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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

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Abstract

Purpose The Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) Study is quantifying the association between cumulative radiation exposure from fetal and/or childhood medical imaging and subsequent cancer risk. This manuscript describes the study cohorts and research methods.

Methods The RIC Study is a longitudinal study of children in two retrospective cohorts from 6 U.S. healthcare systems and from Ontario, Canada over the period 1995–2017. The fetal-exposure cohort includes children whose mothers were enrolled in the healthcare system during their entire pregnancy and followed to age 20. The childhood-exposure cohort includes children born into the system and followed while continuously enrolled. Imaging utilization was determined using administrative data. Computed tomography (CT) parameters were collected to estimate individualized patient organ dosimetry. Organ dose libraries for average exposures were constructed for radiography, fluoroscopy, and angiography, while diagnostic radiopharmaceutical biokinetic models were applied to estimate organ doses received in nuclear medicine procedures. Cancers were ascertained from local and state/provincial cancer registry linkages.

Results The fetal-exposure cohort includes 3,474,000 children among whom 6,606 cancers (2394 leukemias) were diagnosed over 37,659,582 person-years; 0.5% had in utero exposure to CT, 4.0% radiography, 0.5% fluoroscopy, 0.04% angiography, 0.2% nuclear medicine. The childhood-exposure cohort includes 3,724,632 children in whom 6,358 cancers (2,372 leukemias) were diagnosed over 36,190,027 person-years; 5.9% were exposed to CT, 61.1% radiography, 6.0% fluoroscopy, 0.4% angiography, 1.5% nuclear medicine.

Conclusion The RIC Study is poised to be the largest study addressing risk of childhood and adolescent cancer associated with ionizing radiation from medical imaging, estimated with individualized patient organ dosimetry.

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Introduction

The use of medical imaging has increased substantially over the last two decades although at a slower pace in recent years [1, 2]. While computed tomography (CT) has improved diagnostic capabilities, it has also increased patient exposure to ionizing radiation, a known carcinogen [3, 4]. Radiography, fluoroscopy, angiography, and nuclear medicine are other imaging modalities that employ ionizing radiation, and

while their rates have declined, use remains high [2]. Exposure to ionizing radiation from medical imaging is especially concerning for children and adolescents whose radiation-induced cancer risks are greater than adults due to rapid cellular turnover and longer life expectancy [5].

Although rare, cancer is the leading cause of death by disease among children in North America. In the United States (U.S.) in 2021, it is estimated that 15,590 children and adolescents age 0 to 19 years will be diagnosed with cancer, and 1,780 will die of their disease [6]. For childhood cancers (age 0–14 years), leukemia is the most common (28%), followed by brain and other nervous system tumors (27%) [6]. For adolescent cancers (age 15–19 years), brain and other nervous system tumors (21%) and lymphoma (19%) are the most common, followed by leukemia (13%) [6]. The causes of most childhood and adolescent cancers are unknown, although genetic mutations, Down syndrome, and fetal and childhood exposure to ionizing radiation are established risk factors, particularly for leukemia [7].

Several epidemiological studies have assessed cancer risk associated with radiation exposure from medical imaging in children, primarily from CT imaging, and each has used a different approach to estimate childhood exposures [4, 8–10]. A large retrospective study conducted in the United Kingdom [4] ($n = 178{,}604$ for leukemia analysis) collected the CT imaging protocols and average machine parameters and used these data to estimate average patient exposures. A study in the Netherlands [10] ($n = 168{,}394$) obtained individual parameters from CT scans to calculate patient-specific doses. Two additional studies from Australia [9] ($n = 10{,}939{,}680$) and South Korea [8] ($n = 12{,}068{,}821$) used administrative claims to assess exposure to CT (and other imaging tests for the South Korean study) without direct quantification of individual organ doses. Overall, these studies found that children and adolescents who underwent CT imaging had a small but statistically significant elevated risk of developing leukemia, brain tumors, and other solid cancers. However, study limitations included lack of detailed information on radiation exposures, no individual dosimetry calculations, and incomplete outcome data. Except for the South Korean study [8], exposures from other imaging modalities were not examined.

In this manuscript, we describe the methods and cohorts for a U.S.-Canadian longitudinal study that we are conducting to determine the association between cumulative exposure to radiation from medical imaging and risk of cancers among children and adolescents followed through age 20 years from six U.S. health care systems and the province of Ontario, Canada. Unlike previous investigations, our study includes detailed individualized organ-specific dosimetry for CT in pregnant women and children, and newly modeled dosimetry to estimate organ absorbed doses associated with other imaging modalities including fluoroscopy,

angiography, radiography, and nuclear medicine. Further, we have detailed clinical data on important confounders such as Down syndrome, as well as clinical indication on a subset of the cohort. Our goal is to enrich the evidence base with one of the largest and most comprehensive studies to date in this very important area of clinical care and public health, focusing on radiation-induced cancer risk from medical imaging in children and adolescents.

Methods

Study sites

The Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) Study is a multi-site, retrospective longitudinal cohort study that collected patient imaging data for CT, fluoroscopy, angiography, radiography, and nuclear medicine from 1995 to 2016 and incidence data for childhood and adolescent cancers from 1996 to 2017 among individuals enrolled in six U.S. healthcare systems and individuals living in Ontario, Canada who were eligible for the Ontario Health Insurance Plan [2, 11]. The U.S. sites were selected to provide a sample of healthcare systems with sociodemographic and geographic diversity, and for whom we could accurately assess the comprehensive use of medical imaging and cancer outcomes. The U.S. systems include Kaiser Permanente (KP) Northern California (KPNC), Hawaii (KPHI), and Northwest (KPNW), each staff model Health Maintenance Organizations. Also included are KP Washington (KPWA), Marshfield Clinic Health System (MC), and Harvard Pilgrim Health Care (HPHC, contributed data from 2000 to 2017 only), which are mixed model organizations where patients received care and/or health insurance from their health systems. Supplemental Table 1 provides details on the U.S. study sites including geographic coverage. Ontario is the largest province by population in Canada, and nearly all residents are eligible to receive care through the Ontario Health Insurance Plan. Together, these sites were pooled to create a large and diverse North American cohort of individuals with comprehensive health insurance coverage of sufficient sample size to conduct overall and sensitivity analyses as guided by key research questions.

This study was approved by institutional review boards at each participating study site. Given this is a minimal risk, medical record review study, participant informed consent was waived.

Data sources

For U.S. sites, complete medical diagnoses and imaging utilization were available through the Virtual Data Warehouse (VDW), a collaborative data model structure developed by

the National Cancer Institute-supported Cancer Research Network and Health Care Systems Research Network [12, 13]. The VDW is a distributed system located behind individual site firewalls and consists of a series of data tables with information on all medical care utilization among enrollees received across delivery settings from clinical and administrative data sources, including the electronic health record (EHR). Imaging received outside the healthcare system is ascertained via claims data. Data for this study were obtained from each site through distributive SAS programs.

For Ontario, complete medical diagnoses and imaging utilization data were ascertained through physician billing records available in the Ontario Health Insurance Plan database, hospital discharge records available in the Discharge Abstract Database, and emergency department visits available in the National Ambulatory Care Reporting System. The Canadian datasets were linked using unique encoded identifiers and analyzed separately before being aggregated with the U.S. data.

Established quality assurance methods including targeted chart review within and across the study sites were used to ensure complete capture of imaging utilization.

Identification of study cohorts

Two study cohorts were developed to examine multiple windows of medical radiation exposure and their possible associations with cancer risk in children and adolescents. These include those exposed only during the fetal period, those exposed only during childhood, and those exposed during both periods. The fetal-exposure cohort includes children for whom fetal exposures could be assessed because their mothers were enrolled in the health care system during gestation, whereas the childhood-exposure cohort includes children born within the healthcare system and with at least 6 months continuous enrollment (Fig. 1).

For the fetal-exposure cohort, eligibility criteria included births with a gestational age between 24 and less than 43 weeks from January 1, 1996 to December 31, 2016 and the mother's enrollment in the health system for the entire pregnancy to ensure complete capture of medical imaging while the child was in utero [11]. The start date of the pregnancy was estimated based on last menstrual period, or if unknown, on the child's birthdate and gestational age at birth. In the U.S., live births were identified from birth registries, linkages to state birth certificate data, and/or International Classification of Diseases, 9th and 10th Revision (ICD-9, ICD-10) and Current Procedural Terminology (CPT) live birth codes. In Ontario, live births were identified by linking newly registered infants in the health plan with their mothers' records of delivery. Children were followed until age 21 years, cancer diagnosis, death, or December 31, 2017, whichever came first (Fig. 2).
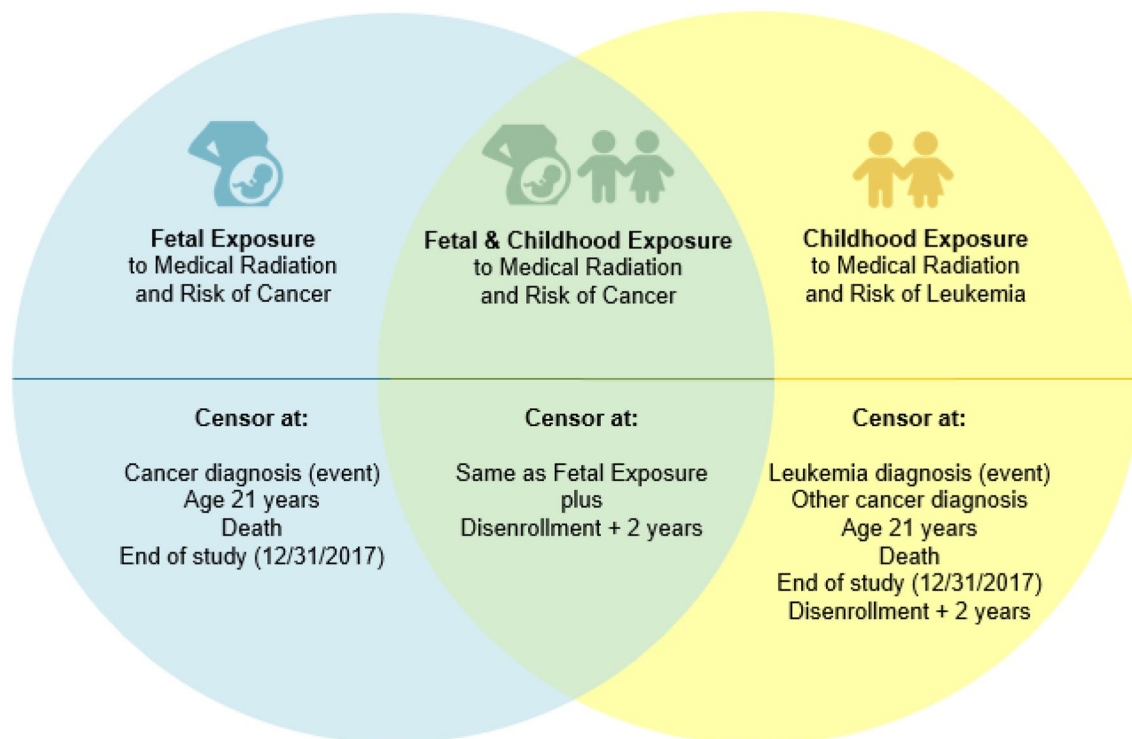

Fig. 1 Study cohorts of the Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) Study, 1996–2016
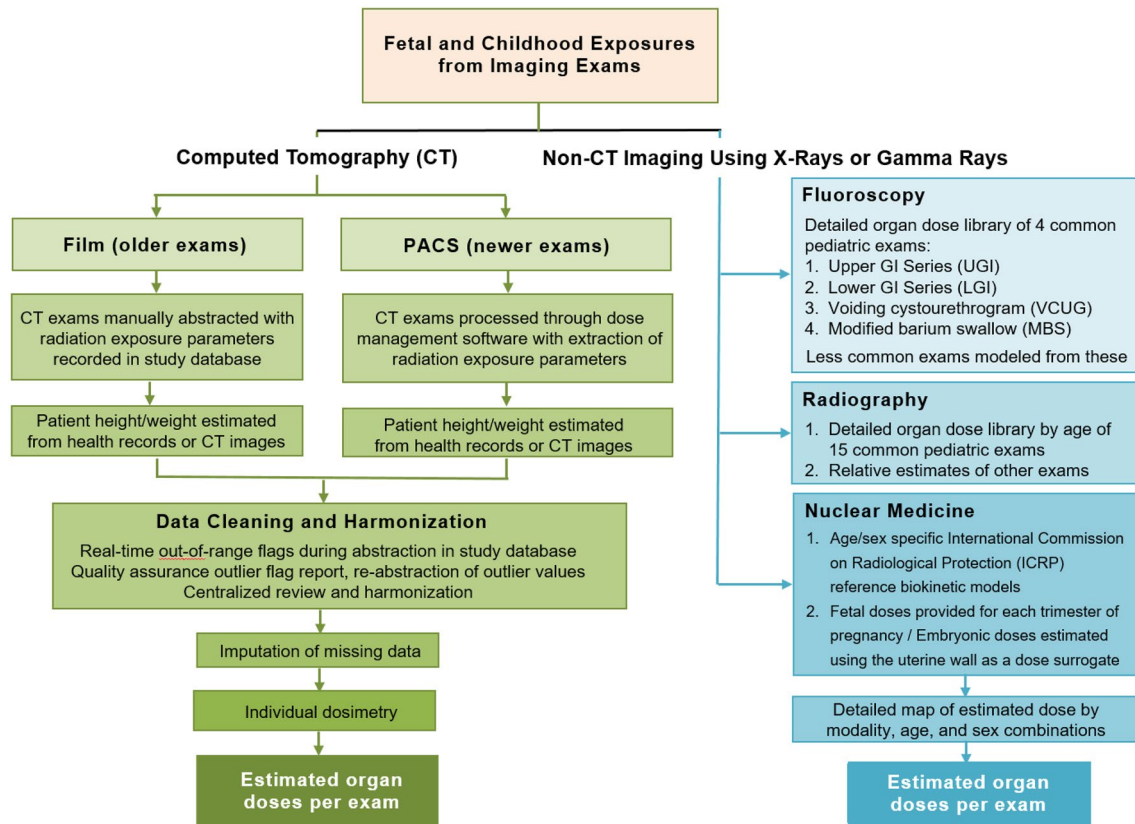
Fig. 2 Radiation dose estimation approaches for imaging exams in the Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) Study, 1996–2016

For the childhood-exposure cohort, eligibility criteria consisted of being born into the health system between January 1, 1996 and April 30, 2016, being continuously enrolled for at least 6 months after birth, being alive and cancer-free at 6 months of life, and having received at least one clinical visit within the health system within first 3 months of life (to exclude children who may be dual-insured). Children were followed until 6 months post-health plan disenrollment (U.S. sites only due to linkage to state cancer registries, see below for details), age 21 years, cancer diagnosis, death, or December 31, 2017, whichever came first. We imposed the 6-month post-disenrollment window because our main risk analyses include a 6-month lag between exposure to medical radiation and potential risk of cancer, and we do not need complete capture of medical imaging during this lag period.

Imaging utilization

Diagnostic imaging in the U.S. cohorts was ascertained using administrative claims based on a combination of Current Procedural Terminology (CPT), International Classification of Disease (ICD-9 and ICD-10), and Healthcare Common Procedure Coding System (HCPCS) billing codes,

including modifiers for the technical, physician, or global components. Exams were included irrespective of the physician specialty billing for the study. Included codes were mapped to an anatomic area and modality to ensure consistency over time [2]. In Ontario, Canadian Classification of Health Intervention codes were used to create a crosswalk with the U.S. codes.

Abstraction and estimation of individualized patient-level radiation absorbed doses for computed tomography (CT)

During the study exposure period (1995–2016), the approach for acquiring, recording, and storing CT images changed, transitioning from film to digital. For CTs in the film era (the exact date varied across participating sites), the radiation exposure parameters were manually abstracted by trained staff at each U.S. site (except HPHC did not participate) and Ontario, following a detailed instruction manual. Manually abstracted data were entered into a custom Microsoft Access database which alerted the abstractor of out of range values in real time so they could be corrected immediately as needed. To ensure consistency

and accuracy of data across all study sites, a quality assurance program developed in SAS was run on each site's abstracted data to flag outliers for re-checking. Then each site resolved all outliers prior to data harmonization. For the digital era, the U.S. sites collected radiation parameters in DICOM format using a radiation dose management software (Radimetrics®, Bayer HealthCare LLC, Whippany, NJ). Consistent with the manually abstracted data, outliers in the DICOM data were flagged and resolved prior to data harmonization. KPWA and Ontario manually abstracted data for CTs regardless of digital availability. Given its large study population, Ontario abstracted a sample of 2,294 CTs from primarily the largest pediatric hospital in the province, The Hospital for Sick Children (40%), along with a convenience sample of CTs done at other small hospitals and clinics in the province. Also, HPHC was unable to directly abstract individual CT dose parameters, thus average doses for a given anatomic area imaged, patient age and size, and exam year will be used. This approach will also be used for exams that sites were unable to abstract for various reasons, e.g., the films were destroyed, or the exam was performed outside the healthcare system. Data were harmonized across study sites and time periods, errors and missingness identified, CTs re-abstracted as needed, and a final exposure dataset created.

The following CT acquisition variables were collected for each irradiating event: anatomic area imaged, use of intravenous contrast, scan length, anterior–posterior and lateral body dimensions on the image slice at the center of the scan range, whether a fixed or modulated tube current was employed, mA (milliampere) or (mAs (milliampere-second) [including min, max, and most frequent if a modulated tube current was employed], kVp (kilovoltage peak), tube rotation time, volume CT dose index (CTDIvol), and dose-length product (DLP).

For each abstracted CT exam from the U.S. sites, the patient's closest height and weight measurement to the date of the imaging study, either before or after, was obtained from the EHR. When either height or weight was not available on the day of the imaging examination, its value was imputed using all height/weight measurements available in the EHR before and following the imaging exam date. For pregnant women, we imputed missing heights using a combination of methods depending on how close available height measurements were to the exam date and the age at exam. This included using a model for pregnant women under 18 years of age, and the closest available height for women older than 18 years. We imputed weight for pregnant women using empirical Bayes estimates from a mixed effects model with a fixed effect for gestational age, modeled as piecewise linear regression with a separate slope for gestational days less than 100 days and more than 100 days, and random slopes and intercepts. When we could not estimate

a height or weight, the 50th percentile was assumed based on the age at exam.

For imaging performed at any age in full-term infants and for pre-term infants, at a gestational age at birth plus current age of 50 weeks and older, biologically implausible height and weight values were identified and removed using publicly available SAS macros [14, 15]. For pre-term infants with imaging performed at a gestational age at birth plus current age of < 50 weeks, we identified implausible values using the same methods as the SAS macros, with LMS (lambda = skew, mu = median, sigma = standard deviation) parameters obtained from Dr. Tanis Fenton [16]. For children under 3 years of age at time of imaging with at least 5 measurements, we imputed height and weight using a modified exponential restricted growth curve $Y = a - be^{-ct}$ where the symbol t stands for age, fitted separately for each child using PROC NLMIXED in SAS. For all other children with at least one measurement, we imputed height and weight using functional principal component analysis [17] fit with the fdapace package in R [18]. When we could not estimate a height or weight, the 50th percentile was assumed based on the age at exam. Height and weight data were not available for abstracted CT exams from Ontario. Instead, effective diameter, calculated from the abstracted anterior–posterior and lateral body dimensions on the exam, was available to estimate patient size.

For childhood exposures, the University of Florida/National Cancer Institute (UF/NCI) hybrid computational phantom library was used for patient-dependent organ dose reconstruction based on detailed CT acquisition parameters and patient size [19]. The UF/NCI phantom library includes an array of 168 whole-body anatomic models of pediatric patients (90 males and 78 females) covering a range of body heights and weights consistent with current U.S. body morphometry data. For fetal exposures, 30 hybrid phantoms of the developing fetus [20] and pregnant mother [21] were created corresponding to five weight percentiles for six gestational ages. Study participants were matched to a given phantom within the UF/NCI library based on height, weight, and/or effective diameter, and for fetal exposures, also gestational age [22, 23]. A separate paper describing the dosimetry work is under development.

Estimation of average organ doses for radiography, fluoroscopy, angiography, and nuclear medicine

Average absorbed doses were estimated for radiography, fluoroscopy, angiography, and nuclear medicine. For radiography, a literature review was performed to determine the scanning parameters for the 16 most common pediatric exam types across film, computed, and digital radiography (4 common exam types in pregnant patients), and comparable fetal and child organ dose libraries are being assembled for these

radiography exams. For child fluoroscopy, we abstracted dose parameters through detailed chart review from KPNC for a sample of patients who underwent the four most common exam types: upper gastrointestinal series, lower gastrointestinal series, voiding cystourethrogram, and modified barium swallow. Using these dose parameters, the UF team developed an organ dose library for these exam types with each exam modeled on 162 individual pediatric phantoms within the UF/NCI library [24]. The remaining fluoroscopy and angiography exams were modeled from these exams. Fetal fluoroscopy doses were extrapolated from the literature for early pregnancy, and three, six, and nine-month gestational ages [25, 26]. For nuclear medicine, child organ dose estimates for 25 exam types were based on age-specific International Commission on Radiological Protection (ICRP) reference biokinetic models for common diagnostic radiopharmaceuticals using estimated administered activities (AA) obtained from review of sample health plan weight-based dosing guidelines which were further constrained by both minimum and maximum values of the AA [27]. Fetal nuclear medicine doses were estimated from the literature [28] and mapped to the same exam types using the uterine wall dose as a fetal organ dose surrogate for very early stages of pregnancy, and whole-body fetal dose estimates at the end of each trimester for later periods of pregnancy.

Cancer outcome ascertainment

For the U.S. sites, we identified cancer diagnoses from January 1, 1996 to December 31, 2017 primarily from the VDW tumor table at each site, which originates from the individual site's linkages with the NCI Surveillance, Epidemiology, and End Results (SEER)-affiliated or local accredited health system cancer registries, with additional linkages to state cancer registries. All International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology and topography codes were extracted. For benign brain tumors, which were not reportable until 2001, we identified cases from ICD-9 and ICD-10 codes from each site's electronic data sources.

Across sites, 40–65% of U.S. patients disenrolled from their health plan prior to the end of the study period. To ensure more complete capture of cancer outcomes in patients who disenrolled from the health plans, we conducted linkages based on geographically close state North American Association of Central Cancer Registries, migration patterns [29], and available resources. KPNC, KPNW, and KPWA did a multi-site linkage with the California, Oregon, and Washington state cancer registries. KPNC conducted an additional linkage with the Texas State Cancer Registry based on migration patterns from California. KPHI conducted a linkage of their disenrolled cohort members with the Hawaii Tumor Registry, MC conducted linkages of all their cohort members with the Wisconsin Cancer Reporting System, and HPHC conducted linkages of all their cohort members with the Massachusetts Cancer Registry.

For Ontario, the Ontario Cancer Registry (OCR) and Pediatric Oncology Group of Ontario Networked Information System (POGONIS) were accessed for cancer diagnoses using the same ICD-O-3 codes. The OCR is a population-based legislatively mandated registry that records all incident malignant tumors within the province. The identification of benign tumors was done through POGONIS only, a population-based active cancer registry that collects data on all tumors that are diagnosed and/or treated at one of five tertiary pediatric care centers in the province.

Childhood leukemia classification

We classified leukemia morphology codes into five categories using a modification of the SEER mapping to International Classification of Childhood Cancer, 3rd Edition (ICCC-3) categories updated for hematopoietic codes based on the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues (2008) [30, 31]. The five categories are acute lymphoid leukemia, acute myeloid leukemia, chronic leukemia and myeloproliferative disease, myelodysplastic syndrome (MDS) and other myeloproliferative disease (not including transient), and unspecified and other specified leukemias. The SEER mapping was modified to create "chronic myeloproliferative disorders and leukemias" a separate category from acute leukemias (Supplemental Table 2). Given that MDS was not reportable in SEER until 2001, we used ICD-9 codes to identify these cases in our electronic data sources followed by confirmation via chart review.

Key confounders

Children with cancer susceptibility syndromes, most importantly Down syndrome, are at increased risk of childhood leukemia [8, 32, 33]. Children with Down syndrome were identified from ICD-9 code 758.0 and ICD-10 diagnosis codes Q90.0, Q90.1, Q90.2, and Q90.9 in the U.S. sites and ICD-10 diagnosis codes only from Ontario [33]. Future analyses will be run excluding children with cancer susceptibility syndromes. Socioeconomic status (SES) [34, 35] and race/ethnicity [36–38] have also been found to be associated with childhood leukemia. Neighborhood-level SES measures including median household income, education, and neighborhood deprivation index [39] were collected in the U.S. sites using the U.S. Census Bureau American Community Survey 5-year estimate data. Addresses for children at the time of birth were geocoded and linked to SES data at the census-tract level. In Ontario, neighborhood income quintile was measured using postal codes at time of birth

for children linked to Canadian census income data. Race/ethnicity data were available in the U.S. sites only for future subgroup analyses. These data were not available in Ontario as residents are not asked to report this information.

Statistical analysis

The current paper reports primarily descriptive characteristics. The cumulative incidence rates for leukemia, other cancer, and death were estimated treating the other two outcomes as competing risks and censoring individuals at the end of follow-up [40]. All analyses were run in SAS 9.4 (SAS Institute, Cary, NC).

Results

Description of the two cohorts

The fetal-exposure cohort includes 3,474,000 children who were born between 24 and 42 weeks of gestation (median 40 weeks, 1st and 3rd quartiles = 38 and 40 in the U.S. sites; median 40 weeks, 1st and 3rd quartiles = 39 and 40 in Ontario) from 3,417,597 unique pregnancies and 2,170,104 women (Table 1). These children were followed through age 20 years or the end of the study period for a median of 11 years (1st and 3rd quartiles = 6 and 16) in the U.S. sites and 10 years (1st and 3rd quartiles = 5 and 16) in Ontario. There were slightly more males (51%) than females (49%). The U.S. children were predominantly white (63%), followed by Asian (24%), Black (9%), Hawaiian/Pacific Islander (3%), and Other (0.7%), with 17% Hispanic ethnicity. A very small proportion of children had Down syndrome (0.1%). Children in the U.S. sites were more likely to live in neighborhoods with higher median household income than the U.S. population, with only 7% having incomes less than the 3rd quartile, whereas the income distribution in Ontario cohort matched the quartiles of the population in that province.

The childhood-exposure cohort includes 3,724,632 children. The median age at end of follow-up was 5 years (1st and 3rd quartiles = 2 and 9) in the U.S. sites and 11 years (1st and 3rd quartiles = 6 and 16) in Ontario (Table 1). The sex, Down syndrome, and racial/ethnic distributions were nearly identical to the fetal cohort.

Childhood cancer and all-cause mortality

In the fetal-exposure cohort, 2,394 childhood leukemia cases, among whom 1,776 were acute lymphoid leukemia and 557 were acute myeloid leukemia, were confirmed over 37,659,582 person-years of follow-up, leading to an estimated cumulative incidence rate through age 20 years of 94/100,000 children in the U.S. and 114/100,000 in Ontario

(Table 2). A total of 4,212 other childhood cancers were confirmed with a cumulative incidence rate of 229/100,000 children in the U.S. sites and 297/100,000 children Ontario. There were 10,950 all-cause deaths with a cumulative incidence rate of 429/100,000 children in the U.S. and 509/100,000 children in Ontario.

In the childhood-exposure cohort, 2,372 childhood leukemia cases, among whom 1,810 were acute lymphoid leukemia and 521 were acute myeloid leukemia, were confirmed over 36,190,027 person-years of follow-up (Table 2). The cumulative incidence rate through age 20 years was 114/100,000 children in the U.S. and 111/100,000 in Ontario. A total of 3,986 other childhood cancers were confirmed with a cumulative incidence of 256/100,000 children in the U.S. and 282/100,000 in Ontario. There were 4,915 all-cause deaths with a cumulative incidence rate of 344/100,000 children in the U.S. and 324/100,000 in Ontario.

Utilization of CT imaging exams

For the fetal-exposure cohort, 0.5% of children's mothers had at least one CT exam during pregnancy, which was more common during the first (33.8%) and third trimesters (31.4%) (Table 3). The majority were CTs of the head and/or neck (48.2%) followed by chest (25.5%) and abdomen (19.4%). 4.1% of exams imaged multiple areas.

For the childhood-exposure cohort, 5.9% had at least one CT exam (Table 3). About 19.4% of CT exams occurred in children less than one year of age, 44.0% in children age 1–9 years, and 36.7% in children age 10–20 years. The majority of CTs were head and/or neck (70.9%) followed by abdomen (13.0%). 4.7% of exams imaged multiple areas.

Utilization of non-CT imaging exams

In the fetal-exposure cohort, 4.0% of mothers had at least one radiography exam, 0.4% had at least one fluoroscopy exam, 0.04% had at least one angiography exam, and 0.2% had at least one nuclear medicine exam (Table 4). In the childhood-exposure cohort, 61.1% had at least one radiography exam, 6.0% had at least one fluoroscopy exam, 0.4% had at least one angiography exam, and 1.5% had at least one nuclear medicine exam (Table 4).

Results for the six individual U.S. sites can be found in Supplemental Tables 3–6.

Discussion

Diagnostic imaging is an important medical advancement that contributes to accurate disease diagnosis and improved treatment. However, potential harmful health

Table 1 Characteristics of fetal-exposure cohort and childhood-exposure cohort from 1996 to 2016

Fetal-exposure cohort	United States		Ontario, Canada		Total	
	n	Col %	*n*	Col %	*n*	Col %
Total children, *n*	881,205		2,592,795		3,474,000	
Total pregnancies, *n*	867,279		2,550,318		3,417,597	
Total singleton pregnancies, *n*	852,103		2,508,849		3,360,952	
Total multiple pregnancies, *n*	15,176		41,469		56,645	
Total unique pregnant women, *n*	636,904		1,533,200		2,170,104	
Gestational age at birth (median, Quartile 1–Quartile 3)	40 (38–40)		40 (39–40)			
Gestational age at birth, *n* (%)						
24–36 weeks (pre-term)	59,359	6.7	144,247	5.6	203,606	5.9
37–40 weeks (full-term)	731,823	83.0	2,212,713	85.3	2,944,536	84.8
41–43 weeks (late-term)	90,023	10.4	235,835	9.1	325,858	9.4
Child's age at end of follow-up (median, Quartile 1-Quartile 3)	11 (6–16)		10 (5–16)			
Child's age at end of follow-up, *n* (%)						
0–5 years	186,583	21.2	709,718	27.4	896,301	25.8
6–10 years	223,687	25.4	637,189	24.6	860,876	24.8
11–15 years	221,870	25.2	590,100	22.8	811,970	23.4
16–20 years	249,065	28.3	655,788	25.3	904,853	26.0
Child's calendar year of birth, *n* (%)						
1996–2000	167,510	19.0	584,528	22.5	752,038	21.6
2001–2005	214,598	24.4	610,178	23.5	824,776	23.7
2006–2010	224,593	25.5	638,610	24.6	863,203	24.8
2011–2016	274,504	31.2	759,479	29.3	1,033,983	29.8
Child sex, *n* (%)						
Male	451,396	51.2	1,330,593	51.3	1,781,989	51.3
Female	429,765	48.8	1,262,202	48.7	1,691,967	48.7
Unknown	44	0.0	0	0.0	44	0.0
Child race (U.S. only), *n* (%)						
White	387,681	44.0	–	–	387,681	44.0
Asian	149,187	16.9	–	–	149,187	16.9
Black	55,807	6.3	–	–	55,807	6.3
Hawaiian/Pacific Islander	15,555	1.8	–	–	15,555	1.8
Native American	4,312	0.5	–	–	4,312	0.5
Other/mixed	1,736	0.2	–	–	1,736	0.2
Unknown or not reported	266,927	30.3	–	–	266,927	30.3
Child ethnicity (U.S. only), *n* (%)						
Not Hispanic or Latino	627,060	71.2	–	–	627,060	–
Hispanic or Latino	153,850	17.5	–	–	153,850	–
Unknown or not reported	100,295	11.4	–	–	100,295	–
Down syndrome, *n* (%)	1,068	0.1	2,750	0.1	3,818	0.1
Geocoded median household Income, *n* (%)						
Q1 (lowest income)	2,240	0.3	567,077	21.9		
Q2	58,510	6.6	517,035	19.9		
Q3	273,565	31.0	526,414	20.3		
Q4	389,417	44.2	536,126	20.7		
Q5 (highest income)	119,894	13.6	433,579	16.7		
Missing	37,579	4.3	12,564	0.5		

Table 1 (continued)

Childhood-exposure cohort	United States		Ontario, Canada		Total	
	n	Col %	*n*	Col %	*n*	Col %
Total children, *n*	931,120		2,793,512		3,724,632	
Child's age at end of follow-up (median, Quartile 1-Quartile 3)[a]	5 (2–9)		11 (6–16)			
Child's age at end of follow-up, n (%)						
0–5 years	479,026	51.4	689,214	24.7	1,168,240	31.4
6–10 years	239,349	25.7	704,793	25.2	944,142	25.3
11–15 years	125,664	13.5	647,970	23.2	773,634	20.8
16–20 years	87,081	9.4	751,535	26.9	838,616	22.5
Child's calendar year of birth, n (%)						
1996–2000	192,169	20.6	672,300	24.1	864,469	23.2
2001–2005	235,641	25.3	676,021	24.2	911,662	24.5
2006–2010	246,005	26.4	698,931	25.0	944,936	25.4
2011–2016	257,305	27.6	746,260	26.7	1,003,565	26.9
Child sex, n (%)						
Male	477,699	51.3	1,432,892	51.3	1,910,591	51.3
Female	453,421	48.7	1,360,620	48.7	1,814,041	48.7
Child race (U.S. only), *n (%)*						
White	409,830	44.0	–	–	409,830	44.0
Asian	157,359	16.9	–	–	157,359	16.9
Black	53,366	5.7	–	–	53,366	5.7
Hawaiian/Pacific Islander	18,020	1.9	–	–	18,020	1.9
Native American	4,646	0.5	–	–	4,646	0.5
Other/mixed	2,382	0.3	–	–	2,382	0.3
Unknown or not reported	285,517	30.7	–	–	285,517	30.7
Child ethnicity (U.S. only), *n (%)*						
Not Hispanic or Latino	633,822	68.1	–	–	633,822	–
Hispanic or Latino	154,383	16.6	–	–	154,383	–
Unknown or not reported	142,915	15.3	–	–	142,915	–
Down syndrome, *n (%)*	1,209	0.1	2,935	0.1	4,144	0.1
Geocoded median household Income, n (%)						
Q1	2,242	0.2	633,317	22.7		
Q2	58,358	6.3	559,654	20.0		
Q3	274,831	29.5	559,670	20.0		
Q4	386,740	41.5	565,210	20.2		
Q5	118,648	12.7	459,046	16.4		
Missing	90,301	9.7	16,615	0.6		

[a]Childhood-Exposure cohort had fewer years of follow-up as continuous enrollment was required in this cohort, whereas it was not required in the Fetal-Exposure cohort

effects of medical imaging must also be understood so they can be weighed against diagnostic benefit. We have previously reported that rates of imaging with ionizing radiation remains high in pregnant women and children [2, 11]. While awareness exists in the U.S. and Canada that medical imaging must be justified and imaging exams in children should be reduced, our previous studies suggest that rates of imaging in children continues to be elevated compared to earlier periods, and use of relatively high-dose exams such as CT continues [1, 2, 41]. The risk of cancer from exposure to routine medical imaging is not fully understood. The RIC Study is using extensive data resources spanning 1995–2017 on exposure to medical imaging in the U.S. and Ontario, Canada, complete capture of member health care utilization, follow-up for cancer diagnosis of members who disenrolled from the U.S. health systems, and detailed demographic and cancer diagnosis information to examine these critical clinical

Table 2 Follow-up for cancer incidence and all-cause mortality in the children of the fetal-exposure cohort and childhood-exposure cohort

Fetal-exposure cohort[a]	United States	Row	Ontario, Canada	Row	Total
Total children, n	881,205	25.4	2,592,795	74.6	3,474,000
Total no. of person-years of follow-up	9,528,259	25.3	28,131,322	74.7	37,659,582
Childhood leukemia cases, n (%)[b]	534	20.3	1,860	70.6	2,394
Cumulative incidence (95% CI) of childhood leukemia at age 20, n/100,000 children	94.0 (84.1, 104.9)		113.9 (107.5, 120.7)		
Childhood acute lymphoid leukemia cases, n (%)	390	22.0	1,386	78.0	1,776
Cumulative incidence (95% CI) of childhood acute lymphoid leukemia at age 20, n/100,000 children	64.3 (57.4, 71.9)		80.3 (75.4, 85.5)		
Childhood acute myeloid leukemia cases, n (%)	83	14.9	474	85.1	557
Cumulative incidence (95% CI) of childhood acute myeloid leukemia at age 20, n/100,000 children	15.9 (12.0, 20.9)		33.6 (29.6, 38.1)		
Other childhood cancers, n (%)	929	19.0	3,283	67.0	4,212
Cumulative incidence (95% CI) of other cancers at age 20, n/100,000 children	228.8 (207.1, 252.3)		297.0 (282.7, 311.9)		
Deaths, n (%)	2,211	20.2	8,739	79.7	10,950
Cumulative incidence (95% CI) of deaths at age 20, n/100,000 children	429.0 (401.3, 458.3)		509.0 (492.6, 525.8)		
Childhood-exposure cohort[a]	United States	Row	Ontario, Canada	Row	Total
Total children, n	931,120	25.0	2,793,512	75.0	3,724,632
Total no. of person-years of follow-up	6,092,540	16.8	30,097,487	83.2	36,190,027
Childhood leukemia cases, n (%)[b]	404	17.0	1,968	83.0	2,372
Cumulative incidence (95% CI) of childhood leukemia at age 20, n/100,000 children	114.2 (91.9, 141.1)		110.9 (104.8, 117.4)		
Childhood acute lymphoid leukemia cases, n (%)	304	16.8	1,506	83.2	1,810
Cumulative incidence (95% CI) of childhood acute lymphoid leukemia at age 20, n/100,000 children	75.9 (64.6, 88.9)		78.8 (74.2, 83.7)		
Childhood acute myeloid leukemia cases, n (%)	59	11.3	462	88.7	521
Cumulative incidence (95% CI) of childhood acute myeloid leukemia at age 20, n/100,000 children	14.7 (9.6, 22.2)		32.2 (28.3, 36.5)		
Other childhood cancers, n (%)	622	15.6	3,364	84.1	3,986
Cumulative incidence (95% CI) of other cancers at age 20, n/100,000 children	256.3 (218.5, 299.4)		282.1 (269.0, 295.8)		
Deaths, n (%)	793	16.1	4,122	83.9	4,915
Cumulative incidence (95% CI) of deaths at age 20, n/100,000 children	343.5 (280.6, 417.5)		323.6 (308.9, 338.9)		

[a]Fetal-exposure cohort had 0 months of lag time for cancer follow-up. Childhood-exposure cohort had 6 months of lag time for cancer follow-up

[b]Childhood leukemia cases included acute lymphoid leukemias, acute myeloid leukemias, chronic myeloproliferative disorders and leukemias, myelodysplastic syndrome and other myeloproliferative disorders, and unspecified and other specified leukemias (Supplemental Table 2)

care and public health issues in a vulnerable population. No such study has been conducted in North America to date.

Significance of the RIC Study

Ionizing radiation is one of the most comprehensively studied carcinogens with extensive evidence linking it to cancer risk. However, many past studies have focused on specific human populations, such as Japanese atomic bomb survivors [42], those exposed to radon and environmental accidents [43], and patients receiving cancer radiation treatment [44, 45]. These specialized populations differ from the general North American population undergoing routine medical imaging.

Several large retrospective studies on medical radiation exposure from CT imaging and childhood and adolescent cancer risk have been conducted. The UK-NCI Study, Dutch Pediatric CT Study, and Australia study reported increased risks of brain cancer [10] or both brain cancer and leukemia

Table 3 Distribution of CT exams in the fetal-exposure cohort and childhood-exposure cohort from 1996 to 2016

Fetal-exposure cohort	United States		Ontario, Canada		Total	
	n	Col %	*n*	Col %	*n*	Col %
Total children	881,205	100.0	2,592,795	100.0	3,474,001	100.0
Number of CT exams during mother's pregnancy per child						
0	874,579	99.2	2,580,910	99.5	3,455,489	99.5
1	6,329	0.7	10,938	0.4	17,267	0.5
2	252	<0.05	853	<0.05	1,105	<0.05
3+	45	<0.05	94	<0.05	139	<0.05
Fetal age at each exam						
<14 weeks (first trimester)	3,269	36.8	4,116	31.7	7,385	33.8
14–<27 weeks (second trimester)	2,647	29.8	2,440	18.8	5,087	23.3
27+weeks (third trimester)	2,964	33.4	3,910	30.1	6,874	31.4
Unknown trimester	0	<0.05	2,516	19.4	2,516	11.5
Total	8,880	100.0	12,982	100.0	21,862	100.0
Exams by anatomic region						
Abdomen	1,508	21.6	2,375	18.3	3,883	19.4
Chest	2,115	30.2	2,979	22.9	5,094	25.5
Head and/or neck	2,984	42.7	6,633	51.1	9,617	48.2
Neck and/or C-Spine	137	2.0	129	1.0	266	1.3
Other, NOS	76	1.1	217	1.7	293	1.5
Multiple areas	172	2.5	649	5.0	821	4.1
Total	6,992	100.0	12,982	100.0	19,974	100.0
Childhood-exposure cohort	United States		Ontario, Canada		Total	
	n	Col %	*n*	Col %	*n*	Col %
Total children, *n*	931,120	100.0	2,793,512	100.0	3,724,633	100.0
Number of CT exams per child						
0	876,047	94.1	2,628,149	94.1	3,504,196	94.1
1	45,057	4.8	126,140	4.5	171,197	4.6
2	6,723	0.7	26,300	0.9	33,023	0.9
3–10	3,142	0.3	12,275	0.4	15,417	0.4
>10	151	<0.05	648	<0.05	799	<0.05
Total	931,120	100.0	2,793,512	100.0	3,724,632	100.0
Age at each exam						
<1 year	15,276	27.7	41,584	17.4	56,860	19.4
1–4 years	17,942	32.6	53,028	22.2	70,970	24.2
5–9 years	11,189	20.3	46,965	19.7	58,154	19.8
10–<21 years	10,666	19.4	97,077	40.7	107,743	36.7
Total	55,073	100.0	238,654	100.0	293,727	100.0
Exams by anatomic region						
Abdomen	11,392	15.5	29,156	12.2	40,548	13.0
Chest	2,218	3.0	10,827	4.5	13,045	4.2
Head and/or neck	53,408	72.5	168,063	70.4	221,471	70.9
Neck and/or C-Spine	2,710	3.7	3,794	1.6	6,504	2.1
Other, NOS	1,663	2.3	14,236	6.0	15,899	5.1
Multiple areas	2,247	3.1	12,578	5.3	14,825	4.7
Total	73,638	100.0	238,654	100.0	312,292	100.0

Table 4 Distribution of non-CT imaging exams in the fetal-exposure cohort and childhood-exposure cohort from 1996 to 2016

Fetal-exposure cohort	United States		Ontario, Canada		Total	
	n	Col %	*N*	Col %	*n*	Col %
Total children	881,205	100.0	2,592,795	100.0	3,474,001	100.0
Radiography						
Number of exams during mother's pregnancy per child						
0	840,329	95.4	2,493,338	96.2	3,333,667	96.0
1	36,267	4.1	87,109	3.4	123,376	3.6
2	3,456	0.4	9,385	0.4	12,841	0.4
3–10	1,132	0.1	2,936	0.1	4,068	0.1
> 10	21	< 0.05	27	< 0.05	48	< 0.05
Fluoroscopy						
Number of exams per child						
0	879,143	99.8	2,579,341	99.5	3,458,484	99.6
1	1,848	0.2	12,607	0.5	14,455	0.4
2	149	< 0.05	664	< 0.05	813	< 0.05
3–10	65	< 0.05	180	< 0.05	245	< 0.05
> 10	0	0.0	3	< 0.05	3	< 0.05
Angiography						
Number of exams per child						
0	880,843	100.0	2,591,757	100.0	3,472,600	100.0
1	314	< 0.05	967	< 0.05	1,281	< 0.05
2	29	< 0.05	53	< 0.05	82	< 0.05
3–10	19	< 0.05	18	< 0.05	37	< 0.05
> 10	0	0.0	0	< 0.05	0	< 0.05
Nuclear medicine						
Number of exams per child						
0	879,874	99.8	2,586,475	99.8	3,466,413	99.8
1	1,284	0.1	6,023	0.2	7,307	0.2
2	45	< 0.05	289	< 0.05	334	< 0.05
3–10	2	< 0.05	8	< 0.05	10	< 0.05
> 10	0	0.0	0	0.0	0	0.0
Childhood-exposure cohort	**United States**		**Ontario, Canada**		**Total**	
	n	Col %	*n*	Col %	*n*	Col %
Total children, *n*	931,120	100.0	2,793,512	100.0	3,724,642	100.0
Radiography						
Number of exams per child						
0	455,469	48.9	993,715	35.6	1,449,130	38.9
1	190,897	20.5	547,692	19.6	738,565	19.8
2	97,829	10.5	355,402	12.7	453,224	12.2
3–10	166,992	17.9	795,178	28.5	962,221	25.8
> 10	19,933	2.1	101,525	3.6	121,502	3.3
Fluoroscopy						
Number of exams per child						
0	889,364	95.5	2,610,327	93.4	3,499,691	94.0
1	33,106	3.6	146,750	5.3	179,856	4.8
2	5,510	0.6	23,017	0.8	28,527	0.8
3–10	3,044	0.3	12,434	0.4	15,478	0.4
> 10	96	< 0.05	984	< 0.05	1,080	< 0.05

Table 4 (continued)

Childhood-exposure cohort	United States		Ontario, Canada		Total	
	n	Col %	n	Col %	n	Col %
Angiography						
Number of exams per child						
0	928,972	99.8	2,782,498	99.6	3,711,470	99.6
1	1,557	0.2	7,496	0.3	9,053	0.2
2	279	< 0.05	1,539	0.1	1,818	< 0.05
3–10	277	< 0.05	1,856	0.1	2,133	0.1
> 10	35	< 0.05	123	< 0.05	158	< 0.05
Nuclear medicine						
Number of exams per child						
0	921,543	99.0	2,748,058	98.4	3,669,581	98.5
1	7,372	0.8	36,278	1.3	43,668	1.2
2	1,378	0.1	5,829	0.2	7,218	0.2
3–10	821	0.1	3,297	0.1	4,119	0.1
> 10	6	< 0.05	50	< 0.05	56	< 0.05

[4, 9] with CT exposure. Two studies in South Korea [8] and Taiwan [46] reported elevated risks of myeloid leukemias, myelodysplasia, breast cancer, and thyroid cancer (South Korea), and benign brain tumors (Taiwan). The EPI-CT consortium is a retrospective cohort from 1977 to 2015 of 948,174 children and young adults who had underwent a CT exam at least once before the age of 22 years with no prior history of cancer and includes patients from nine countries including the UK-NCI Study and Dutch Pediatric CT Study [47]. When comparing characteristics of our RIC childhood-exposure cohort to the EPI-CT consortium, among 948,174 children who had at least one CT exam in EPI-CT, 714,860 (75.4%) had only one exam in EPI-CT vs. 220,436 (77.7%) in RIC, yet children tended to be younger at the time of imaging in RIC (63.4% age 0–9 years) vs. EPI-CT (46.5% age 0–9 years). For both cohorts, the most common scanned anatomical region was head and/or neck (70.9% RIC vs. 65.9% EPI-CT). Direct comparison of childhood cancer incidence between the two cohorts will be interesting once the EPI-CT results are published.

A key limitation to most of these previous studies is radiation dose exposures were based on estimates such as the number of CT scans [8, 46, 48], using average organ dose libraries [4, 9], and protocol-based (e.g., hospital average) doses [49]. In contrast, a significant strength of our forthcoming RIC Study is the collection of individual radiation technique parameters from CT exams, enabling the calculation of individual patient-specific organ doses using modern dose estimation methods. We will also be able to compare previous methods of dose estimation to more precise methods, to help assess the potential for bias in previous reports.

Strengths and limitations of the RIC Study

Our study is one of the largest and most contemporary to examine risk of childhood cancers associated with medical radiation from in utero and childhood exposure over a 22-year span comparing an exposed group to an unexposed group. To ensure the most complete capture of medical imaging exposure possible, the fetal-exposure cohort required pregnant women to be health plan members during their entire pregnancy, and the childhood-exposure cohort required children to be born into the health plan with censoring after disenrollment. CT imaging parameters were collected for a large proportion of exams and will be used to calculate patient-specific absorbed radiation organ doses for those exams. We were unable to collect CT parameters for all exams, especially in Ontario in which data on a sample of 2,300 exams were obtained to represent over 300,000 exams. However, we will use patient-specific absorbed doses to estimate doses for other exams based on several covariates including exam year. Unlike prior studies, our study will include a comprehensive assessment of all imaging modalities that use ionizing radiation, with data obtained from health plan electronic data sources; however, mean doses are being applied for all modalities aside from CT. Finally, we acknowledge that examining the association of medical radiation exposure with risk of solid cancers in the U.S. sites is a limitation given a large proportion of children left the U.S. health plans at a median age of five years.

One major criticism for these types of studies has been the potential for confounding by indication [50, 51]. While we were unable to collect clinical indication for all exams, we were able to obtain this information for a proportion of the exams to assess confounding by indication. In preliminary

analyses, the most common indications appear to be related to craniosynostosis and trauma.

Our study provides a unique representation of the U.S. population insured by similar integrated health care systems, and a complete, population-based view of all residents of Ontario, Canada. Imaging exams performed external to the U.S. health systems could potentially introduce measurement error; however, outside claims for imaging services are routinely included in each U.S. health plan's EHR and are thus trackable as part of the patient's clinical care. In Ontario, given that health care is organized as a single-payer system, exams outside the system would be exceedingly rare. Finally, we did not have individual-level income data and relied on census-based measures.

Future plans of the RIC Study

The primary RIC Study analyses on the association between radiation dose and risk of childhood cancers are forthcoming. Looking toward the future, we have established a rich resource of medical imaging data, radiation dose assessment methods, key covariates, childhood and adolescent cancer outcomes, and large patient cohorts on which to build ancillary research projects at relatively modest cost. Finally, our study is poised to bring further awareness surrounding the topic of medical imaging, its potential overuse or misuse, and its effects on population health.

Declarations

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