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Medical Imaging and Pediatric and Adolescent Hematologic Malignancy Risk

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Abstract

Background: Assessing risk of radiation-induced hematologic malignancy from medical imaging in children and adolescents might support informed decisions on its use.

Methods: A retrospective cohort of 3,724,623 children born between 1996–2016 in six U.S. healthcare systems and Ontario, Canada was followed until the earliest of cancer diagnosis, death, end of healthcare coverage, age 21, or 12/31/2017. Radiation doses to active bone marrow from medical imaging were quantified. Associations between hematologic malignancies and cumulative radiation exposure (vs, no exposure), lagged 6 months, were estimated using continuous-time hazards models.

Results: In >35,715,325 person-years (mean=10.1 years follow-up), 2,961 hematologic malignancies were diagnosed, primarily lymphoid (n=2,349[79.3%]), myeloid malignancies and acute leukemia (n=460[15.5%]), and histiocytic/dendritic cell (n=129[4.4%]). Mean exposure among children exposed to ≥1 mGy was 14 mGy (SD=23, equivalent to one head CT) overall and 25 mGy (SD=36) among children with hematologic malignancy. Relative to no exposure, malignancy risk increased with cumulative dose-- relative risk (RR)=1.41 (95% CI=1.11–1.78) for 1–≤5 mGy, RR=1.82 (95% CI=1.33–2.43) for 15–≤20 mGy, and RR=3.59 (95% CI=2.22–5.44) for 50–<100 mGy. Cumulative bone marrow dose was associated with increased risk for all hematologic malignancies (excess relative risk [ERR] per 100 mGy=2.54, 95% CI=1.70–3.51, p<0.001; RR for 30 vs. 0 mGy=1.76[95% CI=1.51–2.05]), and most tumor subtypes. Excess cumulative incidence of hematologic malignancies by age 21 among children exposed to ≥30 mGy (mean=57 mGy) was 25.6/10,000. We estimated that, in our cohort, 10.1% (95% CI=5.8–14.2) of hematological malignancies may have been attributable to radiation exposure from medical imaging, with higher risks from the higher dose modalities such as CT.

Conclusions: Our study suggests an association among children and adolescents exposed to radiation from medical imaging and a small but significantly increased risk of hematologic malignancy.

In the United States more diagnostic imaging per capita is performed, particularly computed tomography (CT), than in any other country.[1] While essential for diagnosis and disease management, most imaging involves ionizing radiation, a known carcinogen. Extensive evidence demonstrates a dose-response relation between radiation exposure and cancer risk.[2–8] CT, due to its frequency and relatively high doses, is the leading source of radiation exposure from medical imaging.[9–11]

Children are especially susceptible to radiation-induced cancer because of higher radiosensitivity and longer life expectancy.[12] Hematologic malignancies, the most common childhood cancers, are at highest risk.[13,14] Recent international studies, including the European EPI-CT study, have linked childhood CT to increased risk of hematologic malignancies, reporting a 50% higher risk in children undergoing two-to-three versus one

CT.[8,15,16] However, no studies have evaluated these risks in North America or evaluated radiation exposure from radiography, fluoroscopy, angiography, or nuclear medicine.

Here, we report results from the Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) retrospective cohort study to quantify the association between cumulative active bone marrow radiation dose from medical imaging and risk of hematologic malignancies in children in the U.S. and Ontario, Canada.

Methods

Study Cohort

The RIC cohort includes children born between January 1, 1996, and April 30, 2016, in any of 6 integrated U.S. healthcare systems (Kaiser Permanente [KP] Northern California, KP Northwest [Oregon/Southwest Washington], KP Washington [Washington State], KP Hawaii, Marshfield Clinic [Wisconsin], and Harvard Pilgrim Health Care [Massachusetts]) or Ontario, Canada and eligible for the Ontario Health Insurance Plan. Children had to have attended at least one clinical visit within the health system during the first three months of life, have been continuously enrolled for a minimum of 6 months after birth and have been alive and cancer free at 6 months of age. Study design and cohort details have been published.[17] Children were followed from birth until the earliest of any cancer or benign tumor diagnosis, death, emigration from Ontario, 6 months post-US health system disenrollment, age 21, or study end (December 31, 2017). The study received ethics approval from institutional review boards at each U.S. healthcare system; University of California at San Francisco and Davis; University of Toronto, select Ontario hospitals, and the California, Texas, Washington, Oregon, Hawaii, Wisconsin, and Massachusetts state cancer registries.

Radiation Dose Calculation

Medical imaging examinations were identified from administrative databases using codes from Current Procedural Terminology®, International Classification of Disease (ICD-9-CM, ICD-10-CM, ICD-9-PCS, ICD-10-PCS), Healthcare Common Procedure Coding System, and Canadian Classification of Health Interventions. Codes were mapped to an imaging modality and anatomic area.[17,18] Absorbed doses to the active bone marrow were estimated for each imaging examination using patient characteristics including sex, height, and weight extracted from electronic health records (EHR), anatomic area imaged, and technical parameters of the examination. Methods varied by imaging modality[17,19,20] and are summarized in the **Study Procedures and Technical Details.**

Cancer Assessment

U.S. cancer diagnoses were identified from each healthcare system's cancer registry and by linking with North American Association of Central Cancer Registries.[17,18] Ontario diagnoses were identified from the Ontario Cancer Registry and Pediatric Oncology Group of Ontario's Networked Information System. Hematologic malignancies with a malignant behavior code were classified using the International Classification of Childhood Cancer, 3rd Edition and revised WHO classification of lymphoid and myeloid malignancies based on

cell lineage, maturation, and other features, Table 1, **Study Procedures and Technical Details**.[21] Acute lymphoblastic leukemia (ALL) is included in the lymphoid group, and leukemia in the myeloid group refers to non-lymphoid leukemias. Therapy-related malignancies (e.g., post-transplant lymphoproliferative disease) were grouped with other cancers.

Confounding Variables and Examination Indication

Birthdate and sex were obtained from the EHR or Ontario's Registered Persons Database. Children with Down's syndrome were identified through ICD-9-CM and ICD-10-CM codes using a validated algorithm.[22] For all U.S. healthcare systems except one, we ascertained the imaging reason for exams with a bone marrow dose ≥1 mGy to determine whether it could reflect an existing hematologic malignancy (e.g., aplastic anemia, neutropenia, lymphadenopathy, masses) using ICD-9-CM and ICD-10-CM codes. For Ontario, we ascertained the imaging reason for exams with a dose ≥1 mGy obtained in the emergency department or as part of hospitalization (60% of imaging examinations).

Statistical Analysis

We summarized demographic characteristics overall and by hematologic malignancy type. Cumulative exposure was calculated with a 6-month lag in the main analysis and a 24-month lag in a sensitivity analysis, ensuring radiation exposures did not affect risk estimates for the first 6- or 24-months post-exposure. Relative Risks (RRs) and 95% confidence intervals (CIs) of hematologic malignancy associated with categorical time-varying cumulative doses (vs. 0 dose) were estimated using a Cox proportional hazards model, stratified by sex, birth year, Down's syndrome, and site. Relative risks (RR) and excess relative risks (ERR) associated with continuous cumulative dose were estimated using a linear model with the same stratification, overall and by malignancy type. We evaluated effect modification of the dose association by sex and time since exposure, age at exposure, and attained age. We estimated the cumulative incidence of hematologic malignancy by cumulative dose and report excess risk per 10,000 children without Down's syndrome. We estimated the population attributable risk of hematological malignancy associated with radiation exposure from imaging and the attributable risk for children exposed to specific imaging types. Additional details are noted in the **Study Procedures and Technical Details.**

Sensitivity analyses for the linear model included extending the dose-effect lag to 24 months, censoring children when their cumulative bone marrow dose reached 50 or 100 mGy, excluding children diagnosed with cancer or who died within their first year, and excluding children with Down's syndrome.

Results

The RIC cohort included 3,724,623 children with 35,715,325 person-years of follow up, Table 1. Overall, 1,910,587 were male (51.3%), 4,124 had Down's syndrome (0.1%), and 1,590,619 were born between 1996–2004 (42,7%). Children were followed for a mean age of 10.1 years. Most (2,966,746 [79.7%]) were followed until the study end. Others disenrolled from a U.S. healthcare system or moved from Ontario (611,180 [16.4%]), were

diagnosed with a tumor other than a hematologic malignancy (3,742 [0.10%]), attained age 21 years (135,078[3.6%]), or died (4,916[0.13%]).

A total of 2,961 hematologic malignancies were diagnosed, Table 1. Most (n=2,349[79.3%]) were lymphoid, 460 (15.5%) were myeloid or acute leukemia, and 129 (4.4%) were histiocytic and dendritic cells, Table S1. Among cases, 1,722 (58.2%) were male, and half (1,506 [50.9%]) were diagnosed in children under 5 years of age. Children were more likely to be diagnosed with Hodgkin's lymphoma when older, and children with Down's syndrome were more likely to be diagnosed with myeloid malignancy and acute leukemia, Table S1.

Bone Marrow Doses

Bone marrow doses associated with the most common imaging examination types are summarized in Table S2. Head/brain CT, the most frequently performed CT exam, had a mean bone marrow dose of 13.3 mGy and Chest radiography, the most common imaging exam overall, had a mean dose of 0.01 mGy. By the end of follow-up, 7.5% (280,548/3,724,623) of all children, and 9.2% (272/2961) of those who developed a hematologic malignancy had received a cumulative dose ≥1 mGy, Table 1. Among children exposed to ≥1 mGy, the mean cumulative dose was 14.0 mGy (SD=23.1) overall and 24.5 mGy (SD=36.4) in those with hematologic malignancy. Among children exposed to ≥1 mGy, 17.0% overall and 32.7% of hematologic malignancy cases received a cumulative dose of ≥20 mGy, while 9.4% overall and 22.4% of hematologic malignancy cases received a cumulative dose of ≥30 mGy, Table 1. Overall, 2,135 (0.1%) of all children and 10 (0.3%) of cases received a cumulative dose of ≥100 mGy.

Cumulative Bone Marrow Dose and Hematologic Malignancy

Hematologic malignancy risk increased with cumulative dose (Fig. 1, Table S3). Compared to no exposure, malignancy risk was higher in children exposed to >0 to <1 mGy (RR=1.16; 95% CI=1.07 to 1.27), 1 to <5 mGy (RR=1.41; 95% CI=1.11–1.78), 5 to <10 mGy (RR=1.41; 95% CI=1.00–1.93), 15 to <20mGy (RR=1.82; 95% CI=1.33–2.43), 20 to <30 mGy (RR=1.79; 95% CI=1.20–2.55), 30 to <50 mGy (RR=1.97; 95% CI=1.35–2.78), 50 to <100 mGy (RR=3.59; 95% CI=2.22–5.44), and ≥100 mGy (RR=5.64; 95% CI=2.80–39.92), Table S4. Malignancy risk was below 1 for a cumulative dose of 10 to <15 mGy but the CI includes 1 (RR=0.96; 95% CI=0.61–1.41).

Cumulative bone marrow dose was significantly associated with an increased risk for all hematologic malignancies (ERR per 100 mGy=2.54, 95% CI=1.70–3.51, p<0.001; RR for 30 mGy vs. 0 mGy=1.76, 95% CI=1.51–2.05). Cumulative dose was associated with risk of lymphoid malignancies (RR for 30 mGy vs. 0 mGy =1.59, 95% CI=1.33–1.89), myeloid malignancies or acute leukemia (RR=1.55, 95% CI=>1.00–2.21) and histiocytic and dendritic cell (RR=7.0; 95% CI=4.0–11.7), Table 2. Among lymphoid subtypes, cumulative dose was associated with an increased risk of non-Hodgkin's lymphoma (RR=1.77; 95% CI=1.46–2.14), but not Hodgkin's lymphoma (RR=1.00; 95% CI=1.00–1.33). Among non-Hodgkin's lymphoma subtypes, cumulative dose was associated with an increased risk of mature B-cell (RR=3.90; 95% CI=2.66–5.61) and mature T/natural killer-cell lymphoma (RR=3.78; 95% CI=1.86–7.08), but not precursor cell malignancies

(RR=1.09; 95% CI=1.00–1.33). Among those who developed myeloid malignancies and acute leukemia, cumulative dose was associated with an increased risk of myeloproliferative/myelodysplastic syndromes (RR=4.06; 95% CI=2.08–7.24) but not AML and related precursor neoplasms + ALMP/ALAP (RR=1.00; 95% CI=1.00–1.45).

Associations were similar by sex, exposure age, and attained age (Table S4); however, associations tended to weaken with increasing time since exposure, with the strongest association within the first 6 months to 4 years after exposure.

From the linear model including effect modification with continuous time since exposure and categorical age at exposure, associations decreased with time since exposure and were stronger for children exposed ≥5 years of age (Fig. 2, Table S5.) For example, for a 5–10-year-old exposed to 30 mGy, the RR (versus no exposure) was 6.09 (95% CI=3.00–12.4) at 1 year and 2.40 (95% CI=1.48–3.87) at 5 years post-exposure. For a 1–4-year-old exposed to 30 mGy, the RR was 2.81 (95% CI=1.85–4.24) at 1 year and 1.50 (95% CI=1.03–2.17) at 5 years post-exposure. However, the confidence intervals are wide (Table S6).

Relative Risks, Attributable Risks and Cumulative Cancer Incidence

The relative risks of hematologic malignancy and the attributable risks among exposed children for the most common imaging examination types are summarized in Table S6. Head/brain CT, the most frequently performed CT exam with a mean bone marrow dose of 13.3 mGy, had a RR=1.35 (95% CI=1.23–1.48) and an attributable risk of 25.9%. Chest radiography, the most common imaging exam overall with a mean dose of 0.01 mGy, had a RR=1.0003 (95% CI=1.0002–1.0004), and an attributable risk of 0.03%.

Among children without Down's syndrome, the cumulative incidence of hematologic malignancy by age 21 was 39.9 per 10,000 children with a cumulative exposure of ≥30 mGy, compared to 14.3 (95% CI=13.4, 15.3) per 10,000 children with no exposure, resulting in 25.6 excess cancers per 10,000 children exposed (Fig. 3). By our calculation, the population-attributable risk of hematologic malignancy in children and adolescents associated with radiation exposure from medical imaging was 10.1% (95% CI=5.8–14.2).

Indications for Imaging

A total of 829 exams with a bone marrow dose ≥1 mGy were performed on 511 children with hematologic malignancy on or before their diagnosis date (N=272 with exams more than 6 months prior to diagnosis), including 163 exams in 145 children with indications suggestive of a hematologic malignancy. Of these, 154 exams in 138 children (94.5% of exams, 95.0% of affected children) were excluded as they occurred within 6 months of diagnosis (mean, 9 days). In the primary 6-month-lag analysis, 9 exams in 7 children (1.3% of exams, 1.9% of children) had a dose ≥1 mGy and indications suggestive of hematologic malignancy, performed on average 3.1 years before diagnosis. In the 24-month-lag sensitivity analysis, 5 exams in 4 children remained, with an average of 5.0 years before diagnosis.

For children without a hematologic malignancy, 229,305 exams (166,335 children) with a dose ≥1 mGy were performed, including 2,860 exams (2,590 children) with an indication

suggestive of hematologic malignancy. Of these, 2,668 exams were included in the primary analysis. Thus, only 163/3023 (5.4%) exams with an indication suggestive of hematologic malignancy were performed in children diagnosed with a hematologic malignancy, and only 9/2,677 (0.3%) of such exams were included in the primary analysis.

Sensitivity Analyses

Results were robust to sensitivity analyses, Table S7. Increasing the dose-effect lag from 6 to 24 months had little effect on RRs. Excluding children with Down's syndrome and excluding extreme exposures by censoring children when their cumulative bone marrow dose reached 50 or 100 mGy resulted in higher RRs. Excluding children who were diagnosed with cancer or died within the first year of life had no impact on RRs.

Discussion

In this retrospective cohort study of over 3.7 million children born in the U.S. or Ontario, Canada, we found a significant dose-response relation between cumulative bone marrow dose and hematologic malignancy risk. Exposures associated with increased risk were common in clinical practice, for example, a 15–30 mGy exposure equivalent to 1–2 head CTs [23–26] was associated with a 1.8-fold increased risk, rising to 2.5 times greater risk for exposures of ≥30 mGy. The excess cumulative incidence of hematologic malignancies by age 21 was 25.6 per 10,000 among those exposed to ≥30 mGy (mean=57 mGy) and 41 per 10,000 for those exposed to 50–100 mGy. Excess risks were consistent across most hematologic malignancy subtypes and robust to sensitivity analyses.

In our cohort of children and adolescents, we estimated that medical imaging was associated with 10.1% of hematologic malignancies with attributable risks varying by imaging type. For example, among children who underwent a head CT, a quarter of hematologic malignancies were estimated as attributable to radiation exposure, whereas among children undergoing radiographs, such as for a broken bone or pneumonia, a very small percentage (<1%) of hematologic malignancies were estimated as associated with radiation exposure. While CT and other radiation-based imaging modalities may be lifesaving, our findings underscore the importance of carefully considering and minimizing radiation exposure during pediatric imaging to protect children's long-term health. Further, our results quantify the risk of cancer associated with medical imaging through age 21, but cumulative incidence will likely increase with longer follow-up. Research on Japanese atomic bombing survivors found leukemia rates peaked 6–8 years post-exposure with excess risk lasting for over five decades, particularly for acute myeloid leukemia.[4,12,27]

Our study adds to the growing evidence that associates pediatric medical imaging with cancer risk and addresses key limitations of prior studies. We included all imaging modalities, captured complete imaging histories from birth, and directly compared exposed and unexposed children. Unlike earlier studies that relied on survey data or literature-based estimates, we performed detailed patient-level CT dose reconstruction. Despite differences in study design and age distribution, our findings are consistent with prior research. For example, the RR of any hematologic malignancy for 100 mGy versus no exposure is 3.54 (95% CI=2.70–4.51) in our study compared to 2.96 (95% CI=2.10–4.12) in EPI-CT.[8] Both

RIC and EPI-CT found that excess risks did not decrease with age at exposure, as reported in BEIR-VII.[2] However, EPI-CT reported excess risks for Hodgkin's lymphoma, while RIC found large excess risks for myelodysplastic syndromes, also observed by Pearce.[15] Differences in tumor types likely reflect variation in cohort composition. RIC followed all children from birth and included cancers diagnosed between 6 months and 21 years of age, whereas EPI-CT only included children who underwent a CT scan, following them from 2 years post-CT to age 41, resulting in an older cohort.

Concerns about reverse causation–where imaging is performed due to existing cancer symptoms–have been raised in imaging carcinogenicity studies.[28] We lagged exposures by 6 and 24 months, with persistent elevated risks, consistent with other studies.[8,15] Moreover, imaging for hematologic malignancy symptoms was uncommon in exams included in the analysis, and such cancers typically present and are diagnosed rapidly, making a delay >6 months unlikely.[29–31] Thus, reverse causation does not explain our findings.

The increasing use of low-value imaging in children and excessive radiation doses in CT are well documented.[32,33] Our population attributable risk estimates suggest that up to 10% of hematologic malignancies might be prevented by reducing unnecessary radiation exposure through more judicious imaging and dose optimization. While avoiding unnecessary imaging is critical, medically-indicated imaging should not be deferred, as that may result in missed or delayed diagnoses. In many cases, reducing imaging dose or substituting MRI or ultrasound may be more feasible than avoiding imaging altogether.

Strengths of our study include a large cohort representative of the broader US and Canadian population and the comprehensive identification and stratification of Downs's syndrome to control for potential confounding.[34] Other cancer-predisposing syndromes are rare and unlikely to account for the observed relations.[35–39] Limitations include potential under ascertainment of cancers, which we minimized by linking with population-based tumor registries.

In conclusion, this study provides robust, directly observed evidence that ionizing radiation from medical imaging is associated with increased hematologic malignancy risk in children, even at doses below 50 mGy. These findings underscore the need to carefully weigh benefits and risks when imaging children and to minimize radiation exposure whenever clinically feasible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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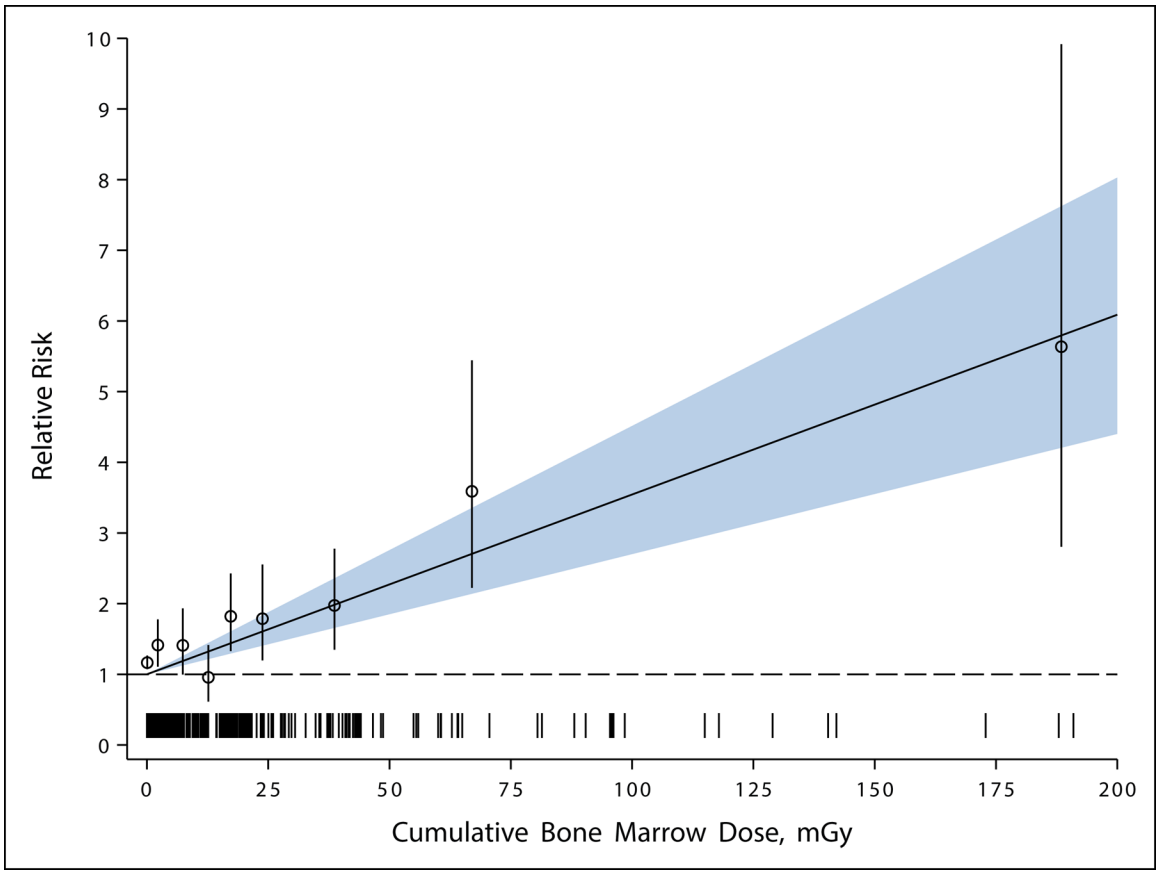

Figure 1.

Relative risks for all hematologic malignancies by cumulative bone marrow dose (in mGy). Dots show estimated relative risks by categories of cumulative dose (see Table S4). Vertical bars show 95% confidence intervals (CI). The solid line represents the fitted dose-response from the linear model (excess relative risk (ERR)=2.54 per 100 mGy exposure). The shaded area represents the upper and lower CIs for the dose-response (95% CI for ERR=1.70 to 3.52). The dashed horizontal line represents the reference value (RR=1.0). The vertical lines at the bottom of the figure show the cumulative doses for children with a hematologic malignancy. Two children with doses above 200 mGy are not included.

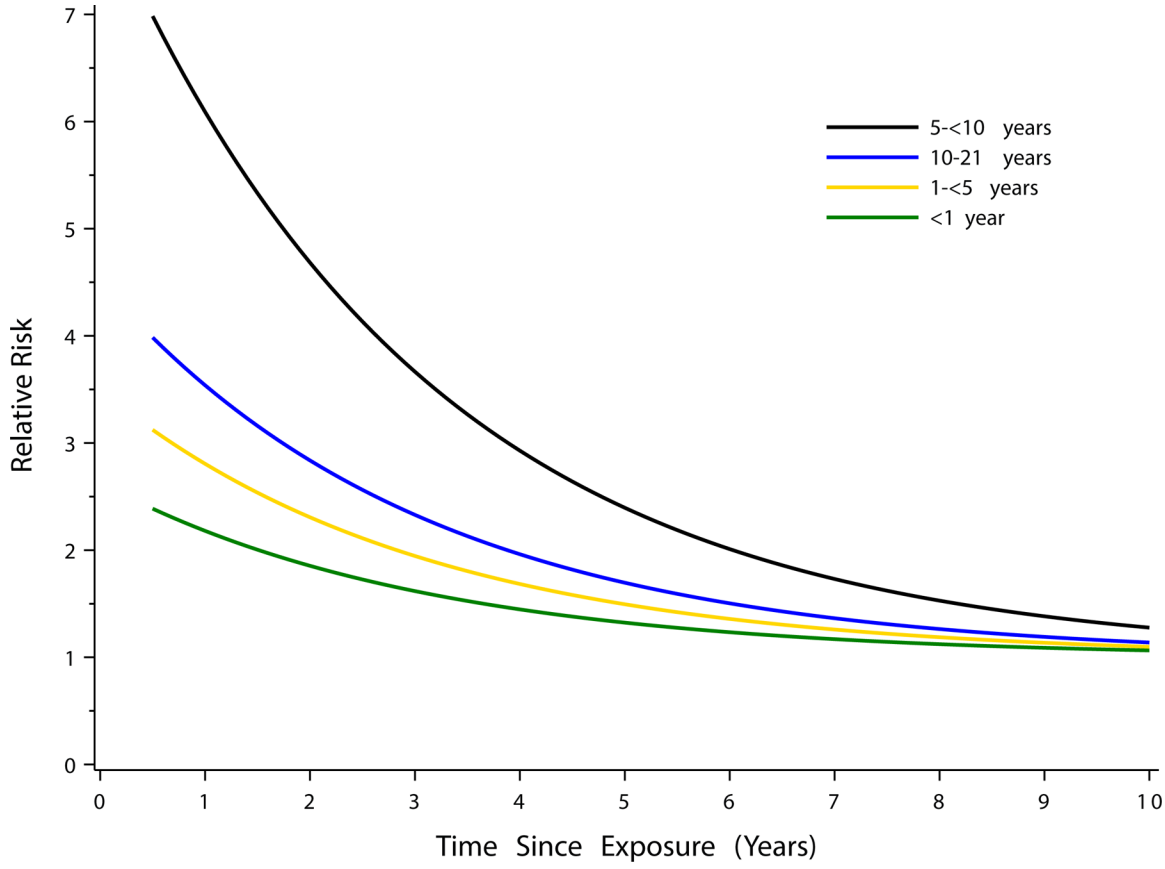

Figure 2.

Relative risk of hematologic malignancy for a dose of 30 mGy (vs. no exposure) by time since exposure (modeled as a continuous variable) with separate lines by age at exposure (modeled as a categorical variable). Results from other dose exposures shown in Table S5. Results from other dose exposures and confidence intervals shown in Table S5.

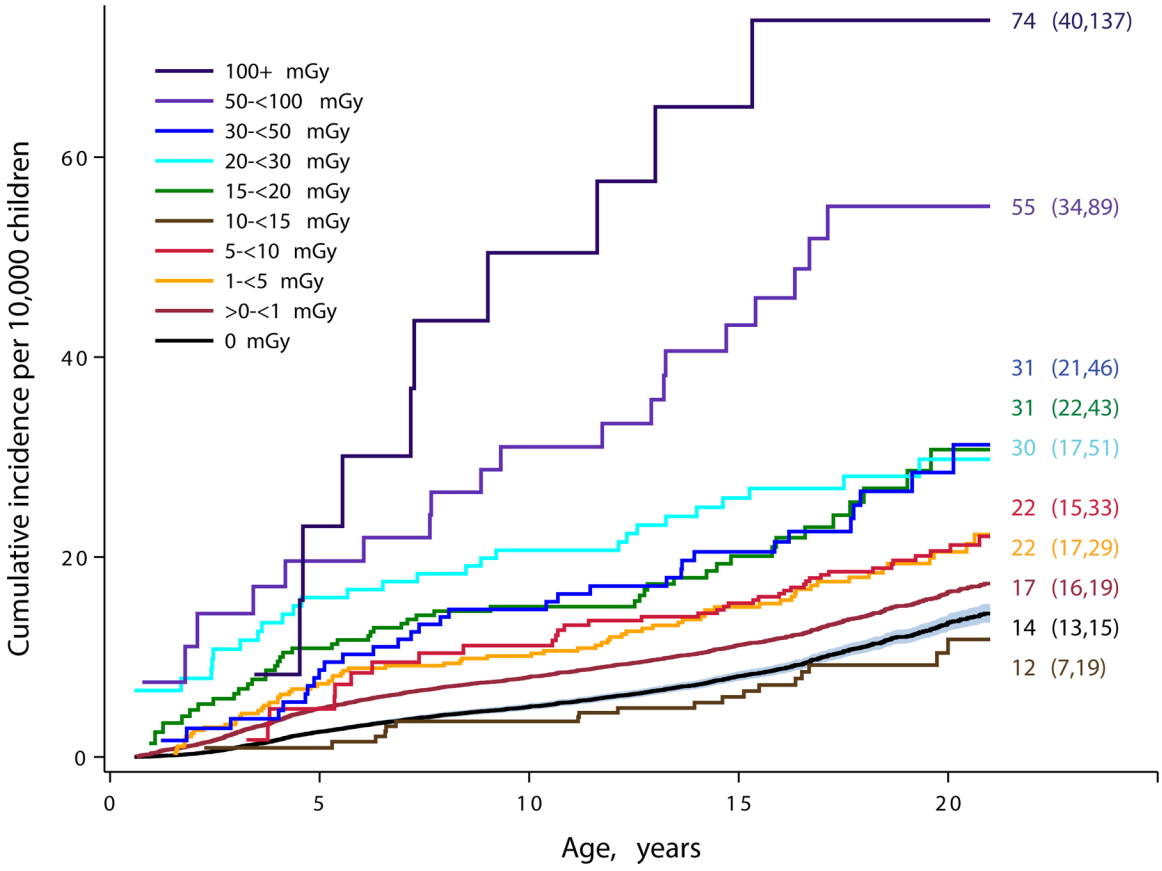

Figure 3.

Cumulative incidence of hematologic malignancy by attained age and active bone marrow dose, among children without Down's syndrome. The cumulative incidence and 95% CI are shown for age 21 years. Shaded blue area represents the 95% confidence interval for the no exposure (0 mGy) group. Confidence bands for other groups are omitted for readability.

Table 1.

Characteristics of study cohort and hematologic malignancies. Column percentages unless otherwise specified.

	Entire Cohort No. (Column %)	Person Years of Follow-up No. (Column %)	All Hematologic Malignancies No. (Column %)
Total	3,724,623 (100.0)	35,715,325 (100.0)	2,961 (100.0)
Country			
Canada	2,793,503 (75.0)	30,089,301 (84.2)	2,487 (84.0)
United States	931,120 (25.0)	5,626,024 (15.8)	474 (16.0)
Sex			
Male	1,910,587 (51.3)	18,315,841 (51.3)	1,722 (58.2)
Female	1,814,036 (48.7)	17,399,483 (48.7)	1,239 (41.8)
Down's syndrome			
Yes	4,124 (0.1)	38,154 (0.1)	110 (3.7)
No	3,720,499 (99.9)	35,677,171 (99.9)	2,851 (96.3)
Birth cohort			
1996 to 1999	687,580 (18.5)	11,342,544 (31.8)	865 (29.2)
2000 to 2004	903,039 (24.2)	11,337,119 (31.7)	842 (28.4)
2005 to 2009	940,931 (25.3)	8,268,078 (23.1)	723 (24.4)
2010 to 2016	1,193,073 (32.0)	4,767,584 (13.3)	531 (17.9)
Age at end of follow-up			
6 months to <5 years	1,019,190 (27.4)	2,503,372 (7.0)	1,506 (50.9)
5 to < 10 years	953,638 (25.6)	6,577,018 (18.4)	695 (23.5)
10 to <15 years	789,050 (21.2)	9,404,954 (26.3)	430 (14.5)
15 to <21 years	962,745 (25.9)	17,229,980 (48.2)	330 (11.1)
Mean follow up time (years)	10.1		6.8
Cumulative bone marrow dose			
0 mGy	1,406,262 (37.8)	8,953,308 (25.1)	1,261 (42.6)
>0 to <1 mGy	2,037,813 (54.7)	22,777,331 (63.8)	1,428 (48.2)
1 to <5 mGy	84,380 (2.3)	1,194,532 (3.3)	77 (2.6)
5 to <10 mGy	63,552 (1.7)	1,035,818 (2.9)	38 (1.3)
10 to <15 mGy	49,614 (1.3)	615,186 (1.7)	23 (0.8)
15 to <20 mGy	35,266 (1.0)	443,659 (1.2)	45 (1.5)
20 to <30 mGy	21,360 (0.6)	301,692 (0.8)	28 (1.0)
30 to <50 mGy	17,779 (0.5)	265,994 (0.7)	31 (1.1)
50 to <100mGy	6,462 (0.2)	96280 (0.3)	20 (0.7)
>100 mGy	2,135 (0.1)	30,985 (0.1)	10 (0.3)
Cumulative bone marrow dose among those who received an exposure ≥1 mGy			
Mean (SD), mGy	14.0 (23.1)		24.5 (36.4)
90th percentile, mGy	28.7		55.9
Reason for end of follow-up[2]			
Hematologic malignancy	2,961 (0.08)	18,765 (0.05)	
Other malignant or benign tumor	3,742 (0.10)	25,435 (0.07)	

	Entire Cohort No. (Column %)	Person Years of Follow-up No. (Column %)	All Hematologic Malignancies No. (Column %)
Death	4,916 (0.13)	27,808 (0.08)	
Age 21	135,078 (3.6)	2,768,558 (7.8)	
End of healthcare coverage[1]	611,180 (16.4)	2,476,343 (6.9)	
End of study follow-up	2,966,746 (79.7)	30,398,415 (85.1)	

[1] Disenrolled from United States healthcare system or emigrated from Ontario.

[2] Patients are censored when the first reason for end of follow up occurs.

Table 2.

Excess relative risk (ERR) per 100 mGy increase in exposure, and relative risks (RR) for 10 mGy, 30 mGy, and 100 mGy vs. no exposure (0 mGy) and 95% confidence intervals (CI) of hematologic malignancy associated with bone marrow dose, overall and by hematologic malignancy type and subtype.

Malignancy type and subtype	No. of Cases		Relative Risk (RR) vs 0 exposure		
		Excess Relative Risk (ERR) per 100 mGy	10 mGy (95% CI)	30 mGy (95% CI)	100 mGy (95% CI)
All Hematologic Malignancies [1]	2 961	2.54 (1.70, 3.51)	1.25 (1.17, 1.35)	1.76 (1.51, 2.05)	3.54 (2.70, 4.51)
Lymphoid[2]	2 349	1.95 (1.09, 2.97)	1.20 (1.11, 1.30)	1.59 (1.33, 1.89)	2.95 (2.09, 3.97)
Non-Hodgkin's Lymphoma	2 059	2.56 (1.52, 3.81)	1.26 (1.15, 1.38)	1.77 (1.46, 2.14)	3.56 (2.52, 4.81)
Mature B cell	229	9.68 (5.53, 15.4)	1.97 (1.55, 2.54)	3.90 (2.66, 5.61)	10.68 (6.53, 16.4)
Mature T / NK Cell	76	9.26 (2.86, 20.3)	1.93 (1.29, 3.03)	3.78 (1.86, 7.08)	10.26 (3.86, 21.3)
Precursor Cell [3]	1 745	0.32 (0.00, 1.22)	1.03 (1.00, 1.12)	1.09 (1.00, 1.37)	1.32 (1.00, 2.22)
Hodgkin's Lymphoma [3]	279	0.00 (0.00, 1.10)	1.00 (1.00, 1.11)	1.00 (1.00, 1.33)	1.00 (1.00, 2.10)
Myeloid Malignancies and Acute Leukemia[4]	460	1.82 (>0.00, 4.02)	1.18 (>1.00, 1.40)	1.55 (>1.00, 2.21)	2.82 (>1.00, 5.02)
AML and related precursor neoplasms + ALMP/ALAP [3,5]	304	0.00 (0.00, 1.49)	1.00 (1.00, 1.15)	1.00 (1.00, 1.45)	1.00 (1.00, 2.49)
Myeloproliferative / myelodysplastic	124	10.19 (3.61, 20.8)	2.02 (1.36, 3.08)	4.06 (2.08, 7.24)	11.19 (4.61, 21.8)
Histiocytic and Dendritic Cell	129	20.01 (10.0, 35.7)	3.00 (2.00, 4.57)	7.00 (4.00, 11.7)	21.01 (11.0, 36.7)

[1] Includes 23 tumors of unspecified type.

[2] Includes acute lymphoid leukemia (ALL) and 11 lymphoid tumors that could not be classified as Non-Hodgkin's Lymphoma or Hodgkin's Lymphoma.

[3] The lower bound of the confidence interval was constrained to 0 for the excess relative risk and 1 for the relative risk.

[4] Myeloid Malignancies and Acute Leukemia includes 32 tumors that could not be classified into subtypes.

[5] AML = acute myeloid leukemia, ALMP = acute leukemia of mixed phenotype, ALAP = acute leukemia of ambiguous lineage. Leukemias in the myeloid group refer to non-lymphoid leukemias.