DOI: 10.1002/pul2.12282

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI | WILEY

Associated radiation exposure from medical imaging and excess lifetime risk of developing cancer in pediatric patients with pulmonary hypertension

Malini Mahendra[1,2] | **Philip Chu**[3] | **Elena K. Amin**[4] | **Hythem Nawaytou**[4] | **James R. Duncan**[5] | **Jeffrey R. Fineman**[1,6] | **Rebecca Smith-Bindman**[2,3,7]

[1]Department of Pediatrics, Division of Pediatric Critical Care, UCSF Benioff Children's Hospital, University of California at San Francisco, San Francisco, California, USA

[2]Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, California, USA

[3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

[4]Department of Pediatrics, Division of Pediatric Cardiology, UCSF Benioff Children's Hospital, University of California at San Francisco, San Francisco, California, USA

[5]Interventional Radiology Section, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA

[6]Cardiovascular Research Institute, University of California, San Francisco, California, USA

[7]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, California, USA

Correspondence
Malini Mahendra, Department of Pediatrics, Division of Pediatric Critical Care, UCSF Benioff Children's Hospital, University of California at San Francisco, 550 16th St, San Francisco, CA 94158, USA.
Email: Malini.mahendra@ucsf.edu

Funding information
Patient-Centered Outcomes Research Institute, Grant/Award Number: CDCD-1304-7043-1304-7043 and DI-2018C1-11375)

Abstract

Pediatric patients with pulmonary hypertension (PH) receive imaging studies that use ionizing radiation (radiation) such as computed tomography (CT) and cardiac catheterization to guide clinical care. Radiation exposure is associated with increased cancer risk. It is unknown how much radiation pediatric PH patients receive. The objective of this study is to quantify radiation received from imaging and compute associated lifetime cancer risks for pediatric patients with PH. Electronic health records between 2012 and 2022 were reviewed and radiation dose data were extracted. Organ doses were estimated using Monte Carlo modeling. Cancer risks for each patient were calculated from accumulated exposures using National Cancer Institute tools. Two hundred and forty-nine patients with PH comprised the study cohort; 97% of patients had pulmonary arterial hypertension, PH due to left heart disease, or PH due to chronic lung disease. Mean age at the time of the first imaging study was 2.5 years (standard deviation [SD] = 4.9 years). Patients underwent a mean of 12 studies per patient per year, SD = 32. Most (90%) exams were done in children <5 years of age. Radiation from CT and cardiac catheterization accounted for 88% of the total radiation dose received. Cumulative mean

effective dose was 19 mSv per patient (SD = 30). Radiation dose exposure resulted in a mean increased estimated lifetime cancer risk of 7.6% (90% uncertainty interval 3.0%−14.2%) in females and 2.8% (1.2%−5.3%) in males. Careful consideration for the need of radiation-based imaging studies is warranted, especially in the youngest of children.

KEYWORDS

bronchopulmonary dysplasia, cancer risk, congenital heart disease, pulmonary hypertension

INTRODUCTION

Pediatric pulmonary hypertension (PH) is a chronic condition with high illness severity.[1] Advances in diagnostic and therapeutic management strategies have led to decreasing mortality rates and improved quality of life.[2] Diagnostic and treatment guidelines for pediatric PH recommend the use of cardiac catheterizations, chest computed tomography (CT), nuclear medicine studies, and radiographs to diagnose, risk stratify, and guide management decisions.[3] A significant side effect of using these imaging modalities is increased exposure to low dose ionizing radiation (radiation).

Radiation used in medical imaging is associated with increased cancer risk, cardiovascular disease, immune dysfunction, cataracts, and neurologic disorders.[4–6] The Linear No Threshold Model is a model commonly used by public health regulatory bodies and occupational oversight organizations that proposes no safe threshold dose exists below which there is zero increased cancer risk from radiation. This means that even at low doses, the cancer risk is linearly proportional to the radiation dose.[7] Evidence supporting this model has been contributed by cohort studies that have documented an increased cancer risk associated with exposure to CT, where the observed cancer risks are consistent with what would be predicted based on this model.[8,9]

Radiation dose exposures needs to be quantified to estimate future cancer risk. However, understanding patient exposures from routine medical imaging is challenging. First, machine generated radiation dose metrics and exam characteristics must be merged with patient characteristics to quantify organ doses which are needed to estimate cancer risk; bone marrow doses are associated with leukemia risks, whereas breast doses are associated with breast cancer risk. Details of patient size, position in the scanner, and anatomy are necessary to understand which organs may be directly or indirectly irradiated during each irradiation event. These data are then used to estimate organ doses, which are in turn are used to calculate cancer risk.[8,9]

The number, type, and intensity of irradiation events used during the diagnosis and ongoing treatment of pediatric patients with PH have not been previously reported. Acquiring and analyzing these data is the first step in exploring how radiation use might be optimized for these patients and reduced where appropriate. The goal of this study was to characterize sources of radiation exposure, compute radiation doses received, and calculate the associated excess lifetime cancer risk in pediatric patients with PH given typical exposures at a tertiary care, pediatric PH center of excellence.

METHODS

Patients

Patients with PH were identified using the Pediatric Pulmonary Hypertension Registry at University of California San Francisco (UCSF). Patients were included in this registry if they were evaluated by the pediatric pulmonary hypertension service between 2012 and 2022 and had evidence of PH on cardiac catheterization evaluation. Children always had imaging as part of their evaluation Because of this, length of follow-up was defined as the time between first and last imaging study done at UCSF. To adjust for length of follow-up, total number of imaging studies and associated radiation dose per patient were divided by the number of years each patient was seen at UCSF. Etiology of PH was categorized using the Nice classification system.[10]

Radiation dose data extraction and dose estimation

Patient demographic data, PH diagnosis information, tally of imaging exams that utilize radiation (e.g., radiographs, CT, cardiac catheterization, nuclear medicine studies, and fluoroscopic procedures) were extracted from the electronic health record (EHR).

For CT, the dose metric and dose-length product (DLP) were extracted from CT imaging reports found in the EHR.[11] When DLP was unavailable, doses were imputed using the available technical parameters. For cardiac catheterization, the dose metric, dose area product (DAP) was extracted for each run (individual irradiating event) in the Digital Imaging and Communications In Medicine (DICOM) report created from cardiac catheterization equipment. In addition to DAP, data including beam energy, height, width, and location of the irradiated field, and beam angle were extracted from the DICOM report. Because beam location was not accurately reported in DICOM reports, location was estimated to be directly in the anteroposterior (AP) plane and centered on the chest. As a result, the exam's total DAP was modeled as a single long exposure. Using an organ-centric approach to estimate dose localization has been accepted for cardiac catheterization cases given current capacity of available technology and models used.[12] When DICOM reports were unavailable, DAP was extracted from procedure notes describing the cardiac catheterization case in the EHR. When X-ray beam data were unavailable, beam energy, height, width, and location of the irradiated field, and beam angle measurements were imputed using median of data based on age.

Organ specific radiation doses and effective doses for each exam were estimated using Monte Carlo simulations using a previously described methodology.[13] Organ doses for cardiac catheterization were computed using Monte Carlo simulations through the National Cancer Institute dosimetry system.[14] Doses for nuclear medicine and radiographs were estimated using a detailed dose map generated for an unrelated National Institutes of Health funded study.[15] Radiation doses for fluoroscopy exams (swallow evaluations, upper and lower gastrointestinal [GI] studies, and upper GI studies with small bowel follow through) were estimated using a detailed exam specific estimate created for an unrelated study quantifying cancer risk in children.[16] If patients underwent less common fluoroscopy studies, doses were not included. The UCSF Institutional Review Board (IRB) approved this study and provided a waiver for individual informed consent (IRB Number 21-34589).

Effective radiation doses

Effective dose is defined as the tissue weighted sum of the radiation doses to each of the organs irradiated where the weightings reflect the radiosensitivity of the organ irradiated and future cancer detriment.[17] This dose metric allows radiation doses from different types and anatomic locations of imaging studies to be compared with each other because it reflects the stochastic health risk of radiation for the whole body. Mean effective doses per patient by imaging modality and Nice classification group were described.

Statistical analysis

Summary statistics for patient demographics were reported. Total number of studies done by modality, per patient overall, and per year observed in the cohort by Nice classification group were calculated. Total number of studies by year of birth and total number of studies by age at which the study was done were plotted. Individual data points reflecting total number of studies per patient were not shown for patients in Groups 4 and 5 because of concern for sharing protected health information, given the small number of patients present in each group. Mean effective dose by Nice classification and imaging type are also described.

Cancer risk calculation

The estimated organ doses were averaged within strata defined by sex, age, and study type. These doses were used to compute the mean excess lifetime cancer risk for each stratum using the radiation risk assessment tool version 4.3 developed by the National Cancer Institute.[18] Stratum-specific risks were then summed to estimate excess lifetime cancer risk for the entire cohort given the appropriate weighting of each stratum. This method was equivalent to calculating the risk to each patient given the entirety of their different exposures and then summing these risks across the cohort. The mean excess risk is the excess absolute cancer risk beyond baseline that is attributed to radiation from the medical imaging.[13] Cancer risk is reported as the mean excess increased cancer risk with the 90% uncertainty interval. A sensitivity analysis of excess lifetime cancer risk in patients who were alive at the end of the study period was also performed.

RESULTS

There were 249 patients with PH with mean age of first imaging study of 2.5 years (SD = 4.9 years). Mean length of follow-up was 3.2 years (standard deviation [SD] = 4.0 years). Patients in Groups 1−3 (pulmonary arterial hypertension, PH due to left heart disease and chronic lung disease) comprised 97% of the cohort (Table 1).

TABLE 1 Patient demographic and imaging use by Nice classification of pulmonary hypertension.

	Pulmonary arterial hypertension (group 1)	Pulmonary hypertension due to left heart disease (group 2)	Pulmonary hypertension due to chronic lung disease (group 3)	Chronic thromboembolic pulmonary hypertension (group 4)	Pulmonary hypertension with unclear multifactorial mechanisms (group 5)
Patient demographics					
Number of patients	125	14	103	3	4
Sex (*N* [%] male)	57 (46%)	7 (50%)	53 (51%)	1 (33%)	3 (75%)
Mean age (SD) at first imaging study	3.1 (5.6)	1.5 (3.3)	1.5 (3.4)	10.6 (9.2)	7.0 (7.2)
Mean age (SD) at last follow-up	6.1(6.5)	4.4 (4.2)	4.7 (5.5)	18.2 (2.6)	11.4 (10.2)
Death (*N* [%])	18 (14%)	4 (29%)	21 (20%)	0	0
Imaging studies: mean number of exams performed per patient (SD)					
Cardiac catheterization	1.9 (1.6)	1.8 (1.2)	1.5 (1.1)	1 (0)	1 (0)
CT scan	1.4 (1.6)	2.2 (3.3)	1.4 (3.2)	4 [2]	9.5 [10]
Nuclear medicine studies	0.6 (1.3)	0.4 (0.9)	0.5 (1.3)	1.3 (1.5)	0.25 [5]
Fluoroscopy exams	0.9 (1.3)	1.6 (2.4)	0.9 (1.5)	0	0
Radiographs	58.0 [75]	136.0 (158)	72.0 [81]	11.0 [8]	25.0 [20]
Mean number of imaging studies per year followed (SD)	35.0 [50]	61.0 [71]	40.0 [47]	5.0 [3]	10.0 [7]

Abbreviations: CT, computed tomography; SD, standard deviation.

Stratification of the etiology of PH for Groups 1−3 is shown in Supporting Information: Table 1. Overall, 17% of patients died during the follow-up period, with a mean age at the time of death of 2.8 years (SD = 4.9 years). The mortality was highest in patients with PH due to left heart disease (Group 2) at 29% (4/14).

A total of 18,199 medical imaging exams that used ionizing radiation were performed. On average, patients received a total of 73 imaging studies (SD = 88) with a mean of 12 studies per patient per year (SD = 32) - (Figure 1). Average number of studies per patient per year ranged from 5.0 (SD = 3.0) in patients with chronic thromboembolic with PH (Group 4) to 61.0 (SD = 71.0) in patients with PH due to left heart disease (Group 2) (Table 2). Most imaging exams were performed in younger children: 70% of exams were done on children <1 year of age, and 90% were done on children <5 years of age (Figure 2). Radiographs (chest, abdomen, and combined chest and abdomen) were the most commonly performed imaging exam in all groups (Table 1). CT scans were performed commonly in the youngest children in this cohort. For patients with pulmonary arterial hypertension (Group 1) and PH due to chronic lung disease (Group 3) disease, 50% of CT scans were done in children less than 7 months of age. For children with left sided heart disease (Group 2) 30% of CT scans were done in patients who were less than 7 months of age (Figure 2). Patients in Group 2 received a mean of 1.8 cardiac catheterizations per patient (SD = 1.2), the highest of all groups. Those with pulmonary vein stenosis received the highest mean number of catheterizations per patient (mean = 2.4, SD = 1.9).

Cumulative mean effective dose was 19 mSv per patient (SD = 30) and varied across groups and ranged from 18.6 mSv per patient (SD = 21.2) in patients with pulmonary arterial hypertension (Group 1) to 107.0 mSv per patient (SD = 129.0) in patients with PH with unclear multifactorial mechanisms, Group 5 (Figure 3). Patients with pulmonary vein stenosis had an average cumulative exposure per patient of 27.5 mSv per patient (SD = 32.8). Average total dose per patient per year ranged from 5.6 mSv (SD = 5.6) in patients with PH from chronic lung disease (Group 3) to 21.0 mSv (SD = 23.2) in patients with chronic thromboembolic PH (Table 2).

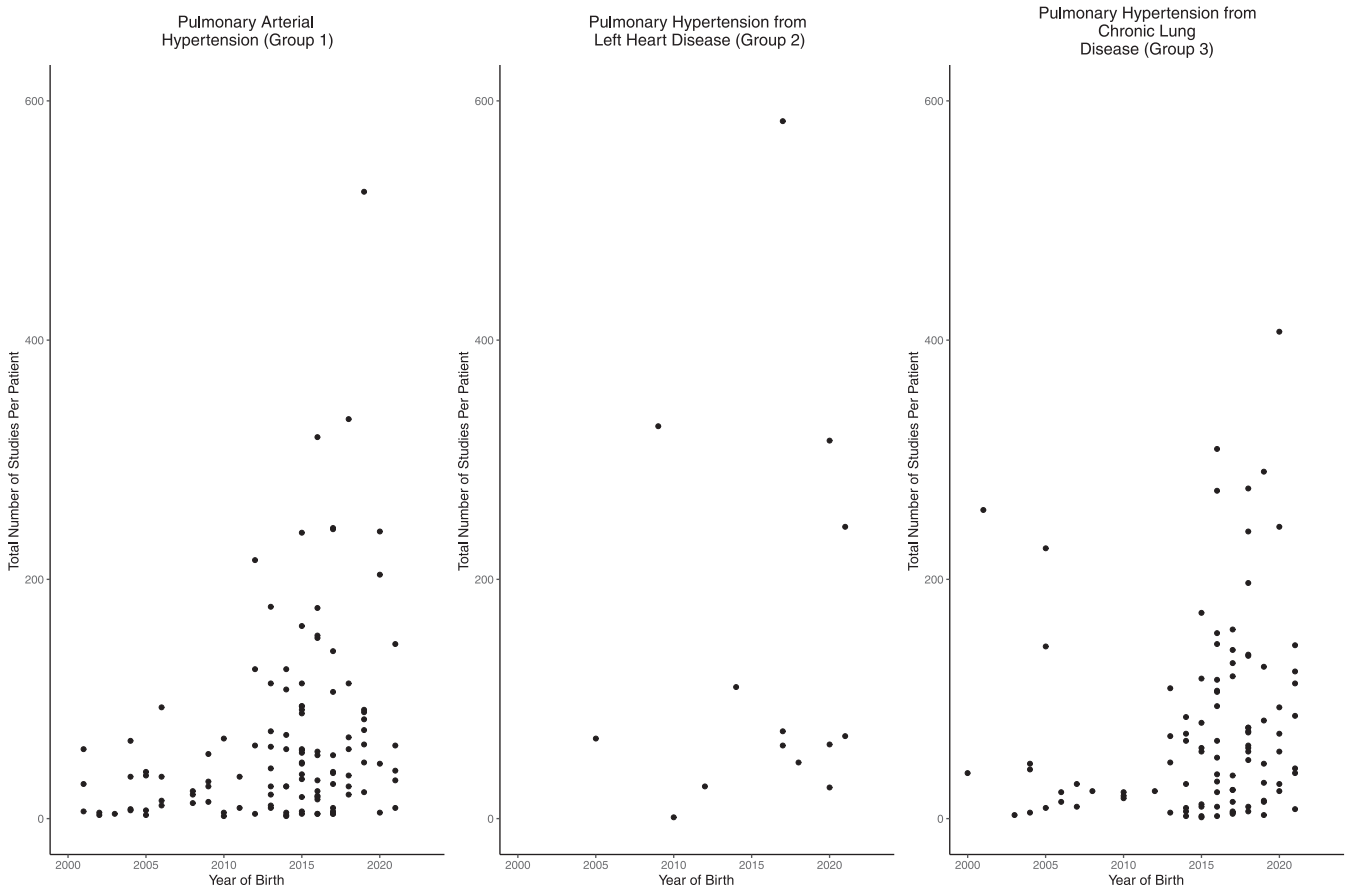

FIGURE 1 Total number of radiation-based imaging studies done per patient by Nice classification. Each dot represents the total number of radiation-based imaging studies one patient received.

TABLE 2 Mean number of imaging studies and cumulative effective dose received per patient per year followed by Nice classification group.

Mean per patient per year	Pulmonary arterial hypertension (group 1)	Pulmonary arterial hypertension due to left heart disease (group 2)	Pulmonary hypertension due to chronic lung disease (group 3)	Chronic thromboembolic with pulmonary hypertension (group 4)	Pulmonary hypertension with unclear multifactorial mechanisms (group 5)
Total					
Count (SD)	35.0 (50.0)	61.0 (71.0)	40.0 (47.0)	5.0 (3.0)	10.0 (7.0)
Dose in mSv (SD)	8.8 (10.4)	10.5 (12.1)	5.6 (5.6)	21 (23.2)	16.1 (15.5)
Cardiac catheterization					
Count (SD)	0.9 (0.7)	0.7 (0.3)	0.8 (0.6)	0.4 (0.5)	0.4 (0.4)
Dose in mSv (SD)	2.5 (4.4)	4.1 (8.1)	1.2 (2.7)	3.6 [6]	0.4 (0.5)
CT					
Count (SD)	1.1 (1.0)	1.2 (0.8)	0.9 (0.6)	1.1 (0.9)	2.1 (1.1)
Dose in mSv (SD)	8.3 (8.0)	8.5 (6.0)	6.3 (4.4)	10.7 (8.8)	20.2 (12.4)
Nuclear medicine					
Count (SD)	0.9 (0.8)	0.6 (0.4)	0.9 (0.6)	1.6 (2.0)	0.1 (NA)
Dose in mSv (SD)	1.8 (2.3)	0.4 (0.4)	0.8 (0.7)	10 (9.7)	2.1 (NA)
Fluoroscopy					
Count (SD)	1.1 (1.2)	1.1 (1.0)	0.9 (0.7)	0	0
Dose in mSv (SD)	0.1 (0.2)	0.2 (0.1)	0.1 (0.2)	0	0
Radiographs					
Count (SD)	34.0 (49.0)	63.0 (71.0)	39.0 (47.0)	2.0 [1]	8.0 (7.0)
Dose in mSv (SD)	0.4 (0.6)	0.8 (0.8)	0.5 (0.5)	0.04 (0.03)	0.1 (0.08)

Abbreviations: CT, computed tomography; SD, standard deviation.

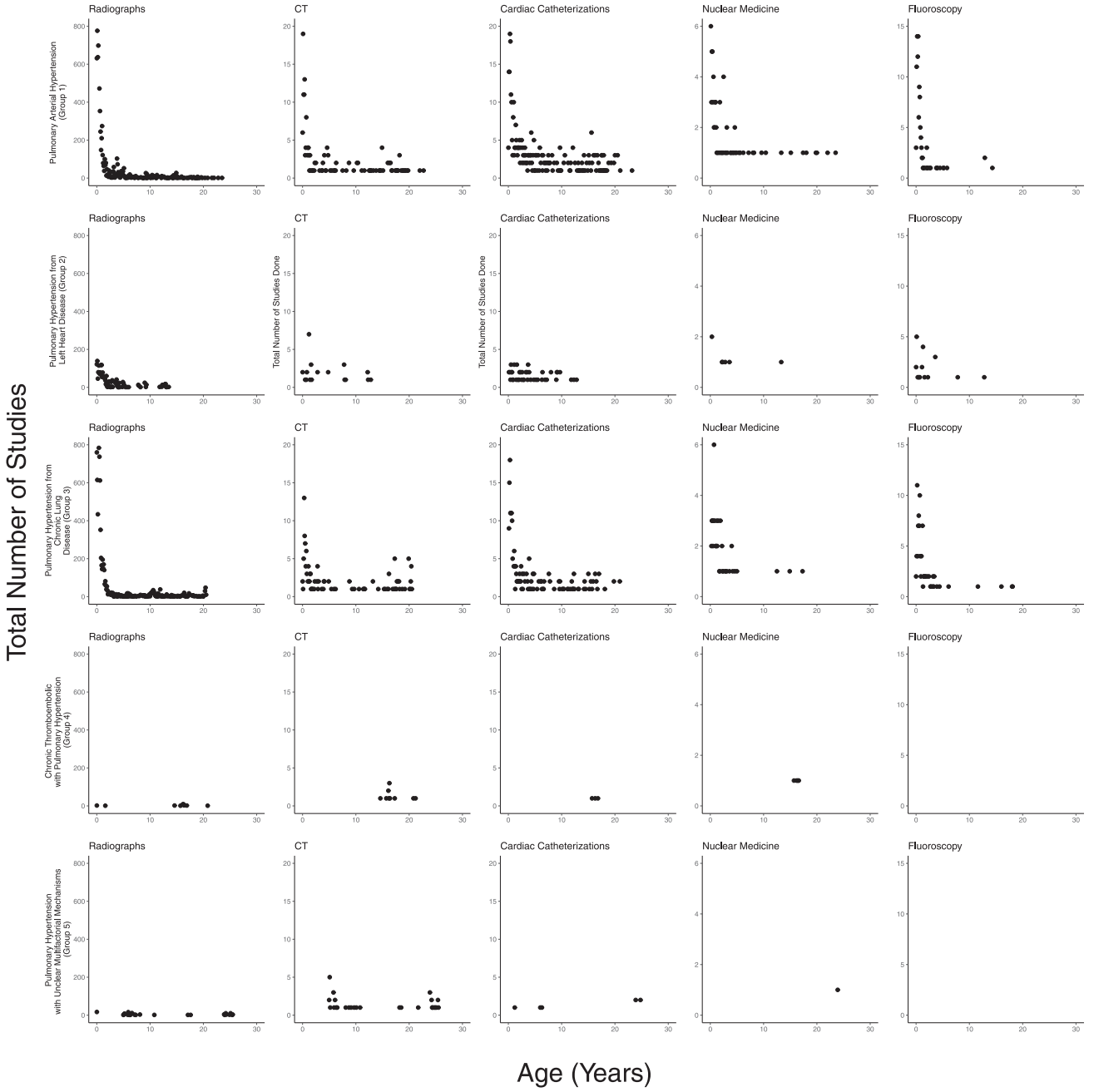

FIGURE 2 Number of studies done at every age by imaging study type and Nice classification. Each dot represents the total number of studies done for all patients in the Nice classification group at a given age.

Overall, 66% of radiation was received from CT, 22% from cardiac catheterization, 7% from nuclear medicine studies, 4.5% from radiography, and 0.5% from fluoroscopy. Doses from CT accounted for most of the radiation exposure across all groups, ranging from 57% of total effective dose in patients with pulmonary arterial hypertension (Group 1) to 93% in patients with PH with unclear multifactorial mechanisms (Group 5) (Figure 3). Corresponding mean effective dose per patient per year from CT ranged from 6.3 mSv/year (SD = 4.4) in patients with PH due to chronic lung disease (Group 3) to 20.2 mSv/year (SD = 12.4) in Group 5 patients (Table 2). Less than 1% of CT scans used an effective dose of <0.1 mSv. Most CT scans (85%) in this cohort of patients occurred in or after 2016.

Cardiac catheterization accounted for the second largest source of radiation ranging from 2.2% of total effective dose in Group 5 patients to 33% in patients with PH due to left sided heart disease (Group 2). The contribution of nuclear medicine studies ranged between for 1.2% of effective dose in Group 2 patients to 22% in patients with chronic thromboembolic PH (Group

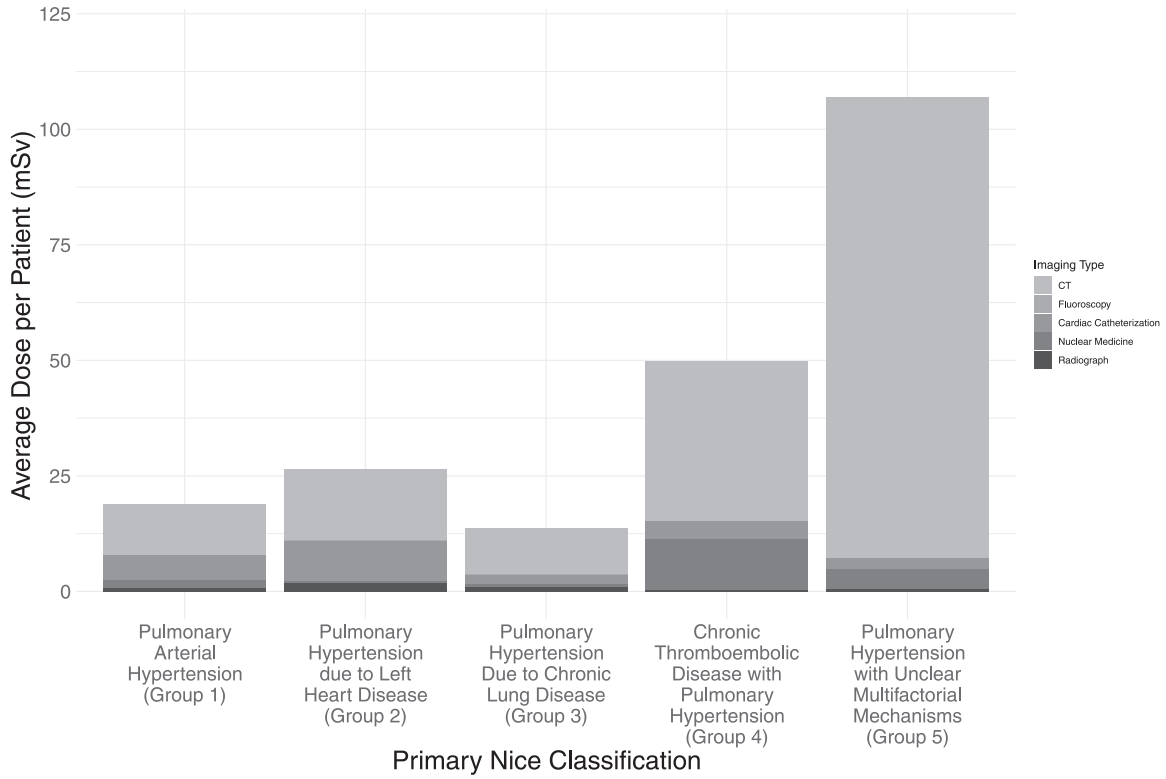

FIGURE 3 Mean effective dose by Nice classification and modality.

4) (Figure 3). Radiographs ranged between 0.5% of effective dose in Group 5 patients to 7% in Group 3 patients with PH due to chronic lung disease (Figure 3). However, for some patients, the effective dose from radiographs was comparable to doses delivered from CT scans; 23%, 43%, and 31% of patients with pulmonary arterial hypertension (Group 1), left side disease (Group 2), and chronic lung disease/hypoxia (Group 3), respectively.

Cancer risks

Overall, patients in this cohort have a mean excess lifetime cancer risk of 7.6% in females (90% uncertainty interval 3.0%−14.2%) and 2.8% in males (1.2%−5.3%) (Table 3). Patients with pulmonary arterial hypertension (Group 1, the largest group) have the highest excess cancer risk; female: 7.9% (3.3%−14.6%) and male: 2.9% (1.3%−5.0%). Patients with PH secondary with unclear multifactorial mechanisms (Group 5) had the lowest excess cancer risk; females: 1.3% (0.5%−2.5%) and males: 0.6% (0.3%−1%) (Table 3). A sensitivity analysis of excess cancer risk in patients who survived to the end of the study showed similar increased cancer risk for the whole population: females; 7.9% (3.0%−14.3%) and males: 2.2% (0.9%−4.0%) (Supporting Information: Table 2).

DISCUSSION

Patients with PH underwent large numbers of imaging procedures that used low dose ionizing radiation. Most of the radiation exposures came from CT (66%) followed by cardiac catheterizations (22%) and most were performed in children less than 5 years; an age when children are most sensitive to developing cancer from such exposures. For a significant minority of patients, radiation from radiographs resulted in radiation exposure comparable to the dose received in CT scans because they received so many chest and abdomen radiographs. The radiation exposure from medical imaging studies resulted in a mean increased absolute lifetime risk that is considered higher than what is trivial: 7.6% in females (90% uncertainty interval 3.0%−14.2%) and 2.8% in males (1.2%−5.3%). Similar increased absolute lifetime risk of cancer was found after excluding patients who died during the study period.

Cancer risks are driven by doses received and the age when doses were received. Older patients presenting with PH received (on average) significantly more effective radiation dose than children who presented with PH in early childhood. However, the risk of cancer in children receiving their CT and cardiac catheterization studies at older ages was significantly less than those receiving these studies in infancy. The greater risks based

TABLE 3 Excess lifetime risk of developing cancer and 90% uncertainty range.

	Total population	Pulmonary arterial hypertension (group 1)	Pulmonary arterial hypertension due to left heart disease (group 2)	Pulmonary hypertension due to chronic lung disease (group 3)	Chronic thromboembolic with pulmonary hypertension (group 4)	Pulmonary hypertension with unclear multifactorial mechanisms (group 5)
Male	2.8% (1.2%–5.3%)	2.9% (1.3%–5.0%)	1.6% (0.6%–2.9%)	1.2% (0.7%–2.4%)	0.3% (0.2%–0.5%)	0.6% (0.3%–1.0%)
Female	7.6% (3.0%–14.2%)	7.9% (3.3%–14.6%)	5.0% (1.8%–10.0%)	5.5% (2.3%–10.0%)	1.6% (0.6%–3.0%)	1.3% (0.5%–2.5%)

on age at exposure is likely due to a combination of biology and probability. The organs of younger children are more radiosensitive organs compared to adolescents and adults because growing children have a larger percentage of actively dividing cells.[19] Additionally, the longer lifespan that younger children have compared to adolescents and adults also contributes to higher cancer risk because young children have more years over which a cancer can develop. The 17% overall mortality rate of this cohort suggests that these children also have a very high illness severity. For some critically ill patients, short-term benefits from radiation-based imaging studies are extremely important to consider as the potential benefits of these imaging modalities may outweigh the potential long-term cancer risks. However, it is also important to consider how to balance optimization of radiation exposure with caring for the critically ill patient because the majority of children in this cohort are surviving.

Current guidelines recommend obtaining CT angiography and cardiac catheterization to evaluate the etiology of PH, assess severity of the disease, and guide treatment decisions.[20] However, magnetic resonance imaging (MRI) and interventional cardiac magnetic resonance catheterizations provide alternatives to CT and fluoroscopy that do not use ionizing radiation.[21,22] In addition to providing diagnostic information, MRI can provide additional hemodynamic information. The downside of MRI is that it usually requires longer scan time, necessitating sedation. Thus, the need for sedation should be balanced against the radiation exposures. Additionally, given the current technical limitations of MR signal in the lung secondary to the low proton density of lung tissue, MRI may not be the optimal imaging modality for evaluation of lung parenchyma in some clinical indications.[23] Use of MRI based imaging procedures should strongly be considered when the same clinical information can be obtained as a CT scan and if there are no metallic implant or other contraindications to an MRI scan.

Study for study, radiography delivers little radiation compared with CT[24] However, 25% of patients received so many radiographs during their treatment course, they received radiation doses from radiographs equivalent to CT scans. Children with prolonged hospital length of stays such as those with bronchopulmonary dysplasia or patients with complex congenital heart disease receive hundreds of radiographs during their admissions.[20] Assessing the clinical indication for every radiograph that is ordered in these patients is important to minimize unnecessary exposures, as some radiographs contribute little to clinical decision making.[25]

Current radiation doses used for CT are at dose ranges that can cause harm to patients, especially for patients receiving multiple CT scans at young ages. While CT doses have decreased from the 1990s, there has been relatively little change in typical radiation dosing used for CT during the study period included in these analyses.[26] Newer technology (such as ultra-low dose CT) are not commonly used in children.[27] Only 1% of CT scans included in our cohort used such ultra-low doses. Environmental radiation exposure contributes very little to the increased cancer risk this cohort of patients receives as doses used for CT scans in children are significantly higher than annual background environmental radiation exposure.[28]

Survivors of congenital heart disease experience significantly higher rates of cancer than the baseline population.[29,30] It is unknown if the observed increased risk of cancer is caused by a genetic susceptibility to cancer (associated with their congenital heart disease), the radiation doses associated with their treatment, an increased susceptibility to radiation, or a combination of factors.[30–32] Given the high illness severity pediatric patients with PH experience, we anticipate that the need to use multiple radiation-based imaging technologies to aid in diagnosis and treatment will be necessary despite advances in technology to use nonionizing radiation-based imaging modalities. Careful attention to reduce the use of radiation delivering modalities, and to reduce the radiation from each exposure is imperative to decrease unnecessary exposure and risk.

Our study has several strengths. UCSF is a pediatric PH center of excellence that follows a large and diverse cohort of patients. We have leveraged use of the EHR and were able to link clinical data with patient specific radiation dose data to quantify risk of cancer in clinically relevant cohorts. We also used state of the art modeling to estimate organ doses and estimated increased cancer risk. Modeled organ doses from CT were similar to previously reported values.[6] Cancer risk estimates were on the same scale as other patients receiving cardiac catheterization for congenital heart disease.[33] The study also has several limitations. Doses for procedures received at other hospitals were not captured, and UCSF exposures before the introduction of the EHR at UCSF (2012) are not reliably available. Importantly, radiation doses overall are likely higher than we report because of missing data, and therefore estimates are conservative. While our data show that children born after 2015 have more radiation-based imaging, this likely reflects improved record keeping in the EHR in recent years. In addition, fluoroscopy units at UCSF were not configured to collect DICOM reports so estimates were used for fluoroscopic exams, and technical parameters were missing for some patients including many with cardiac catheterization and had to be imputed. While novel and state-of-the are models were used to estimate organ dosing for cardiac catheterization, the estimates are imprecise with large error bars in part because we did not know the exact locations of organs irradiated. There were only a handful of patients with Groups 4 and 5 PH in our cohort reflecting the rarity of these diagnoses. However, the small number of patients made generalization about these patient groups difficult. Finally, this study is a single-center study. Differences in diagnostic approaches amongst centers warrant investigation in additional centers.

Children with PH are at high risk for needing on going radiation-based procedures such as CT scans and cardiac catheterizations given the illness severity and chronic nature of the disease. The excess lifetime risk for cancer secondary to medical radiation in this cohort of patients will therefore grow, making the risk of radiation from imaging even greater than we report. To better characterize radiation exposure, improved dosimetry is needed for cardiac catheterization to take into account positioning, and different pediatric anatomies (e.g., heterotaxy or congenital diaphragmatic hernia). In attempt to reduce future cancer risks, careful consideration for the need of radiation-based imaging and modality of imaging is warranted, especially in the youngest of children. Consideration of calculating a cumulative lifetime of imaging and radiation exposure in these children may be warranted to influence their future exposures, but more comprehensive data are needed to do this.

AUTHOR CONTRIBUTIONS

Malini Mahendra conceptualized and designed the study, coordinated data collection, performed data analysis, interpreted data, and drafted the initial manuscript. Philip Chu aided with data collection, data analysis, and interpretation of data and revision of manuscript. Elena K. Amin, Hythem Nawaytou, and James R. Duncan contributed significantly to data interpretation reviewed and revised the manuscript for important intellectual content. Jeffrey R. Fineman and Rebecca Smith-Bindman conceptualized and designed the study, interpreted data analyses, and reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

This work was funded by the Patient-Centered Outcomes Research Institute (CD-1304-7043 and DI-2018C1-11375). Funders had no role in study design, collection, analysis,

interpretation, and reporting of data; or decision to publish. The views in this article are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its Board of Governors or Methodology Committee or other funders. Malini Mahendra, MD, is the guarantor.

CONFLICTS OF INTEREST STATEMENT

Dr. Rebecca Smith-Bindman is a cofounder of Alara Imaging, Inc., a company focused on improving the clinical and operational aspects of health systems, including collecting and reporting radiation dose and image quality associated with computed tomography as part of payor-led quality programs. Alara Imaging played no role in any aspect of the paper and the work does not overlap with Alara's commercial activities. Dr. Rebecca Smith-Bindman has never received funding from Alara Imaging. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The corresponding author should be contacted for inquiries regarding data. Data cannot be empirically released due to the presence of protected health information.

ETHICS STATEMENT

The UCSF Institutional Review Board (IRB) approved this human subjects research study and provided a waiver for individual informed consent (IRB Number 21-34589). This is stated in the methods section.

ORCID

Malini Mahendra http://orcid.org/0000-0002-8082-7977
Philip Chu http://orcid.org/0000-0002-9160-1957
Jeffrey R. Fineman http://orcid.org/0000-0001-9740-405X

REFERENCES

1. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension. Circulation. 2012;125(1):113–22.
2. Hansmann G. Pulmonary hypertension in infants, children, and young adults. JACC. 2017;69(20):2551–69.
3. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL. Pediatric pulmonary hypertension. Circulation. 2015;132(21):2037–99.
4. Belzile-Dugas E, Eisenberg MJ. Radiation-induced cardiovascular disease: review of an underrecognized pathology. J Am Heart Association. 2021;10(18):e021686. https://doi.org/10.1161/JAHA.121.021686
5. National Academies of Sciences, Engineering, and Medicine, Division on Earth and Life Studies, Nuclear and Radiation Studies Board, Committee on Developing a Long-Term Strategy for Low-Dose Radiation Research in the United States. Leveraging Advances in Modern Science to Revitalize Low-Dose Radiation Research in the United States. 2022. National Academies Press.
6. Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, Feigelson HS, Roblin D, Flynn MJ, Vanneman N, Smith-Bindman R. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatrics. 2013;167(8):700–7.
7. de González AB, Kim KP, Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Smith-Bindman R, Yee J, Kuntz KM, van Ballegooijen M, Zauber AG, Berg CD. Radiation-related cancer risks from CT colonography screening: a risk-benefit analysis. Am J Roentgenol. 2011;196(4):816–23.
8. Hauptmann M, Byrnes G, Cardis E, Bernier MO, Blettner M, Dabin J, Engels H, Istad TS, Johansen C, Kaijser M, Kjaerheim K, Journy N, Meulepas JM, Moissonnier M, Ronckers C, Thierry-Chef I, Le Cornet L, Jahnen A, Pokora R, Bosch de Basea M, Figuerola J, Maccia C, Nordenskjold A, Harbron RW, Lee C, Simon SL, Berrington de Gonzalez A, Schüz J, Kesminiene A. Brain cancer after radiation exposure from CT examinations of children and young adults: results from the EPI-CT cohort study. Lancet Oncol. 2023;24(1):45–53.
9. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Craft AW, Parker L, Berrington de González A. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380(9840):499–505.
10. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. JACC. 2013;62(25):D34–41.
11. Alex Padilla EA. Radiation Reporting-SB 1237, California State Assembly; 2010.
12. Fum WKS, Wong JHD, Tan LK. Monte Carlo-based patient internal dosimetry in fluoroscopy-guided interventional procedures: A review. Phys Med. 2021;84:228–40.
13. Geyer AM, O'Reilly S, Lee C, Long DJ, Bolch WE. The UF/NCI family of hybrid computational phantoms representing the current US population of male and female children, adolescents, and adults—application to CT dosimetry. Phys Med Biol. 2014;59(18):5225–42.
14. NCIRF: National Cancer Institute dosimetry system for radiography and fluoroscopy. NCI; 2021.
15. Kwan ML, Miglioretti DL, Bowles EJA, Weinmann S, Greenlee RT, Stout NK, Rahm AK, Alber SA, Pequeno P, Moy LM, Stewart C, Fong C, Jenkins CL, Kohnhorst D, Luce C, Mor JM, Munneke JR, Prado Y, Buth G, Cheng SY, Deosaransingh KA, Francisco M, Lakoma M, Martinez YT,

Theis MK, Marlow EC, Kushi LH, Duncan JR, Bolch WE, Pole JD, Smith-Bindman R. Quantifying cancer risk from exposures to medical imaging in the risk of pediatric and adolescent cancer associated with medical imaging (RIC) study: research methods and cohort profile. Cancer Causes Control. 2022;33(5):711–26.
16. Marshall EL, Rajderkar D, Brown JL, Stepusin EJ, Borrego D, Bolch WE. A scalable database of organ doses for common diagnostic fluoroscopy examinations of children: procedures of current practice at the University of Florida. Phys Med Biol. 2019;64(13):135023.
17. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, Berrington de González A, Miglioretti DL. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med. 2009;169(22):2078–86. https://doi.org/10.1001/archinternmed.2009.427
18. de Gonzalez AB, Iulian Apostoaei A, Veiga LHS, Rajaraman P, Thomas BA, Owen Hoffman F, Gilbert E, Land C. RadRAT: a radiation risk assessment tool for lifetime cancer risk projection. J Radiol Prot. 2012;32(3):205–22.
19. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med. 2007;357(22):2277–84.
20. Cerro MJ, Moledina S, Haworth SG, Ivy D, Dabbagh MA, Banjar H, Diaz G, Heath-Freudenthal A, Galal AN, Humpl T, Kulkarni S, Lopes A, Mocumbi AO, Puri GD, Rossouw B, Harikrishnan S, Saxena A, Udo P, Caicedo L, Tamimi O, Adatia I. Cardiac catheterization in children with pulmonary hypertensive vascular disease: consensus statement from the pulmonary vascular research institute, pediatric and congenital heart disease task forces. Pulm Circ. 2016;6(1):118–25.
21. Rosenzweig EB, Feinstein JA, Humpl T, Ivy DD. Pulmonary arterial hypertension in children: diagnostic work-up and challenges. Prog Pediatr Cardiol. 2009;27(1–2):7–11.
22. Amin EK, Campbell-Washburn A, Ratnayaka K. MRI-guided cardiac catheterization in congenital heart disease: how to get started. Curr Cardiol Rep. 2022;24(4):419–29.
23. Wild JM, Marshall H, Bock M, Schad LR, Jakob PM, Puderbach M, Molinari F, Van Beek EJR, Biederer J. MRI of the lung (1/3): methods. Insights Imag. 2012;3(4):345–53.
24. United States EPA. Radiation sources and doses. 2022. https://www.epa.gov/radiation/radiation-sources-and-doses
25. Hendrikse KA, Gratama JWC, Ten Hove W, Rommes JH, Schultz MJ, Spronk PE. Low value of routine chest radiographs in a mixed medical-surgical ICU. Chest. 2007;132(3):823–8.
26. Thierry-Chef I, Ferro G, Le Cornet L, Dabin J, Istad TS, Jahnen A, Lee C, Maccia C, Malchair F, Olerud HM, Harbron RW, Figuerola J, Hermen J, Moissonnier M, Bernier MO, de Basea MB, Byrnes G, Cardis E, Hauptmann M, Journy N, Kesminiene A, Meulepas JM, Pokora R, Simon SL. Dose estimation for the european epidemiological study on pediatric computed tomography (EPI-CT). Radiat Res. 2021;196(1):74–99.
27. Kroft LJM, van der Velden L, Girón IH, Roelofs JJH, de Roos A, Geleijns J. Added value of ultra–low-dose computed tomography, dose equivalent to chest X-ray radiography, for diagnosing chest pathology. J Thorac Imaging. 2019;34(3):179–86.
28. Center for Disease Control and Prevention. Radiation from space (cosmic radiation) [Internet]. [cited May 22, 2023]. https://www.cdc.gov/nceh/radiation/terrestrial.html.
29. Beauséjour Ladouceur V, Lawler PR, Gurvitz M, Pilote L, Eisenberg MJ, Ionescu-Ittu R, Guo L, Marelli AJ. Exposure to low-dose ionizing radiation from cardiac procedures in patients with congenital heart disease. Circulation. 2016;133(1):12–20.
30. Mandalenakis Z, Karazisi C, Skoglund K, Rosengren A, Lappas G, Eriksson P, Dellborg M. Risk of cancer among children and young adults with congenital heart disease compared with healthy controls. JAMA Network Open. 2019;2(7):e196762.
31. Cohen S, Liu A, Gurvitz M, Guo L, Therrien J, Laprise C, Kaufman JS, Abrahamowicz M, Marelli AJ. Exposure to low-dose ionizing radiation from cardiac procedures and malignancy risk in adults with congenital heart disease. Circulation. 2018;137(13):1334–45.
32. Campolo J, Annoni G, Giaccardi M, Andreassi MG. Congenital heart disease and the risk of cancer: an update on the genetic etiology, radiation exposure damage, and future research strategies. J Cardiovasc Development Dis. 2022;9(8):245.
33. Journy N, Dreuil S, Rage E, De Zordo-Banliat F, Bonnet D, Hascoët S, Malekzadeh-Milani S, Petit J, Laurier D, Bernier MO, Baysson H. Projected future cancer risks in children treated with fluoroscopy-guided cardiac catheterization procedures. Circulation: Cardiovasc Interve. 2018;11(11):e006765. https://doi.org/10.1161/CIRCINTERVENTIONS.118.006765

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mahendra M, Chu P, Amin EK, Nawaytou H, Duncan JR, Fineman JR, Smith-Bindman R. Associated radiation exposure from medical imaging and excess lifetime risk of developing cancer in pediatric patients with pulmonary hypertension. Pulm Circ. 2023;13:e12282. https://doi.org/10.1002/pul2.12282