, risks of cancer at other sites than breast are given per 10,000 pocedures

Figure 1. Projected cumulative excess risks of cancer incidence subsequent to radiation exposures from cardiac catheterization procedures in children --the example of Patent Ductus Arteriosus occlusion