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## 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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29 **ABSTRACT**

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

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

43 Results: Median equivalent doses were 1-4 mSv (ASD closure), 8-17 mSv (PDA occlusion), and  
44 10 mSv (pulmonary valvuloplasty) to both the lungs and breasts depending on patient age, and  
45  $\leq 10$  mSv to other organs. There was a large individual variability, even for a given CCP type and  
46 patient age group. Median LARs ranged between 0.3 and 1.4 (ASD closure), 0.6 and 5.0 (PDA  
47 occlusion), and 1.0 and 12.0 (pulmonary valvuloplasty) per 1000 procedures, depending on  
48 patient gender and age at treatment. These excess risks from CCP radiation exposure would  
49 represent 0.4% to 6.0% of children' total lifetime cancer risk. For the 10% of procedures (all

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

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

58

59 **INTRODUCTION**

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

67 Fluoroscopy used during CCPs to obtain hemodynamic images of the circulatory system is  
68 typically associated with effective radiation doses ranging from 3 to 15 mSv, and can result in  
69 organ equivalent doses exceeding 50 mSv for some complex procedures<sup>6,7</sup>. At those dose levels,  
70 the risk of radiation induced effects is to be considered, all the more so because children are  
71 particularly sensitive to ionizing radiation<sup>8</sup> and, as mentioned above, many of those born with  
72 CHD have now a long life expectancy<sup>4</sup>. The only two epidemiological studies to date that have  
73 reported cancer risks in patients receiving CCPs found opposite results, but they involved very  
74 small numbers of cases (N=13 in Canada<sup>9</sup>, 11 in Israel<sup>10</sup>) and had no dosimetry<sup>9,10</sup>. Other cohort  
75 studies are currently set-up in France<sup>11</sup> and in the United Kingdom (UK)<sup>7</sup> with inclusion of large  
76 populations, collection of detailed treatment data and estimation of individual radiation doses to  
77 palliate the limitations of previous studies. Considering that radiation-related cancers may have  
78 latency times up to 20-25 years after exposures<sup>12</sup> and that tumors at the most exposed organs  
79 (e.g. breasts, lungs and stomach) are mainly diagnosed after the age of 40 years, it is nevertheless  
80 unlikely to observe excess risks before decades of follow-up after CCPs in children. In the

81 meanwhile, the use of existent biological and epidemiological knowledge on the effects of  
82 radiation exposures allows projecting risks (with numerical simulations) and informing on  
83 potential future cancer risks CHD survivors would face in adolescence and adulthood<sup>13</sup>.

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

## 88 **METHODS**

### 89 **Study population**

90 The study included all children aged 15 years or less who underwent ASD closure, PDA  
91 occlusion or pulmonary valvuloplasty between 2009 and 2013 in two reference pediatric cardiac  
92 catheterization centers in France (APHP-Necker pediatric hospital in Paris and Marie  
93 Lannelongue hospital in Le Plessis-Robinson). The included children were all participants of the  
94 *Coccinelle* cohort study which aims at investigating the long-term incidence of leukemia and  
95 solid cancers among children treated in France with a CCP<sup>11</sup>. Exclusions consisted in children  
96 with missing mandatory information to assess radiation doses or belonging to a non-  
97 representative exposure scenario group (see below). The study was approved by the French  
98 National Agency regulating Data Protection [Commission Nationale Informatique et Liberté]  
99 (CNIL agreement no. 911112, published on 12 December 2011).

### 100 **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.cm<sup>2</sup>) 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)<sup>14</sup>. Exposure



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

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

126 Previous studies reported very low mortality rates from CHD (in particular, ASD, PDA and  
127 pulmonary artery stenosis) in individuals who survived beyond the age of 1 year<sup>15, 16</sup>. We thus  
128 assumed a life expectancy comparable to that of the general population in children alive at age 1.  
129 While all-cause mortality, baseline and radiation-induced cancer risks depends on smoking  
130 behaviors, we nevertheless had to account for the presumably less frequent smoking history of  
131 CHD survivors as compared to the general population. Without information on smoking  
132 behaviors in CHD survivors in France, we projected cancer risks for lifelong non-smokers only.  
133 We estimated baseline (i.e. in the absence of radiation exposure from CCP) age- and gender-  
134 specific survival probabilities in lifelong non-smokers based on the 2010-2012 life tables for the  
135 French (mainland) general population published by the National Institute for Demographic  
136 Studies<sup>17</sup>, where we deducted the proportion of all-cause deaths attributable to smoking. The  
137 attributable fraction of all-cause mortality to smoking was derived from a previous report of  
138 tobacco-attributable mortality in France<sup>18</sup> and national statistics of all-causes deaths<sup>19</sup>. Baseline  
139 incidence rates of lung cancer in lifelong non-smokers were extracted from a pooled study of  
140 eight cohorts in European descents<sup>20</sup>. For the other cancer sites, we calculated theoretical  
141 incidence rates in never-smokers by deducting the site-specific attributable fraction to smoking  
142 from the 2012 incidence rates in the French general population<sup>21</sup>. Attributable fractions of cancer  
143 incidence to smoking were derived from tobacco-related risks published in the literature and age-  
144 standardized prevalence of smoking in the general population. Details of the applied methods

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

### 147 **Projection of radiation-related cancer risks from CCPs**

148 For each CCP and child's weight category, we projected future gender-specific cancer risks  
149 subsequent to radiation exposure from CCP using RadRAT (National Cancer Institute, Bethesda,  
150 MD, United States, freely accessible at <https://irep.nci.nih.gov/radtrat>)<sup>22</sup>. This risk assessment  
151 tool incorporates an extended list of cancer-specific BEIR VII (Committee on Biological Effects  
152 of Ionizing Radiation VII, National Research Council, Washington, DC, United States) risk  
153 models derived from cohort studies of the survivors of the Hiroshima and Nagasaki atomic  
154 bombings and patients exposed to x-rays for benign health conditions<sup>23</sup>. Those models estimate  
155 age-specific excess risk (which would occur in addition to baseline risk, i.e. here without  
156 receiving a CCP) per dose unit depending on age at exposure, time since exposure and gender.  
157 Projected risks at each attained age are accumulated up to age 100 while accounting for gender-  
158 and age-specific survival probabilities and risks of developing a cancer without receiving a CCP  
159 in childhood (baseline risks), thus providing estimates of Lifetime Attributable Risk (LAR)<sup>24</sup>. To  
160 incorporate organ doses distributions and baseline mortality and cancer incidence rates for non-  
161 smokers as above described, we used the home version of RadRAT built with Analytica®  
162 (Lumina Decision Systems, Inc., Los Gatos, CA, USA). Risk projection uncertainties and  
163 individual dose variability were propagated through projected LARs by Monte Carlo simulations  
164 to produce uncertainty intervals (UIs). Uncertainties in dose-response model parameters,  
165 minimum latency period between radiation exposure and cancer occurrence, high-to-low doses  
166 risk extrapolation and population-to-population risk transport were incorporated in RadRAT as it  
167 has been detailed in the original publication<sup>22</sup>. To account for individual organ dose variability,

168 we considered a triangular probability distribution for each exposure scenario with minimal,  
169 modal, and maximal values defined as the 5th, 50th and 95th percentiles of the dose distribution  
170 in the study population. The results are displayed as median simulated LAR values (per 1000  
171 CCPs) with 95% UI. Due to very high uncertainties in risks at very low doses (<1 mSv), LARs  
172 were projected only for cancer sites which received at least 1 mSv, i.e. oesophagus, lung, breast  
173 (in females only), stomach, liver, pancreas, leukemia except chronic lymphoid leukemia (related  
174 to mean whole-body dose to red bone marrow). LARs were then summed over the seven cancer  
175 sites, for each CCP type and age group at the time of the CCP (<1 year, 1 to <5 years, 5 to <10  
176 years, 10 to 15 years).

## 177 **RESULTS**

178 After exclusion of children with missing  $P_{KA}$  (n=114), missing age (n=16) or non-representative  
179 exposure scenario (i.e. age < 1 year for ASD closure or  $\geq 5$  years for pulmonary valvuloplasty,  
180 n=27), the study population consisted in 1175 children (sex-ratio: 1.7 girls/1 boy) who  
181 underwent 1251 procedures in 2009-2013 (Table 1). Median age at CCP was 8.7 years for ASD  
182 closure (n=297), 2.7 years for PDA occlusion (n=685) and 1 month for pulmonary valvuloplasty  
183 (n=269).

184 Radiation exposure was the highest to the lungs and breasts with estimated median equivalent  
185 doses ranging respectively from 3 to 17 mSv and 1 to 16 mSv, depending on the type of  
186 procedure and patient age (Table 1). Median doses were 2-9 mSv to the esophagus, 1-5 mSv to  
187 active bone marrow, stomach, liver and pancreas median doses, and below 1 mSv to the other  
188 organs (Appendix A - Table S2). A wide individual variability was nevertheless estimated, even  
189 within age groups. For a given procedure, the 95<sup>th</sup> percentile intervals of breast and lung doses

190 (i.e. ratios between 97.5<sup>th</sup>/2.5<sup>th</sup> percentile values of the dose distribution) by age group ranged  
191 from 15 to 80 mSv (Table 1).

192 Pulmonary valvuloplasty was the procedure associated with the highest median projected LARs,  
193 ranging from 5 to 12 per 1000 procedures in girls and 1 to 2 per 1000 procedures in boys. For  
194 PDA occlusion, median LARs ranged from 4 to 7 per 1000 in girls and 0.5 to 1 per 1000 in boys,  
195 depending on the age group (Table 2). For ASD closure, median LARs were about 1 and 0.5 per  
196 1000 in girls and boys respectively. The 25% of CCPs with highest radiation exposure (i.e.  
197 effective dose >5 mSv) were associated with LARs of 9 (95%UI: 4-20) per 1000 procedures in  
198 girls and 2 (95%UI: >1-6) per 1000 procedures in boys, and the 10% of CCPs with effective dose  
199 >10 mSv were associated with LARs of 22 (95%UI: 7-46) per 1000 in girls and 4 (95%UI: 1-13)  
200 per 1000 in boys (Table 3).

201 The projected LARs were highest in the youngest patients, except for pulmonary valvuloplasty  
202 (Table 2). In these latter procedures, LAR in children aged less than 1 year were half those in  
203 children aged 1-5 years due to a much reduced  $P_{KA}$ . Overall, projected LARs were 3 to 7 times  
204 higher in girls than in boys (Table 2), mainly due to breast exposure and higher risks of lung  
205 cancer in females than males (Appendix C - Table S6). In boys, lung cancer accounted for 70-  
206 80% of the projected CCP-related risks whereas, in girls, lung cancer accounted for 20-60% and  
207 breast cancer for 30-80%, depending on the procedure type at age at treatment (Appendix C -  
208 Figure S1). Other cancer sites accounted each for less than 15% of the projected LARs.

209 To put the projected LARs in the context of baseline risks, we calculated that radiation exposure  
210 from a CCP in childhood would account for 0.4-0.7% (ASD), 0.8-3.7% (PDA occlusion), and  
211 1.5-6.0% (pulmonary valvuloplasty) of the total lifetime risk of developing a cancer in children

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

## 216 **DISCUSSION**

217 Among children treated in 2009-2013 for a CHD in two of the largest catheterization centers in  
218 France, the projected LARs of cancer incidence ranged from 0.3 to 12.0 per 1000 procedures,  
219 depending on the procedure type, patient's gender and age at treatment (Table 2). Assuming a  
220 normal life expectancy and a lifelong non-smoking history, excess cancer risks subsequent to  
221 radiation exposure from a childhood CCP would represent 0.4% to 6.0% of the children' total  
222 lifetime cancer risks, with lung and breast cancers accounting for the vast majority of the  
223 radiation-related risk.

224 The LARs of cancer would be higher for pulmonary valvuloplasty and PDA occlusion than for  
225 ASD closure. They would also be higher in children treated before age 5 than in older patients,  
226 and in girls who had 3 to 7 times higher LARs than boys due to breast exposure but also higher  
227 radiation-related risks of lung cancer per dose unit in females<sup>22</sup>. There was nevertheless a very  
228 large variability in individual radiation doses (and projected subsequent risks), even for a given  
229 type of CCP, gender and age group (Table 1). For the 10% most irradiating procedures,  
230 radiation-related cancer risks would account for 5.0% and 10.7% of boys' and girls' total lifetime  
231 cancer risks (Table 3).

232 A large variability in radiation exposures among children undergoing CCPs has already been  
233 reported in previous studies<sup>7, 25-27</sup>. The survey conducted by Cevallos et al, which collected  
234 dosimetry information at nine US congenital cardiac catheterization center in 2014-2015, showed  
235 ratios of the 95<sup>th</sup> percentile to the 50<sup>th</sup> percentile values of individual P<sub>KA</sub> distributions ranging  
236 from 4 to 12 depending on the age group for ASD closure (n=289), PDA occlusion (n=445) and  
237 pulmonary valvuloplasty (n=250)<sup>26</sup>. Other studies have also reported a large individual  
238 variability in dosimetry indexes (i.e. fluoroscopy times, P<sub>KA</sub>)<sup>25</sup>, but relatively few studies have  
239 assessed its impact on organ equivalent doses<sup>7, 14, 27</sup>. The largest one was conducted at three  
240 hospitals in the UK and achieved dose reconstruction for 10,257 diagnostic and therapeutic CCPs  
241 performed between 1994 and 2013<sup>7</sup>. In this study, the interquartile ratios of lung and breast doses  
242 ranged between 5 and 14 depending on the weight group, for all procedure types combined.

243 Previous studies have projected potential subsequent cancer risks from practices in few hospitals  
244 in Israel<sup>28</sup>, US<sup>29</sup>, and UK<sup>13</sup>. Among 59 children aged 2.8 years on average at the time of a  
245 diagnostic or interventional CCP in 2007, Ait-Ali et al projected LARs of 0.6 per 1000 (in boys)  
246 and 0.9 per 1000 (in girls) associated with cumulative exposures from CCPs and prior x-ray  
247 examinations corresponding to cumulative effective doses of 7-9 mSv<sup>28</sup>. Johnson et al projected  
248 LARs of 0.06 (UI: 0.04-0.11) per 1000 children undergoing an ASD closure (n=21) and 0.13  
249 (UI: 0.09-0.22) per 1000 children undergoing an atrial switch operation (n=24) for both genders  
250 combined, corresponding to mean cumulative effective doses of 0.2-0.6 mSv which included  
251 both CCPs and other x-ray examinations received within the first 3 years of life<sup>29</sup>. These two  
252 single-institution studies had nevertheless limited sample sizes to account for the variability of  
253 practices and clinical situations. The use of effective doses, rather than organ equivalent doses,  
254 also limited their interpretation. As previously underlined, the concept of effective dose, which is

255 useful to compare radiation exposures from different sources or protocols, is not appropriate for  
256 risk projection, especially for children and medical exposures targeting specific body regions<sup>30</sup>.  
257 <sup>31</sup>. The study conducted by Harbron et al used organ equivalent doses from a large sample (2749  
258 CCPs, of which 1641 ASD, PDA occlusion procedures or pulmonary valvuloplasty)<sup>13</sup>. From the  
259 supplementary tables provided by the authors, we derived median LARs of cancer incidence for  
260 all sites (lung, stomach, liver, thyroid, breast and leukemia) of 0.4, 0.9 and 1.5 per 1000  
261 procedures for ASD closure, PDA occlusion and pulmonary valvuloplasty, respectively, in boys,  
262 and 0.9, 2.7 and 2.6 per 1000 procedures for ASD closure, PDA occlusion, and pulmonary  
263 valvuloplasty in girls, at reference ages. The lower median doses for PDA occlusion and  
264 pulmonary valvuloplasty in this population as compared to the present study were associated  
265 with lower risks in girls but not in males. The assumption the authors made on similar smoking  
266 behaviors in CHD survivors than in the UK general population when deriving baseline cancer  
267 and mortality risks probably contributed in projecting higher LARs per dose unit in males who  
268 are more frequently smokers than females. In this study, the possibility of a reduced life  
269 expectancy in CHD survivors was considered by accumulating excess risks up to various  
270 attained ages (in a similar manner than it is shown in Figure 1) but without reducing the survival  
271 probabilities at each prior age, which might have led to overestimate the LARs at intermediate  
272 ages for individuals with a reduced early life expectancy.

273 The present study assumed a normal life expectancy beyond the age of 1 year in CHD survivors  
274 undergoing an ASD closure, a PDA occlusion or a pulmonary valvuloplasty, in agreement with  
275 results from long time series of mortality rates in similar populations<sup>15, 16</sup>. Subsequently, the  
276 current risk projections do not apply to specific cases where the cardiac disease or subsequent  
277 comorbidities substantially reduce the survival probability after CCP. More generally, those risk

278 projections must not be used for prediction of individual risks, which can be modified by a  
279 variety of clinical, genetic, environmental and lifestyle factors. The usefulness of LAR projection  
280 is rather to provide the clinicians with information on the potential cancer burden in the  
281 population of CHD survivors that might justify long term surveillance and prevention strategies  
282 for all or in some patient groups. Smoking prevention could be a component of such strategies in  
283 view of the existing evidence of higher radiation-related risks of lung cancer among low-to-  
284 moderate smokers (1-20 cigarettes per day) than in non-smokers<sup>32</sup>. For other cancer sites, there  
285 has been no detailed investigation to our knowledge at low radiation doses, but a multiplicative  
286 interaction between radiation exposure and smoking is plausible, as well as is a reduction of  
287 LARs due to a shortened life span among smokers.

288 The methodology applied to project future cancer risks potentially induced by x-ray exposures  
289 from CCPs is undoubtedly subjected to uncertainties. As it has been extensively discussed in the  
290 literature<sup>23, 33</sup>, the main sources of uncertainty are related to the shape of the dose-response  
291 relationship, particularly at doses below 100 mSv and after childhood exposures, the joint effect  
292 of radiation and other risk factors for cancer and the latency time between radiation exposure and  
293 cancer diagnosis. Propagation of uncertainties by Monte Carlo simulations as it is implemented  
294 in RadRAT accounts for these uncertainties to provide ranges of possible risk values<sup>22</sup>. However,  
295 it only considers one set of risk models and does not allow for different modelling of the dose-  
296 response relationship and modifying effects for particular cancer sites. Published and ongoing  
297 epidemiological studies focusing on radiation exposures, such as computed tomography (CT)  
298 scans, during childhood, adolescence and young adulthood are contributing in better  
299 characterizing the long-term risks for children medically exposed to ionizing radiations<sup>34-36</sup>.



300 Current evidence is supporting the assumptions we made for risk projection, at least for brain  
301 cancer and leukemia<sup>36</sup>.

302 Other important sources of uncertainty were the lack of information on beam collimation in the  
303 patient medical records and the inability to account for the inhomogeneous radiation exposure to  
304 parallel organs/tissues (e.g. breasts, lungs) and those partially located within the primary beam  
305 (e.g. esophagus) with the use of PCXMC software. Based on the current state of knowledge, we  
306 considered mean doses to organs (and the two sides of parallel organs) assuming that the risk  
307 was not modified by a heterogeneous low-dose distribution, but further investigations could  
308 invalidate this assumption. Last, the present study only considered CCPs in CHD management,  
309 which accounts for the largest part of the radiation exposure but do not reflect the total  
310 cumulative exposure from diagnostic and therapeutic x-ray procedures<sup>28, 29</sup>. Other imaging  
311 procedures, such as CT scans, could also increase the long-term cancer risks in children with  
312 CHD, in particular if they are repeated over time<sup>37</sup>.

### 313 **Conclusion**

314 In a large population of children who underwent a CCP, this study shows a large variability in  
315 patient radiation doses, even for a given age group and procedure type. The potential subsequent  
316 cancer risks would also widely vary among children, and could reach 2.2% among girls and  
317 0.4% among boys who received the highest doses. In the future, the ongoing *Coccinelle* cohort  
318 study should contribute to better evaluate the potential long-term cancer risks among those  
319 children<sup>11</sup>. At the present time, the high degree of individual dose variability and the possible  
320 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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448

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<sub>KA</sub> values are respectively rounded at the nearest 5 and 0.5 unit.

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465

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.



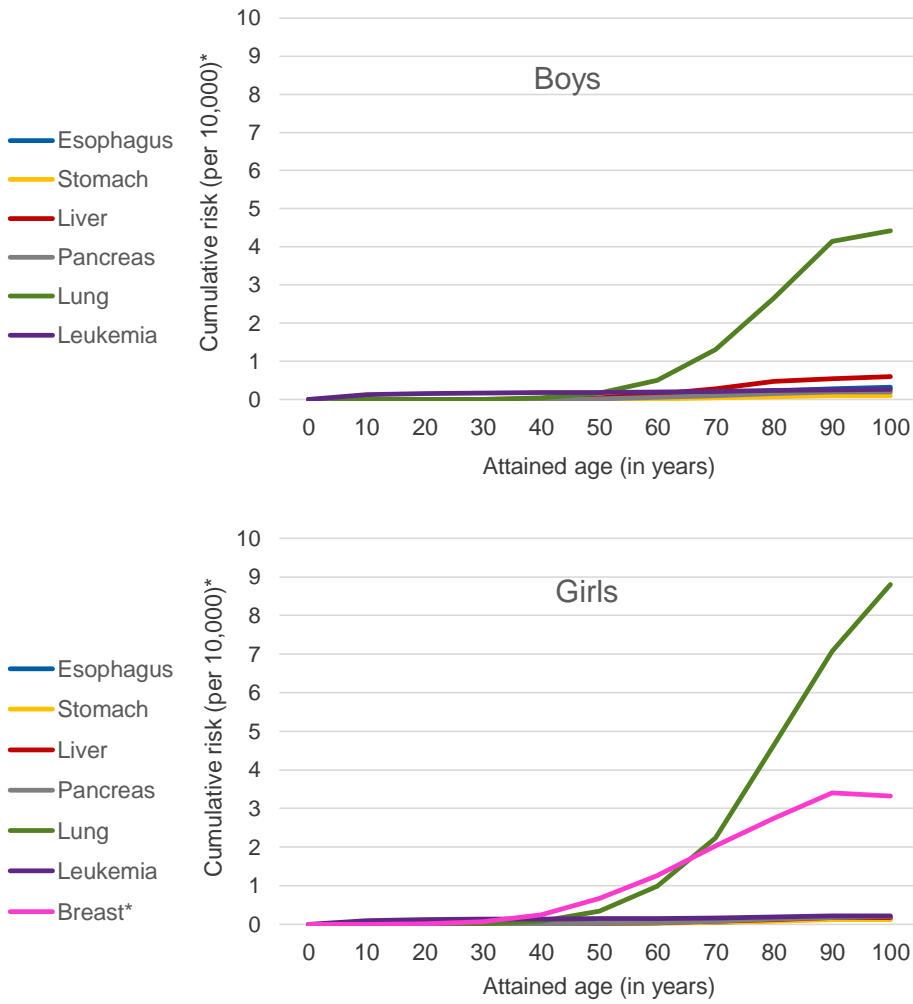
468 Table 3. Radiation exposure and projected lifetime attributable risks among children who received highest  
 469 effective doses

	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%)

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\*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