Risk of Hematopoietic Cancer in Children with Congenital Heart Disease

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DEDICATION

To my father

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ABSTRACT

Children with congenital heart disease (CHD) have an elevated risk of cancer compared with the general population. In particular, hematopoietic cancer (HC) is the most common childhood cancer, accounting for more than half of the cancer incidence among this vulnerable pediatric population. The possible multifactorial mechanism underlying the association between CHD and cancer includes genetic syndromes and radiation exposure from imaging and therapeutic cardiac procedures. Studies exploring the role of known genetic syndromes on the association have reported conflicting findings. Most studies on the association between radiation exposure and cancer among children with CHD are limited by sample size, providing insufficient and inconsistent evidence.

Moreover, the existence of a threshold level of radiation dose at which the carcinogenic effect starts to rise is not well-explored, owing to limited sample size and insufficient follow-up. Thus, the need for further research based on a large nationwide database with extended follow-up is particularly compelling. This current research examined a series of questions to assess the risk of HC in children with CHD and potential risk factors to add to the limited but growing body of knowledge for pediatric patients with CHD.

The first study was conducted to provide evidence on the incidence of HC as a consequence of genetic predisposition among children with CHD. The second and third studies explored the HC incidence due to patient management through cardiac imaging and the potential threshold effect of low-dose ionizing radiation (LDIR) from such imaging procedures on incident cancer cases among children with CHD, respectively. These studies were based on the Canadian CHD (CanCHD) database, created by merging the Quebec CHD database (1983-2017) and the Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD), which

collects hospitalization and day surgery records from Canada's other 12 provinces and territories (1993-2017). The CanCHD database comprises 495,495 patients with CHD from across the country, followed for up to 35 years. Using the database, the current research constructed a pan-Canadian birth cohort of children with CHD, including 143,794 patients born between 1999 and 2017 and followed from birth to age 17.

To better understand the role of known genetic syndromes on the incidence of HC, **the first question is**: Does having a genetic syndrome increase the risk of HC among children with CHD? To answer the question, a retrospective cohort study was designed using the pan-Canadian birth cohort of children with CHD. All patients were followed from birth until the earliest of March 31, 2018, first HC diagnosis, heart transplant, death, or the 18th birthday. HC incidences in children with CHD were compared to the general pediatric population using the Canadian Cancer Registry (CCR). Overall and HC subtype-specific (Acute myeloid leukemia, AML, and Acute lymphoblastic leukemia, ALL) cumulative incidence was estimated using a modified Kaplan-Meier (KM) curve analysis (with 95% confidence intervals, CI) up to 18 years of age, with death as a competing risk and stratified by the genetic syndrome status. The results showed a 13-fold risk of HC among children with a genetic syndrome compared to the general pediatric population (SIR=13.4; 95% CI: 11.7-15.1). Children with a genetic syndrome had a 2.44% (95% CI: 2.11-2.76%) cumulative incidence of developing HC from birth to 18 years of age compared with 0.79% (95% CI: 0.72-0.87%) without a syndrome, demonstrating a three-fold increase in the risk of HC. There was a preponderance of AML over ALL, with an incidence earlier in childhood. The results are clinically important. They provide contextual information on the genetic component to the carcinogenesis of syndromic CHD patients, thereby allowing for

effective cancer detection and therapeutic approaches for CHD patients with syndromes at as early an age as necessary.

The second question is: Is LDIR exposure from cardiac imaging a risk factor for HC in children with CHD? To this end, the cumulative *effective* dose of the ionizing radiation corresponding to cardiac diagnostic and therapeutic procedures was quantified considering a 6-month exposure lag. A recency-weighted cumulative exposure (WCE) model, a spline-based extension of Cox's proportional hazards (PH) model, was used to assess the association between LDIR exposure and HC. Children with any HC were exposed to radiation earlier in life (median age at first exposure: 6 vs. 10 months; p=0.03) and received higher cumulative doses than their counterparts (mean dose: 2.3 vs. 1.1 mSv; CI for absolute difference: 0.61-1.79 mSv). Similar patterns were observed for HC without lymphoma. The WCE model demonstrated an association between HC and LDIR cumulative dose depending on the recency of the LDIR exposure among children with CHD. Specifically, the cumulative LDIR doses within five years were associated with an increased risk of HC, with or without lymphoma, with the maximum association magnitude around 2 years. This association necessitates monitoring radiation doses among children with frequent cardiac imaging. A patient-centered surveillance system may be helpful for better management of doses delivered during each cardiac imaging procedure and, thus, ensure radiation safety in children with CHD.

The third question is: Is there any threshold for the effect of LDIR on the incidence of HC among children with CHD? To this end, I used generalized additive models (GAM) to identify thresholds and estimate their locations. A restricted search algorithm was employed to locate potential thresholds in a neighborhood identified based on a numerical second derivative, a measure of local curvature in the GAM curve. A Chi-square test comparing the deviances of

the fitted threshold model and a simpler alternative model was used as the criterion for determining if a threshold association exists. I demonstrated that the risk of HC starts to increase as the cumulative effective dose reaches a threshold of 6.0 mSv, with or without lymphoma. However, comparing the fitted threshold model and the simpler model with log-transformed cumulative dose indicated that the association might be non-linear but without a threshold. These results indicated the apparent difficulty of distinguishing between a threshold and a non-linear association in a setting where only a fraction of the study population was exposed.

Taken together, the findings presented in this thesis help to better understand the possible underlying pathways leading to the elevated incidence of HC in pediatric CHD patients. Both genetic syndromes and LDIR exposure from cardiac imaging are identified to be risk factors of HC for this patient population. In light of these findings, cancer surveillance is suggested for pediatric CHD patients with genetic syndromes or frequent cardiac imaging.

RÉSUMÉ

Les enfants atteints d'une cardiopathie congénitale (CC) ont un risque élevé de cancer comparouge avec la population générale. En particulier, le cancer hématopoïétique (CH) est le cancer infantile le plus courant, représentant plus de la moitié de l'incidence du cancer parmi cette population pédiatrique vulnérable. Le mécanisme multifactoriel possible sous-jacent à l'association entre la coronaropathie et le cancer comprend les syndromes génétiques et l'exposition aux rayonnements par imagerie et les procédures cardiaques thérapeutiques. Des études explorant le rôle des syndromes génétiques connus sur l'association ont rapporté des résultats contradictoires. La plupart des études sur l'association entre l'exposition aux rayonnements et le cancer chez les enfants atteints de coronaropathie sont limitées par la taille de l'échantillon, fournissant des preuves insuffisantes et incohérentes.

En outre, l'existence d'un seuil de dose de rayonnement auquel l'effet cancérogène commence à augmenter n'est pas bien explorée, en raison de la taille limitée de l'échantillon et d'un suivi insuffisant. Ainsi, la nécessité de poursuivre les recherches fondées sur une vaste base de données nationale avec un suivi étendu est particulièrement convaincante. Cette recherche actuelle a examiné une série de questions visant à évaluer le risque de CH chez les enfants atteints de coronaropathie et les facteurs de risque potentiels pour ajouter à l'ensemble limité mais croissant de connaissances pour les patients pédiatriques atteints de coronaropathie.

La première étude a été menée pour fournir des preuves sur l'incidence du CH en raison de la prédisposition génétique chez les enfants atteints de coronaropathie. Les deuxième et troisième études ont exploré l'incidence du HC due à la prise en charge des patients par imagerie cardiaque et l'effet seuil potentiel des rayonnements ionisants à faible dose (RIFD) de ces procédures d'imagerie sur les cas incidents de cancer chez les enfants atteints de coronaropathie,

respectivement. Ces études étaient basées sur la base de données canadienne sur les maladies coronariennes (CanCHD), créée par la fusion de la base de données québécoise sur les maladies coronariennes (1983-2017) et de la base de données des résumés de congé (DAD) de l'Anadian Institute for Health Information (CIHI), qui recueille les dossiers d'hospitalisation et de chirurgie d'un jour des 12 autres provinces et territoires du Canada (1993-2017). La base de données CanCHD comprend 495 495 patients atteints de coronaropathie de partout au pays, suivis jusqu'à 35 ans. À l'aide de la base de données, la recherche actuelle a permis de construire une cohorte de naissance pancanadienne d'enfants atteints de coronaropathie, dont 143 794 patients nés entre 1999 et 2017 et suivis de la naissance à l'âge de 17 ans.

Pour mieux comprendre le rôle des syndromes génétiques connus sur l'incidence de l'CH, **la première question est la suivante** : Le fait d'avoir un syndrome génétique augmente-t-il le risque de CH chez les enfants atteints de coronaropathie ? Pour répondre à la question, une étude de cohorte rétrospective a été conçue à l'aide de la cohorte de naissance pancanadienne d'enfants atteints de coronaropathie. Tous les patients ont été suivis depuis la naissance jusqu'au plus tôt le 31 mars 2018, le premier diagnostic de CH, la transplantation cardiaque, le décès ou le 18e anniversaire. L'incidence des CH chez les enfants atteints de coronaropathie a été comparée à celle de la population pédiatrique générale à l'aide du Registre Canadien du Cancer (CCR). L'incidence cumulative globale et spécifique du sous-type CH (leucémie myéloïde aiguë, LMA et leucémie lymphoblastique aiguë, LLA) a été estimée à l'aide d'une analyse modifiée de la courbe de Kaplan-Meier (KM) (avec des intervalles de confiance à 95 %, IC) jusqu'à l'âge de 18 ans, avec le décès comme risque concurrent et stratifié par le statut du syndrome génétique. Les résultats ont montré un risque 13 fois plus élevé de CH chez les enfants atteints d'un syndrome génétique par rapport à la population pédiatrique générale (SIR = 13,4 ; IC à 95%: 11,7-15,1).

Les enfants atteints d'un syndrome génétique avaient une incidence cumulative de 2,44 % (IC à 95 % : 2,11-2,76 %) de développer une CH de la naissance à 18 ans, comparativement à 0,79 % (IC à 95 % : 0,72-0,87 %) sans syndrome, ce qui démontre une multiplication par trois du risque de CH. Il y avait une prépondérance de la LMA sur la LLA, avec une incidence plus précoce dans l'enfance. Les résultats sont cliniquement importants. Ils fournissent des informations contextuelles sur la composante génétique de la cancérogenèse des patients atteints de coronaropathie syndromique, permettant ainsi une détection efficace du cancer et des approches thérapeutiques pour les patients atteints de coronaropathie atteints de syndromes à un âge aussi précoce que nécessaire.

La deuxième question est la suivante : l'exposition au RIFD par imagerie cardiaque est-elle un facteur de risque de CH chez les enfants atteints de coronaropathie ? À cette fin, la dose *efficace* cumulative du rayonnement ionisant correspondant aux procédures diagnostiques et thérapeutiques cardiaques a été quantifiée en tenant compte d'un décalage d'exposition de 6 mois. Un modèle d'exposition cumulative pondérée en fonction de la récence (WCE), une extension basée sur les splines du modèle de risques proportionnels (PH) de Cox, a été utilisé pour évaluer l'association entre l'exposition au RIFD et le CH. Les enfants atteints d'un HC ont été exposés à la radiation plus tôt dans la vie (âge médian à la première exposition : 6 contre 10 mois ; $p = 0,03$) et ont reçu des doses cumulatives plus élevées que leurs homologues (dose moyenne : 2,3 vs 1,1 mSv ; IC pour différence absolue : 0,61-1,79 mSv). Des tendances similaires ont été observées pour les HC sans lymphome. Le modèle WCE a démontré une association entre la dose cumulative de CH et de RIFD en fonction de la récence de l'exposition au RIFD chez les enfants atteints de coronaropathie. Plus précisément, les doses cumulatives de RIFD dans les cinq ans étaient associées à un risque accru de CH, avec une magnitude

d'association maximale d'environ 2 ans, avec ou sans lymphome. Cette association nécessite une surveillance des doses de rayonnement chez les enfants ayant une imagerie cardiaque fréquente. Un système de surveillance centré sur le patient peut être utile pour une meilleure gestion des doses administrées lors de chaque procédure d'imagerie cardiaque et, par conséquent, assurer la radioprotection chez les enfants atteints de coronaropathie.

La troisième question est la suivante : Existe-t-il un seuil pour l'effet de la RIFD sur l'incidence du CH chez les enfants atteints de coronaropathie ? À cette fin, j'ai utilisé des modèles additifs généralisés (GAM) pour identifier les seuilset estimer leur emplacements. Un algorithme de recherche restreint a été utilisé pour localiser des seuils potentiels dans un quartier identifié sur la base d'une dérivée numérique seconde, une mesure de la courbure locale dans la courbe GAM. Un test du chi carré comparant les déviances du modèle de seuil ajusté et un modèle alternatif plus simple a été utilisé comme critère pour déterminer s'il existe une association de seuil. J'ai démontré que le risque de CH commence à augmenter à mesure que la dose efficace cumulative atteint un seuil de 6,0 mSv, avec ou sans lymphome. Cependant, la comparaison du modèle de seuil ajusté et du modèle plus simple avec la dose cumulative transformée logarithmique a indiqué que l'association pourrait être non linéaire mais sans seuil. Ces résultats ont indiqué la difficulté apparente de faire la distinction entre un seuil et une association non linéaire dans un contexte où seule une fraction de la population étudiée a été exposée.

Pris ensemble, les résultats présentés dans cette thèse aident à mieux comprendre les voies sous-jacentes possibles menant à l'incidence élevée de CH chez les patients atteints de coronaropathie pédiatrique. Les syndromes génétiques et l'exposition au RIFD par imagerie cardiaque sont identifiés comme des facteurs de risque de CH pour cette population de patients.

À la lumière de ces résultats, la surveillance du cancer est suggérée pour les patients pédiatriques atteints de coronaropathie présentant des syndromes génétiques ou une imagerie cardiaque fréquente.

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STATEMENT OF ORIGINALITY

The work in this thesis makes several original contributions that advance knowledge about the multifactorial mechanism underlying carcinogenic predisposition in children with CHD and illustrates novel analytic methods to properly measure time-varying LDIR exposures and its associated risk with cancer outcomes. Manuscript 1 provides the characterization of HC risk in children with CHD with and without known genetic syndromes. It further compares the childhood cancer risk in congenital heart disease children with the risk in the general pediatric population in Canada. It helped determine the genetic component of cancer in this population. Manuscript 2 is the first study to use novel flexible spline-based extensions of the Cox Proportional Hazards models to provide insight into the mechanism linking cumulative LDIR exposure from cardiac imaging to the risk of malignancy. Previous studies have demonstrated that lifetime cumulative LDIR dose elevates the cancer risk, we took a step further, showing not only the time-varying LDIR exposure but also the timing of the exposure is an important component of the association under study. Finally, Manuscript 3 is one of the only studies to use a non-parametric smoothing spline modeling approach to explore the threshold dose of LDIR exposure from cardiac imaging on HC incidence among children with CHD. It elucidates the possible dose-response of LDIR exposure on the risk of radiation-induced hematopoietic cancer incidence in children with CHD. The knowledge gained from this thesis work is instrumental in suggesting extensive cancer surveillance for pediatric CHD patients with known genetic syndromes or frequent cardiac imaging.

CONTRIBUTION OF AUTHORS

Manuscript 1:

Hasan MS, Ganni E, Liu A, Guo L, Mackie AS, Kaufman JS, Marelli, AJ. The Canadian Congenital Heart Disease (CanCHD) Study of Hematopoietic Cancers in Children with and without Genetic Syndromes.

The idea and objective of this study were conceptualized by Dr. Marelli, Dr. Liu, and me. I was principally responsible for carrying out this research, including conducting literature reviews, determining appropriate statistical methods, preparing data for analyses, performing all data analyses, interpreting the results, and drafting the manuscripts. Mr. Ganni was involved in managing diagnostic codes for analyses and discussion of the manuscript. Dr. Kaufman provided support regarding the statistical methodology, substantive and editorial feedback, and interpretation of results in the manuscript. Dr. Marelli and Dr. Liu were also involved in the discussions of the methodologies used and the interpretation of the findings. All co-authors critically reviewed the manuscript for important intellectual content.

Manuscript 2:

Hasan MS, Liu A, Guo L, Abrahamowicz M, Kaufman JS, Marelli AJ. Flexible modeling of the association between cumulative exposure to low-dose ionizing radiation from cardiac procedures and risk of hematopoietic cancer in children with congenital heart disease.

The idea and objective of this study were conceptualized by Dr. Marelli, Dr. Liu, and me. I was principally responsible for carrying out this research, including conducting literature reviews, determining appropriate statistical methods, preparing data for analyses, performing all data analyses, interpreting the results, and drafting the manuscripts. Dr. Abrahamowicz provided support regarding the statistical methodology, substantive and editorial feedback, and

interpretation of results in the manuscript. Dr. Marelli and Dr. Liu were also involved in the discussions of the methodologies used and the interpretation of the findings. All co-authors critically reviewed the manuscript for important intellectual content.

Manuscript 3:

Hasan MS, Liu A, Guo L, Abrahamowicz M, Kaufman JS, Marelli AJ. Threshold Effect of Low-dose Ionizing Radiation from Cardiac Imaging on Hematopoietic Cancer incidence in Children with Congenital Heart Disease.

The idea and objective of this study were conceptualized by Dr. Marelli, Dr. Liu, and me. I was principally responsible for carrying out this research, including conducting literature reviews, determining appropriate statistical methods, preparing data for analyses, performing all data analyses, interpreting the results, and drafting the manuscripts. Dr. Abrahamowicz provided support regarding the statistical methodology, substantive and editorial feedback, and interpretation of results in the manuscript. Dr. Marelli and Dr. Liu were also involved in the discussions of the methodologies used and the interpretation of the findings. All co-authors critically reviewed the manuscript for important intellectual content.

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LIST OF ABBREVIATIONS

ACHD	Adults with Congenital Heart Disease
AIC	Akaike Information Criterion
ALARA	As Low As Reasonably Achievable
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
CanCHD	Canadian Congenital Heart Disease
CCI	Canadian Classification of Health Interventions
CCP	Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures
CCR	Canadian Cancer Registry
CHD	Congenital Heart Disease
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
CM	Congenital Malformation
CML	Chronic Myelogenous Leukemia
CT	Computed Tomography
CYP-C	Cancer in Young People in Canada
DAD	Discharge Abstract Database
GAM	Generalized Additive Model
GLM	Generalized Linear Models
HC	Hematopoietic Cancer
HIFa	Hypoxia-Inducible Factor Alpha
HR	Hazard Ratio
ICD	International Classification of Diseases
IR	Incidence Rate
IRR	Incidence Rate Ratio
KM	Kaplan-Meier
LAR	Lifetime Attributable Risk
LDIR	Low-Dose Ionizing Radiation

LNT	Linear No-Threshold
LSS	Life Span Study
MDS	Myelodysplastic Syndrome
MPN	Myeloproliferative Neoplasms
MSE	Mean Squared Error
mSv	MilliSieverts
NACRS	National Ambulatory Care Reporting System
NaN	Not a Number
NASEM	National Academies of Science, Engineering, and Medicine
OR	Odds Ratio
PAF	Population Attributable Fraction
PV	Polycythemia Vera
PY	Person-years
RAMQ	Régie de l'Assurance Maladie du Québec
SIR	Standardized Incidence Ratio
TMD	Transient Myeloproliferative Disease
US	United States
WCE	Weighted Cumulative Exposure

CHAPTER 1: INTRODUCTION

1.1. Overview

Congenital heart disease (CHD) is a congenital disorder in heart walls, valves, or blood vessels, representing nearly one-third of all congenital anomalies[1], and has a prevalence of approximately 9 per 1,000 live births in recent years.[2-4] The survival of children with CHD has increased,[5] thanks to the evolution in pediatric care and surgical therapies. Regardless of the continued improvement in prognosis and quality of life that the improved medical techniques offer, the concern about age-related non-cardiac disease morbidities in children with CHD remains.

The cancer risk in children with CHD is higher compared to the general pediatric population.[6-9] Among all childhood cancers, hematopoietic cancer (HC, cancers of blood and lymphatic cells and tissues) is the most common cancer, accounting for more than half of the cancer incidence among this vulnerable pediatric population. Therefore, elucidating the underlying pathways leading to the elevated cancer risk in children with CHD is necessary.

Genetic syndromes[10] and radiation exposure from cardiac imaging and therapeutic procedures[11] are suggested risk factors underlying the association between CHD and cancer. However, this multifactorial mechanism is poorly understood in this high-risk patient population due to the lack of consistent research findings. Several analytical approaches, including adjustment of syndromes in the regression model or excluding patients with syndromes, yielded conflicting findings.[6, 7, 12] Moreover, studies on the association of low-dose ionizing radiation (LDIR) and cancer among CHD children were challenged by insufficient sample size and follow-up time or methodological limitations. Furthermore, evidence on the threshold associated with LDIR and cancer incidence in children with CHD is scant. There is, therefore, a need for

research among children with CHD to provide evidence to guide CHD management in the high-risk population. Specifically, quantification of cancer risk among children with CHD and known genetic syndromes could help target high-risk patients who would require intensive monitoring and cancer surveillance; characterizing the association between cumulative LDIR exposure and cancer may inform the implementation of surveillance for patients and make judicious choices of imaging procedures to avoid the "malignant price of cardiac care";[13] exploring the threshold association will help determine the point at which radiation surveillance should be strengthened. The knowledge gained from this thesis could help outline guidelines for appropriate screening for cancer and surveillance modalities in CHD patients, which are currently non-existent.

1.2. Thesis Objectives

This doctoral dissertation aims to generate knowledge to improve CHD management in children while addressing the growing concern of cancer in this patient population. I proposed three objectives to accomplish this:

1. To assess HC risk in children with CHD, with and without known genetic syndromes.
2. To estimate the association between cumulative exposure to LDIR from cardiac imaging procedures and HC risk in children with CHD.
3. To investigate the threshold effect of LDIR exposure from cardiac imaging on HC risk in children with CHD.

1.3. Organization of thesis

This is a manuscript-based thesis, which includes three manuscripts, each with its research objective. I begin Chapter 2 by presenting the background on the current evidence of risk factors associated with cancer children CHD patients. I present the three manuscripts in Chapter 3, 4, and 5. Chapter 3 quantifies the risk of HC among children with CHD, with and without known

genetic syndromes (Manuscript 1). Chapter 4 describes the association between cumulative LDIR exposure from cardiac imaging and HC among children with CHD (Manuscript 2). Chapter 5 focused on exploring the threshold effect of LDIR exposure on HC among children with CHD (Manuscript 3). Finally, Chapter 6 provides an overall discussion of the findings, implications, and suggestions for future research. Tables and figures are presented at the end of each manuscript. References are placed at the end of the thesis.

CHAPTER 2: BACKGROUND

2.1 Children with Congenital Heart Disease

Congenital heart disease (CHD) is the most common birth defect worldwide, affecting millions of newborns annually.[2] It is typically defined as a gross structural abnormality of the heart walls, valves, or blood vessels that occur during embryonic development.[14] The birth prevalence of CHD increased from 0.6 (95% CI: 0.4 to 0.8) per 1,000 live births in 1930-1934 to 9.1 (95% CI: 9.0 to 9.2) per 1,000 live births in 2017, worldwide.[2] Similarly, a systematic review and meta-analysis by Liu and colleagues marked a substantial increase in birth prevalence of CHD worldwide: from 4.5 (95% CI: 3.7 to 5.5) per 1,000 live births in 1970-74 to 9.4 (95% CI: 8.6 to 10.2) per 1,000 live births in 2010-2017.[4] The prevalence of CHD in 2006 was 13.08 per 1000 live births in Taiwan.[15] In Canada, the overall CHD prevalence in 2010 was 13.11/1,000 in children.[16] A more recent systematic review found that the overall CHD birth prevalence in China increased continuously over time, from 0.20% in 1980–1984 to 4.9% in 2015–2019.[17] The increased prevalence of CHD may be due to improved diagnostic techniques, parental lifestyles, changes in genetic and environmental factors[18], or a combination of these factors.[17]

Despite the continued improvement in prognosis and quality of life owing to improved medical techniques, the age-related non-cardiac disease morbidities in children with CHD are of concern.

2.2 Cancer in Children with CHD

Cancers in children typically differ from those in adults. In the general pediatric population, the most frequent cancers are embryonal, or hematopoietic.[19, 20] Data from the Cancer in Young People in Canada (CYP-C) surveillance system estimated an age-standardized incidence rate of 4.9 per 100,000 children aged less than 15 years for leukemia and 2.0 per 100,000 for

lymphoma, between 2001 and 2006.[20] In children with CHD, the incidences are expected to be higher owing to shared genetic and environmental factors.[10] However, conflicting findings regarding the association between CHD and cancer in children have been reported. In a population-based cohort study of 5.2 million children in Norway and Sweden, the standardized incidence ratio (SIR) of cancer in patients with CHD was not significantly higher than in the general population.[21] On the contrary, several observational studies reported an elevated cancer risk among children with CHD.[6-9, 12, 22] More recently, using Swedish Health Registers, a matched case-control study among children born between 1930 and 2017 was conducted. The authors reported a 4-fold higher incidence of HC in children with CHD compared to the healthy control (Incidence rate, IR: 2.20 vs. 0.50 per 100,000 person-years).[7] Similarly, a population-based cohort study identified 4,178,722 children born between 1973 and 2014 in Sweden—including 66,892 children with CHD.[6]The study showed that children born with CHD were at increased risk of leukemia, lymphoma, and hepatoblastoma compared to non-CHD children.[6] Moreover, a population-based nested case-control study was conducted in the Nordic countries (Denmark, Finland, Norway, and Sweden) to compare 62 295 cancer cases (0-46 years) and 72 4542 frequency-matched controls (matched on country and birth year), born between 1967 and 2014.[23] Cancer risk was 53% higher in children with CHD compared to the matched controls (OR=1.53; CI: 1.26 to 1.86).[23] Using the Danish National Hospital Registry and the Danish Cancer Registry, Sun and colleagues[22] identified 1,547,126 children who entered the cohort at birth regardless of when the congenital malformation (CM) was diagnosed between 1977 and 2007 and reported weaker associations in the subtypes of CHD.[22] In the context of the North-American patient population, Lupo et al. [24] conducted a multistate, population-based registry linkage study combining statewide data on births, birth defects, and cancer from Texas,

Arkansas, Michigan, and North Carolina.[24] The study included 10 181 074 children born from 1992 to 2013 and reported an increased hematopoietic cancer risk associated with CHD compared to children without a birth defect.[24] However, the association was weaker depending on the cancer type, owing to insufficient sample size.[24] A population-based cohort study conducted in 3 US states observed a similar trend of increased cancer risk.[25] Comparing 11,211 children aged less than 15 years with non-chromosomal CHD with a cohort of 147,940 matched children, the study reported a 3-fold higher cancer incidence in patients with CHD relative to the reference cohort (IRR 2.9, 95% CI 1.9-4.3).[25] In Taiwan, a nationwide population-based cohort study identified 31,961 patients with a recent CHD diagnosis from 1998 to 2006 and reported a significantly elevated risk of hematologic malignancies (SIR 4.04, 95% CI 2.76-5.70) compared to the general population.[25]

Thus, the high cancer risk, especially hematopoietic cancers, in children with CHD highlights the necessity of further research for a better understanding of the common underlying mechanisms, giving particular attention to the associated risk factors is compelling.

2.3 The knowledge gaps

Congenital anomalies and cancer are associated due to shared genetic and environmental factors. However, the relationship between CHD and HC risk remains conflicting and poorly understood. While the suggested biological mechanisms underlying such a relationship include shared genetic syndromes, radiation exposure from imaging, and therapeutic cardiac procedures, many research questions regarding these risk factors remain. There is a paucity of large population-based risk estimates of HC incidence in the presence of known genetic syndromes among children with CHD. More evidence on the LDIR-induced HC risk in CHD children is required for whom longitudinal follow-ups are available. Moreover, identifying a possible

threshold effect is significant for policy recommendations to improve prevention. It is crucial to comprehensively understand the current evidence on the risk factors for carcinogenic outcomes among CHD children to stratify high-risk patients. Therefore, my thesis focuses on the risk factors of HC among children with CHD.

2.4 Genetic syndromes as a risk factor for cancer in CHD patients

The current body of evidence points to shared genetic abnormalities impairing normal development that could manifest both birth defects and cancer predisposition.[26] Studies confirmed that CHD is one of the co-occurring medical conditions associated with Down syndrome.[27, 28] In a recent review, Santoro and Steffensen reported a total prevalence of CHD ranging from 20 to 58% in the population with Down syndrome.[29] Moreover, around 10-20% of cases of CHD can be attributable to known chromosomal abnormalities, including Down syndrome, Noonan syndrome, 22q11.2 deletion syndrome, Edwards syndrome, Turner syndrome, Klinefelter syndrome, non-syndromal single-gene disorders, or teratogens. Regarding malignancies, the most common syndrome with a 10- to 20-fold higher risk of leukemia in the general children population is Down syndrome.[30-34] Deletion of 22q11.2 and renin-angiotensin system pathologies (RASopathies) could also manifest as both CHD and a predisposition to cancer. [10] However, studies exploring the association between risk of leukemia and major congenital anomalies reported relatively weaker or no evidence of increased risk of leukemia in children after excluding patients with Down syndrome.[12, 25, 35-40] Using the Danish National Registry of Patients, Olsen et al. observed no significant elevation in overall cancer risk among children with CHD when patients with Down syndrome were excluded.[12]

Similar attenuated associations between CHD and cancer, primarily leukemia, were observed in studies adjusted for Down syndrome in the regression models.[6, 32, 41] However, more

recently, Karazisi and colleagues reported an elevated risk of childhood cancers among children with CHD, even after excluding the patients with syndromes and organ transplant patients from the analytical cohort.[7] Similar to this finding, Rankin et al. also noted that the association between congenital anomalies and childhood leukemia remained after the exclusion of Down Syndrome.[42] Surprisingly, however, in Taiwan, a nationwide population-based cohort study on newly diagnosed CHD patients between 1998 and 2006 observed that chromosomal anomalies were not a risk factor for cancer.[8] Therefore, the role of known genetic syndromes on cancer incidence, particularly HC among children with CHD, needs further exploration to provide substantial additional prognostic insight.

Thus, the first objective of this thesis is to quantify the risk of HC by the presence of genetic syndrome among children with CHD.

2.5 Low-dose ionizing radiation and malignancy in children with CHD

2.5.1 Exposure to ionizing radiation is on the rise

Another potential risk factor for increased risk for cancer among children with CHD is exposure to low-dose ionizing radiation from cardiac imaging. Medical diagnostic and therapeutic procedures using ionizing radiation have proliferated over the past decades. In the general pediatric population, 42% of 355,088 patients underwent at least one imaging procedure, including chest x-rays, computed tomography (CT) scans, or nuclear scans.[43] The number of medical procedures using ionizing radiation grew at a compound average growth rate of 2% per year in the US.[44] In comparison, the collective dose grew at an average compound rate of 8% per year from 1980 to 2006. [44] Notable increase in the use of cardiac catheterization for therapeutic interventions was observed in children,[45] with higher doses of radiation owing to technical complexity and prolonged fluoroscopy.[46] This is particularly relevant in CHD patients with a

lifelong chronic disease requiring repeated interventions. In a longitudinal population-based study conducted by our group, we showed that the number of LDIR-emitting cardiac procedures rose from 18.5 to 51.9 per 1,000 CHD patients per year between 1990 and 2005, with a decreased median age at the first LDIR procedure among children with CHD from 5 years to 9.6 months.[47]

Thus, supported by previously published data on the general and CHD pediatric populations, the potential carcinogenic effect of ever-growing LDIR exposure from cardiac imaging needs further exploration.

2.5.2 Association between LDIR and cancer risk in children with CHD

Studies in general pediatric populations exposed to radiation from medical imaging, particularly from CT, suggested an increased cancer risk.[11, 48-56] Leukemia is an established radiogenic malignancy with the shortest latency among all cancer types that can appear sooner than any other cancer, particularly among children.[57, 58] In the general population, there is substantial evidence of the radiation-related excess risk for major subtypes of leukemia, particularly acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL).[55, 57, 59] Recent evidence also suggested that radiogenic risk was associated with myelodysplastic syndromes.[55] The evidence on the association between LDIR and lymphoma, especially non-Hodgkin lymphoma (NHL), was mixed and thus remained inconclusive.[60, 61] While several studies on medical exposure reported NHL to be associated with ionizing radiation,[49, 62-64] others suggested otherwise.[65-67] The evidence on chronic lymphoblastic leukemia (CLL), mostly coming from LSS studies, suggested CLL be non-radiogenic. [58, 68] Multiple myeloma, another subtype of NHL,[69] was documented to be non-radiogenic,[62, 67] so was Hodgkin lymphoma (HL).[53, 70]

Due to repeated exposure to LDIR-related procedures, coupled with high sensitivity to radiation effects, children with CHD have an increased risk for developing radiation-induced cancers than general pediatric population patients.[71] Unlike the association between LDIR and cancer in the non-CHD pediatric population, the association in CHD patients, particularly among children, is not well explored. Currently, no study exists assessing whether radiation exposure during cardiac imaging procedures in children with CHD is independently associated with cancer risk. A few studies compared the cancer incidence in children with CHD who underwent at least one cardiac catheterization with the general population.[72-76] However, due to the absence of an appropriate comparison group of unexposed-to-radiation children with CHD, these studies could not assess whether the increased cancer risk was due to radiation exposure or other cancer-predisposing factors that have been reported in patients with CHD. Moreover, the findings of these studies were conflicting: A retrospective cohort study conducted in Canada among children who had at least one cardiac catheterization procedure between 1950 and 1965 did not demonstrate a significant increase in leukemia risk,[74] while others observed increased cancer risk in children exposed to radiations, with an excess mainly due to the higher incidence of leukemia, lymphoma, and melanoma.[73, 75] More recently, an observational study on the cohort of children who underwent cardiac catheterization in German[76] reported an increased cancer risk in the first year of life compared to the general population. Similarly, a French cohort reported increased risks for all cancer, leukemia, and lymphoma among children with CHD compared to the general population, without a dose-response analysis.[72] Most of these studies were insufficiently powered due to the small sample size. Other shortcomings include short follow-up time, insufficient radiation-induced latency, failure to account for diagnostic workup for cancer, risking 'reverse causality' bias, and indication bias.[10, 11, 77] Therefore, the evidence on the

association between LDIR from cardiac imaging and HC incidence in CHD children is inadequate and inconclusive. Uncertainty regarding which subtype of hematopoietic cancer is associated with radiation in children with CHD also exists. Although a credible body of evidence exists in the general pediatric population, dedicated research efforts within the CHD population are warranted.

Therefore, the second objective of the thesis is to explore the potential association between timed-dependent cumulative exposure to LDIR from cardiac imaging and HC incidence in children with CHD.

2.6 Threshold effect of LDIR exposure from cardiac imaging

The line of evidence on the stochastic effect of low-dose ionizing radiation comes from the sources of data on atomic bomb survivors, environmental studies, medical studies, and occupational studies.[56, 78, 79] Although extrapolating the acute effect of the atomic blast to the protracted effect of medical radiation is challenging, studies suggest that repeated medical imaging can be as harmful as getting an equivalent acute dose.[80] Followed by an extensive literature review, Brenner et al. concluded that there was good epidemiological evidence for an increased risk of malignancy in humans from medical diagnostics and procedures for prolonged exposures down to 50-100 mSv.[80] Assessing the cancer risk at the low dose range from medical exposure remained challenging. However, most studies exploring the association between low-dose ionizing radiation and cancer were based on the arguable linear no-threshold (LNT) dose-response model assumption. The national and international regulatory and advisory bodies adopt the LNT model for radiation-induced cancer based on the principle that there is no safe level of radiation.[80] While several observational studies reasonably fit the data with LNT model,[81] others argued against it, stating that it does not account for credible evidence of the threshold for cancer induction.[82-85] Studies on LSS

survivors aimed to explore the dose-response for leukemia suggested non-linearity (upwardly curved), with some indication of threshold dose.[86-88] However, an absence of threshold had also been suggested in favor of LNT model.[89] Nonetheless, the question about the potential threshold effect of LDIR exposure from cardiac imaging on HC risk in children with CHD remained unanswered.

Thus, the third objective of this thesis is to explore the threshold association between cardiac LDIR exposure and HC among children with CHD.

2.7 Summary

In sum, children with CHD are at greater risk of developing childhood cancers. There is a paucity of data on the underlying risk factors of hematopoietic cancers, primarily genetic syndromes and LDIR exposure in children with CHD. Based on a large, longitudinal database of the CHD population across Canada, the findings of this thesis should inform surveillance guidelines aimed at CHD management in children while addressing the growing concern of cancer in this patient population.

CHAPTER 3: Manuscript 1- The Canadian Congenital Heart Disease (CanCHD) study of Hematopoietic Cancers in Children with and without Genetic Syndromes

3.1. Preface

The first manuscript presents the results of a descriptive study describing the cumulative incidence of hematopoietic cancer in children with CHD, with and without genetic syndrome. I intended to assess the cancer risk in children with CHD compared with the risk in the general pediatric population in Canada. To this end, I estimated the standardized incidence ratio (SIR) using the incidence rate of cancer among the general pediatric population obtained from Canadian Cancer Registry (CCR) database. In addition, I used a modified Kaplan-Meier (KM) approach to evaluate the cumulative incidence of HC, adjusting for death as a competing event. Genetic syndrome-specific incidence rate was also estimated. The findings can provide evidence for clinicians to be aware of the additional risk associated with the presence of genetic syndrome in a CHD patient and be vigilant about the symptoms associated with HC.

This manuscript is now under revision for the *Journal of American Heart Association (JAHA)*, as of March 29, 2023.

3.2. TITLE PAGE

The Canadian Congenital Heart Disease (CanCHD) Study of Hematopoietic Cancers in Children with and without Genetic Syndromes

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3.3. ABSTRACT

Background: Individuals with genetic syndromes can manifest both congenital heart disease (CHD) and cancer due to possible common underlying pathways. However, reliable risk estimates of hematopoietic cancer (HC) among children with CHD based on large population-based data remain scant. This study sought to quantify the risk of HC by the presence of genetic syndrome among children with CHD.

Method: A nationwide database on CHD (1999-2017) was created by merging the Canadian Institute for Health Information -Discharge Abstract Database with the Quebec CHD database. Hematopoietic cancer and syndromes were identified by ICD9/10 codes from hospitalization diagnoses. HC incidences in children with CHD were compared to the general pediatric population using the Canadian Cancer Registry (CCR), and standardized incidence ratios (SIR) were calculated. A modified Kaplan-Meier curve analysis was used to estimate the cumulative incidence of HC with death as a competing risk.

Result: A total of 143,794 children (age: 0-17) with CHD were followed from birth up to age 18 for 1,314,603 person-years. Of them, 8.6% had genetic syndromes, and 898 HC cases were observed. Children with known genetic syndromes had a substantially increased risk of incident HC compared to the general population (SIR=13.4; 95% confidence interval [CI]: 11.7-15.1). The cumulative incidence of HC up to age 18 was 2.44% (95% CI: 2.11-2.76%) among children with a genetic syndrome and 0.79% (95% CI: 0.72-0.87%) without a syndrome. The incidence was higher in the first six years of life than in the subsequent 6-year intervals up to adulthood. Acute myeloid leukemia had a higher cumulative incidence during early childhood than acute lymphoblastic leukemia.

Conclusion: This is the first large population-based analysis documenting that known genetic syndromes in CHD children are a significant predictor of HC. The finding could be essential in informing risk-stratified policy recommendations for cancer surveillance in children with CHD.

3.4. INTRODUCTION

The prevalence of congenital heart disease (CHD) in children has increased steadily, with a population-based study demonstrating an increase of 11% between 2000 and 2010.[16] A growing number of children are becoming adults with a longer time window to express morbidities associated with birth defects.[90] There is an increasing need to understand these morbidities better to provide data for early detection and intervention.

Children and young adults with CHD have an increased risk of developing cancer. A large registry-based prospective cohort study with 21,982 children and young adults with CHD and 219,816 healthy matched controls reported a hazard ratio of 2.24 (95% CI, 2.01-2.48) for the cancer risk associated with CHD.[9] In this study, CHD-associated cancers were predominantly in the hematologic system, central nervous system, and head and neck.[9] The underlying causes of the CHD-cancer association were likely to be multifactorial, including shared genetic mutation[8, 10], radiation exposure from medical imaging[6, 7, 48-50, 52-54, 56, 73, 75, 80, 91-97], and genetic syndromes[10, 12]. In particular, Genetic predisposition has been considered as a major contributing factor to the elevated CHD-cancer risk because chromosomal abnormalities are often found in the pediatric CHD population[98, 99] and are thought to be associated with increased risks of developing certain types of hematopoietic cancers (HC) in the general pediatric population.[100-104] Nevertheless, research focusing specifically on HC in pediatric patients with CHD has remained sparse, with conflicting findings[6-8, 12]. To meet this knowledge gap, our group sought to investigate the incidence of HC among patients with CHD with or without genetic syndromes.

3.5. METHODS

Data Sources

We created the Canadian CHD (CanCHD) database by merging data between the Quebec CHD database and CHD data from Canada's other 12 provinces and territories to comprise 495,000 patients from birth to late adulthood, with CHD from across the country followed for up to 35 years.

In Quebec, Canada, a unique Medicare number is assigned to every individual at birth to systematically link all medical services delivered during a patient's life until death. Using this unique healthcare number, we developed a population-based cohort of CHD patients from 1983 to 2017, linking the province's three administrative databases- the hospital discharge database (Med-Echo), the medical service claim database (RAMQ), and the vital status database.[105] Thus, the resulting Quebec CHD database contains comprehensive longitudinal information on all demographic, diagnostic, and therapeutic records for all Quebec residents with CHD between January 1, 1983, and March 31, 2018 inclusive.

Hospital discharges and day surgeries in all Canadian provinces except Quebec are contained in the CIHI- Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS). All diagnoses, demographic characteristics, and in-patient diagnostic and therapeutic procedures for all hospital encounters between January 1, 1999, and March 31, 2018, are recorded in these two databases. Similar to the Quebec CHD database, unique IDs can be obtained for each patient to link different hospitalization records in these databases. From them, records on patients with at least one diagnosis of CHD were extracted and combined with the Quebec CHD database to develop the Canadian Congenital Heart Disease Database (CanCHD database) for the overlapping years (1999-2017). The pooled CanCHD

database thus provided longitudinal information of all hospital encounters of CHD patients across Canada for two decades. In the database, the diagnosis codes were based on the *International Classification of Diseases, 9th Revision* (ICD-9) and *10th revision* (ICD-10, since 2006), and the treatment codes were based on the *Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures* (CCP), *Canadian Classification of Health Interventions* (CCI, since 2006), and act codes (for Quebec only).

In Canada, each province and territory is mandated to collect, control, and therefore report all primary malignant cancers among Canadian residents to Statistics Canada to populate the Canadian Cancer Registry (CCR). The CCR describes both the individual with cancer and the characteristics of cancer, including the type and number of primary cancers diagnosed for each person. It has been estimated that the CCR captures at least 95% of all incident cancer cases in Canada.[106] For the purposes of calculating the SIRs, incident cases of hematopoietic cancer (Supplementary Table S3. 1 for cancer codes) diagnosed between 1999 and 2017 were identified.

Study Population

We identified all patients in the CanCHD database who were children (0-17 years) between 1999 and 2017 (Figure 3. 1). Those with unavailable CHD diagnosis codes were excluded. In order to have complete data on hospitalization records since birth, the study population was limited to children born during the observation period (1999-2017) and followed since birth.

Measurements

HC incidence was defined as the first hospitalization with a primary or secondary discharge diagnosis of primary HC. Hematopoietic cancer was categorized as follows: Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML), Polycythemia vera (PV), Myelodysplastic syndrome/ Myeloproliferative neoplasms (MDS/MPN), Unclassified leukemia (non-specific

diagnoses and diagnoses that are unusual in children) and Lymphomas (Table S3. 2). Genetic syndromes were defined as a binary indicator (yes/no) having a hospital discharge diagnosis of any genetic syndrome during the observation period (Table S3. 3). CHD lesions were grouped as follows: Severe CHD lesions (Truncus arteriosus, Transposition complex including complete and congenitally corrected, Tetralogy of Fallot, Univentricular heart including hypoplastic left heart syndrome, Endocardial cushion defect, Ebstein anomaly) and other CHD lesions (atrial or ventricular septal defects, patent ductus arteriosus, aortic coarctation, anomalies of the pulmonary artery or valve, congenital tricuspid valve disease, congenital aortic or mitral stenosis or insufficiency, anomalies of the great veins, and unspecified anomalies of the heart or aorta).

Study Design

We defined a retrospective, population-based cohort of children born in the observation period. Individuals were followed from birth until the earliest of March 31, 2018, first HC diagnosis, heart transplant, death, or the 18th birthday.

Statistical Analysis

Characteristics of the study population, stratified by genetic syndrome status, were described using proportions, medians, and interquartile ranges.

The incidence of cancers in children with CHD was compared with those in the Canadian general pediatric population using the standardized incidence ratio (SIR). The SIR refers to the ratio of observed to expected incident cancer, where 'expected' is the number expected to occur if CHD children were subject to the same cancer risk as the general population. 95% confidence intervals (CI) for the SIRs were calculated assuming a Poisson distribution.[107]

Overall and HC subtype-specific (ALL and AML) cumulative incidence was estimated using modified Kaplan-Meier curve analysis [108] (with 95% confidence intervals, CI) up to 18 years of

age, with death as a competing risk and stratified by the genetic syndrome status. Lifetime cumulative incidence from different baseline ages (0, 6, and 12 years) was estimated. The CHD lesion-stratified cumulative incidence of HC with and without the genetic syndromes was also estimated. Overall and syndrome type-specific incidence rates of HC were estimated with 95% CI computed based on the Poisson distribution. The population attributable fraction (PAF) was calculated using adjusted incidence rate ratio (IRR) assuming a Poisson distribution.[109, 110] The corresponding 95% confidence intervals were estimated using a non-parametric bootstrap method.[111]

Statistical analyses were performed using SAS software 9.4 (SAS Institute Inc).

3.6. RESULTS

Baseline Characteristics

A total of 143,794 children born between January 1, 1999, and March 31, 2018, were identified and followed since birth for 1,314,603 person-years. In this population, 8.6% had genetic syndromes, and 898 HC cases were observed (Figure 3. 1). The characteristics of the study population are presented in Table 3. 1. Patients with a genetic syndrome had a higher proportion of HC than patients without a genetic syndrome. This higher cancer proportion in the syndromic group was also observed in various HC categories, except lymphomas. Patients with genetic syndromes were hospitalized with HC earlier following birth than their non-syndromic counterparts. More children with genetic syndromes had severe CHD lesions than those without syndromes.

Risk of HC compared to general pediatric populations

There were 251 observed cases of HC in the study versus the 18.8 cases that were expected based on general pediatric population rates (SIR = 13.4, 95% CI = 11.7, 15.1 in Table 3. 2). Down syndrome, Noonan's syndrome, and Alagille's syndrome had elevated ratios in this patient population, and the highest was for Down syndrome (SIR = 23.2, 95% CI = 20.2, 26.9).

Cumulative Incidence of Hematopoietic Cancer

From the mortality-adjusted Kaplan-Meier curve analysis, the overall cumulative incidence of developing hematopoietic cancers from birth to 18 years of age was 2.44% (95% CI: 2.11-2.76%) among children with a genetic syndrome and 0.79% (95% CI: 0.72-0.87%) without the syndrome (Figure 3. 2). The cumulative incidence for Down syndrome was 4.16% (95% CI: 3.53-4.79%) while was 1.10% for Noonan's syndrome (95% CI: 0.57-1.63% in Figure 3. 2). These correspond to the incidence rate of 2.2 (95% CI: 2.0-2.5) for all syndromes, 3.9 (95% CI: 3.4-4.5) and 1.0 (95% CI: 0.6-1.6) per 1000 person-years for Down syndrome and Noonan's syndrome with CHD patients, respectively (Table 3. 3). Down syndrome contributes most to the overall risk and incidence rate estimates since around 45% of patients with known genetic syndromes were diagnosed with down syndrome (Table 3. 3).

The syndrome-stratified mortality-adjusted cumulative incidence at age 0, 6, and 12 depict that most HC cases occur within the first six years of life (Table 3. 4). In syndrome strata, the cumulative incidence was 1.89% (95% CI: 1.64-2.14%) up to 6 years following birth whereas, it was 0.30% (95% CI: 0.17-0.42%) and 0.28% (95% CI:0.10-0.46%) from 6-12 and 12-18 years, respectively. Among the children without any syndrome, the cumulative incidence was 0.36% (95% CI: 0.32-0.39%), 0.20% (95% CI: 0.16-0.23%) and 0.25% (95% CI: 0.20-0.31%) from birth to 6 years, 6-12 years, and 12-18 years, respectively.

The stratified analyses of hematopoietic cancer sub-types (ALL and AML) showed that AML had a higher incidence risk during early childhood than ALL (Figure 3. 3). In panel A, a more consistent accumulation of new ALL cases was observed following birth to age 18. In contrast, for AML in panel B, most cases occurred between 2-3 years following birth.

The severity-specific cumulative incidences of HC up to 18 years are presented in Figure 3. 4 (A-B). The cumulative incidence was 3.02% (95% CI: 2.32-3.71%) in the severe CHD lesion group with a genetic syndrome and 2.23% (95% CI: 1.87-2.60%) in the non-severe CHD lesion group. The estimated population attributable risk was around 20%, assuming causality (PAF: 21.2%; 95% CI: 20.0-22.1%).

3.7. DISCUSSION

This is the first nationwide study in a pediatric CHD population to quantify HC incidence among syndromic and non-syndromic patients. Our results demonstrated that CHD patients with genetic syndrome have a higher risk of HC with an earlier diagnosis age than those without a genetic syndrome. By the age of 18, 2.44% of syndromic patients had a diagnosis of HC, whereas 0.79% of non-syndromic patients had the same. Most patients with known genetic syndromes were diagnosed with Down syndrome, followed by Noonan's syndrome. Analysis of HC sub-types showed that non-syndromic patients most commonly developed ALL and lymphomas. On the other hand, syndromic patients' HC was distributed similarly between ALL, AML, and MPN/ MDS. It is worth noting that the cumulative incidence in ALL showed a trend of progressive accumulation by age. In contrast, AML showed a steep rise in cumulative incidence between ages 0 and 3 in syndromic patients.

Our study showed an elevated risk of HC among children with CHD. The SIR for all known genetic syndromes was 13 times higher compared to the general pediatric population in Canada. The reported risk was more pronounced in Down syndrome patients. Indeed, in a Finnish population-based study, patients with Down syndrome were at higher risk of leukemia (SIR 10.5; 95% CI: 6.6, 15.8) than the general population. A Danish registry-based study reported an 18-fold increased risk of leukemia in patients with Down syndrome (SIR: 17.6; 95% CI: 12.4, 24.4) compared to the general population.[32] The possible reason for our higher SIR is the co-existence of CHD and genetic syndrome in this stratum owing to an additive effect. However, a Danish nationwide cohort study comparing the cancer incidence among CHD patients with Down syndrome and the general population reported a SIR of 1.63 (95% CI: 1.22, 2.13), much lower than our study. However, this study might not be directly comparable with our study in terms of the cohort being studied. Their primary study cohort included CHD patients (all age groups) both with and without syndrome, while ours included CHD children with known genetic syndromes, resulting in higher risk estimates. Moreover, we estimated the expected number of HC cases based on age- and HC cancers-specific incidence rates in CCR rather than all cancer incidents.

Our study demonstrated a three-fold increase in the risk of HC associated with genetic syndromes among children with CHD. Scientific literature has reported an increased risk of cancer, especially HC, for the general CHD population, including children[9, 35, 47, 77]. However, the findings on the role of known genetic syndromes on cancer incidence remained inconsistent. Epidemiological studies taking congenital anomalies, especially Down syndrome into account in the regression models reported an insignificant association between CHD and cancer incidence.[6, 32, 41] On the contrary, a nationwide population-based cohort study from Taiwan showed that

chromosomal anomalies were not a risk factor for cancer.[8] A recent Swedish matched cohort study reported an elevated cancer risk among CHD patients compared to healthy controls, even after excluding patients with syndromes and organ transplant recipients.[7] These findings were consistent with a population-based cohort study from California, suggesting elevated total childhood cancer and lymphoma risks in CHD patients after excluding chromosomal anomalies.[35] However, since the study population did not include patients with chromosomal anomalies, the consistency of the anticipated association with other studies in the presence of such anomalies could not be examined. In a population-based Danish cohort study, however, CHD-cancer association was explained away after excluding Down syndrome patients.[12] To this end, our findings corroborate that of the Swedish study[6], which reported Down syndrome as a risk factor for cancer in patients diagnosed with CHD at birth. The co-existence of CHD and genetic syndromes could confer an even higher risk for this type of malignancy through an additive effect. Indeed, we estimated that around one-fifth of the hematopoietic cancer cases could be attributed to known genetic syndromes among the CHD pediatric population, assuming causality. The presence of a genetic syndrome and CHD could indicate that a more extreme disturbance of the underlying genetic pathways exists. These diseases are believed to share common pathways such as RASopathies, notch signalling disorder, and chromosomal abnormalities.[100-104, 112] The genetic pathways have been thought to increase the risk of HC through dysregulated hematopoietic processes[103, 113, 114] Moreover, the pediatric CHD population is thought to have unique environmental exposures. There has been evidence suggesting an association between cardiac low-dose ionizing radiation (LDIR) exposure and long-term chromosomal damage.[92] Radiation from imaging has been shown to increase the risk of HC in children.[115, 116] In this sense, it may be hypothesized that the risk of HC in pediatric CHD patients

with the genetic syndrome is due to a combination of genetics and CHD-specific exposures such as radiation. [11, 49, 51, 54, 73] Moreover, it is conceivable that there exists an unknown environmental factor that causes both the syndrome and HC. However, which specific environmental factors cause the genetic syndromes studied here are currently unknown and, therefore, could not be adjusted for. It is also unlikely that such a factor would be a strong confounder because this would require an important influence on the syndrome and the cancer outcome, and current research has identified few such examples. [117] Medical comorbidities, on the other hand, can be caused by genetic syndrome, but cannot cause a genetic syndrome, nor does it seem plausible that they are both affected by an unmeasured common cause. Therefore, comorbidities are most likely to be downstream of the exposure, and should not be adjusted for as confounders.[118]

HC subtypes analysis showed more differences between syndromic and non-syndromic CHD patients in HC incidence. The two groups had different ALL to AML ratios than the general population, but the ratio for the non-syndromic group was much closer to that in the general population than the syndromic group.[119] Specifically, our data shows a 1:1 ratio for ALL to AML incidence in the syndromic CHD group, while a predominance of ALL with a ratio of ALL to AML of 4:1 was observed in the non-syndromic CHD group, closer to the ratio of 5.7:1 reported for Canadian children between 1992 and 2010.[119] These findings suggest that the drivers of carcinogenesis in non-syndromic patients with CHD are similar but not limited to that of the general population. This may be due to a combination of CHD-associated exposures, genetic and environmental factors.[101] As for the syndromic CHD group, genetic syndrome is probably one of the most important drivers of carcinogenesis.

Our study also observed that MPN and MDS are present in different proportions between syndromic and non-syndromic CHD patients. We specifically differentiated MPN from PV due

to the fact that our databases do not have codes to distinguish primary from secondary PV. The latter disease could result from the hypoxic conditions found in severe CHD.[120] Studies have suggested that MPN and MDS are rare diagnoses in the general pediatric population.[121, 122] Nevertheless, these studies have noted that cytogenetic abnormalities, especially chromosomal duplications, are frequently found in these diseases. The role of genetics in the development of childhood MDS has been recognized as a significant factor.[123] The case for genetic contribution in MPN remains possible.[121] The genetic syndromes frequently found in CHD, such as trisomy 18, trisomy 21, DiGeorge syndrome, and others, could represent a population group at risk for developing MDS or MPN. Moreover, these diseases have been known to occasionally evolve into AML or other types of HC.[124, 125] This could also increase the cumulative incidence of AML and alter the HC subtype distribution in CHD patients with genetic syndrome.

The syndromic and non-syndromic CHD groups showed differences in the pattern of cumulative AML risk increase along follow-up time. In the non-syndromic group, the increase was progressive but consistent. The syndromic group showed a more rapid rise and an earlier in-life peak of AML. The etiology of childhood AML remains largely unknown; however, research looking specifically at trisomy 21 suggests that myelogenous leukemogenesis often occurs through a distinct pattern of mutation acquisition.[103, 126] In these cases, the pathogenesis of AML is often preceded by transient myeloproliferative disease (TMD).[127] Similar pathways may exist in other genetic syndromes though has not been formally studied. Environmental exposures could accelerate the pattern of mutation acquisition towards the development of AML in this sub-group, especially in states of TMD that could represent a time of heightened genetic vulnerability. This could possibly explain the rapid accumulation of AML early in life for syndromic patients.

Our study results showed that most HC diagnoses occur before the age of 6 years, irrespective of syndrome status. It has been reported that the early age of onset of cancer in childhood increases the likelihood of the presence of a genetic component.[128] In this sense, the altered molecular pathways specific to pediatric CHD could be hypothesized to predispose this group to cancer. The commonly involved pathways in CHD, such as notch signaling and production of hypoxia-inducible factor alpha (HIFa) have been suggested to increase the risk of HC.[116, 129-133] Nevertheless, specific environmental exposures related to the management of CHD could increase the incidence of HC. Our data suggested that the syndromic group has a significantly higher proportion of severe CHD than the non-syndromic group. Currently, evaluation for correction of severe cardiac anomalies in children generally favors an earlier age for surgery.[134] In this sense, early surgery and associated exposures such as radiation could contribute to HC in this population group. Research in the adult CHD population shows that cardiac LDIR is associated with cancer.[135] Similar studies in children are contradictory and do not evaluate genetic syndromes as a subgroup.[74, 75, 136] Nevertheless, more recent data shows that the pediatric CHD population is exposed to significant doses of cardiac LDIR.[47] Further research is warranted to evaluate environmental exposures in the pediatric CHD population with specific subgroup analysis for patients with genetic syndromes.

Limitations

Several limitations were inherent to our study. A significant limitation is that it was based on administrative data. As previously validated and published by our group, we used diagnostic and procedural codes pertinent to CHD in the administrative databases to identify CHD patients.[105] We defined severe CHD lesions as those with the highest probability of being associated with cyanosis at birth or requiring surgical intervention early in life.[105] This yielded 9.1% of the total CHD

patients in our dataset, a slight under-representation (~13%) of the same in the global context.[4] Using only in-hospital codes might explain the under-representation. In the CCR database, incidence data from the province of Quebec after 2010 were not available and thus limits our study. To this end, we assumed that the incidence rate in Quebec is similar to that observed in the rest of Canada, a conservative but necessary assumption to have some approximation to estimate complete national cancer statistics. We lacked clinical information for this large study population in our database. The availability of such data would have made exploring the underlying molecular pathways regarding the overwhelming presence of Down syndromes in our study population or predominance of AML incidences, for example, possible. The data on death is not complete as we included only in-patient deaths. Therefore, our adjustment for mortality as a competing event might not fully account for the potential overestimation. In addition, some hematopoietic cancer cases might be underreported since they did not require hospitalization. However, using in-patient data to define hematopoietic cancer is less subject to misclassification due to its high data quality.[137, 138] Lastly, our study was not designed to analyze causal inference, such as the effect of genetic syndrome on cancer outcome, requiring not only the absence of confounding but also a means to assign the exposure, which is questionable for genetic syndromes [139]; our focus was on estimating the factual proportion of HC cases among CHD patients with or without specific genetic syndrome.

Children with CHD and genetic syndromes have a higher incidence of HC than those without genetic syndromes. The two groups were also different in HC subtype distribution, where the syndromic group had a higher proportion of ALL, PV, MDS/MPN, and unclassified leukemia than the non-syndromic group. There is evidence to suggest a strong genetic component to the carcinogenesis of syndromic CHD patients. Our findings suggest the necessity of cancer

surveillance for the detection and effective clinical management of CHD patients with syndromes at as early an age as possible. Future studies are needed to examine the contribution of certain environmental exposures to the cancer incidence of these CHD groups.

ACKNOWLEDGMENTS

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DISCLOSURES

All authors declare no conflict of interest.

TABLES

Table 3. 1 Clinical characteristics of the study population, by genetic syndrome status

Characteristics	With Syndrome (n=12,169)	Without Syndrome (n=131,625)
Total person-years	112,479	1,202,124
Male, %	50.7	52.7
HC, %	2.06	0.49
ALL, %	0.63	0.24
AML, %	0.60	0.06
Unclassified leukemias, %	0.38	0.03
Polycythemia vera, %	0.20	0.02
MPN/MDS, %	0.58	0.06
Lymphomas, %	0.05	0.09
Median age at first HC, year (IQR)	1.10 (0.00-3.00)	4.00 (1.80-7.50)
Severe CHD*, %	25.68	7.71

*Includes: Truncus arteriosus, Transposition complex including complete and congenitally corrected, Tetralogy of Fallot, Univentricular heart, Endocardial cushion defect, Ebstein anomaly, and Hypoplastic left heart syndrome.
CHD indicates congenital heart disease; HC, hematopoietic cancers; ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; IQR, Inter-quartile range; MPN, Myeloproliferative neoplasms; MDS, Myelodysplastic syndrome

Table 3. 2 Standardized incidence ratios (SIR) for HC in children with CHD compared to the general population, with and without genetic syndromes

Syndrome status and types	Observed no. of HC	Expected no. of HC	SIR	(95% CI)
All Syndrome	251	18.8	13.4	(11.7-15.1)
Down syndrome	195	8.4	23.2	(20.2-26.9)
Noonan's syndrome	18	2.9	6.2	(3.7-9.9)
Alport/Laurence-Moon (-Bardet)-Biedl / Zellweger syndromes	7	1.0	7.0	(2.9-15.0)
Jacobsen's syndrome	4	0.8	5.0	(1.4-13.5)
Di George's syndrome	3	0.9	3.3	(0.6-9.3)
Alagille's syndrome	5	0.7	7.1	(2.3-16.8)
Turner's syndrome	1	0.4	2.5	(0.0-15.7)
Others*	18	3.4	5.3	(3.2-8.5)
Without syndrome	647	201.2	3.2	(3.0-3.5)

* see Table S3.3 for complete list of the other syndromes

HC, hematopoietic cancers; CHD indicates congenital heart disease; SIR, Standardized Incidence Ratio; CI, Confidence Intervals

Table 3. 3 Distribution of the most common syndromes and incidence rate (per 1000 person-year) of HC in children with CHD

Syndrome status and types	n (%)	n of HC cases	PY	IR (95% CI)
With Syndrome	12169 (8.5)	251	112,479	2.2 (2.2-2.5)
Types of syndromes‡				
Down syndrome	5440 (43.8)	195	49767	3.9 (3.4-4.5)
Noonan's syndrome	1853 (15.0)	18	17286	1.0 (0.6-1.6)
Alport/Laurence-Moon (-Bardet) -Biedl /Zellweger syndromes	625 (5.0)	7	4689	1.5 (0.6-3.1)
Jacobsen's syndrome	501 (4.0)	4	4255	0.9 (0.3-2.4)
Di George's syndrome	619 (5.0)	3	6030	0.5 (0.1-1.5)
Alagille's syndrome	446 (3.6)	5	3293	1.5 (0.5-3.5)
Edwards' syndrome/Trisomy 18, unspecified	328 (2.6)	0	2040	(NaN-1.5)
Turner's syndrome	228 (1.8)	1	2326	0.4 (0.0-2.4)
Others*	2129 (17.1)	18	22793	0.8 (0.4-1.2)
Without syndrome	131625 (91.5)	647	1202124	0.5 (0.5-0.6)

‡ Percentage presented among children with syndromes; * see Table S3.3 for complete list of the other syndromes
HC, hematopoietic cancers; CHD, congenital heart disease; CI, Confidence Intervals; PY, person-years; IR, Incidence rate; NaN, Not a number

Table 3. 4 Mortality-adjusted cumulative incidence of HC with different index ages and follow-up durations by genetic syndrome status

Index age, years	Cumulative incidence of HC, % (95% CI)		
	Follow-up duration: 6-year	Follow-up duration: 12-year	Follow-up duration: 18-year
With syndrome			
0	1.89 (1.64-2.14)	2.17 (1.89-2.45)	2.44 (2.11-2.76)
6	0.30 (0.17-0.42)	0.58 (0.36-0.80)	.
12	0.28 (0.10-0.46)	.	.
Without syndrome			
0	0.36 (0.32-0.39)	0.55 (0.50-0.59)	0.79 (0.72-0.87)
6	0.20 (0.16-0.23)	0.45 (0.38-0.52)	.
12	0.25 (0.20-0.31)	.	.

HC, hematopoietic cancers

FIGURES

Figure 3. 1 Derivation of the study population. CHD indicates congenital heart disease; HC, hematopoietic cancers; and PY, person-years.

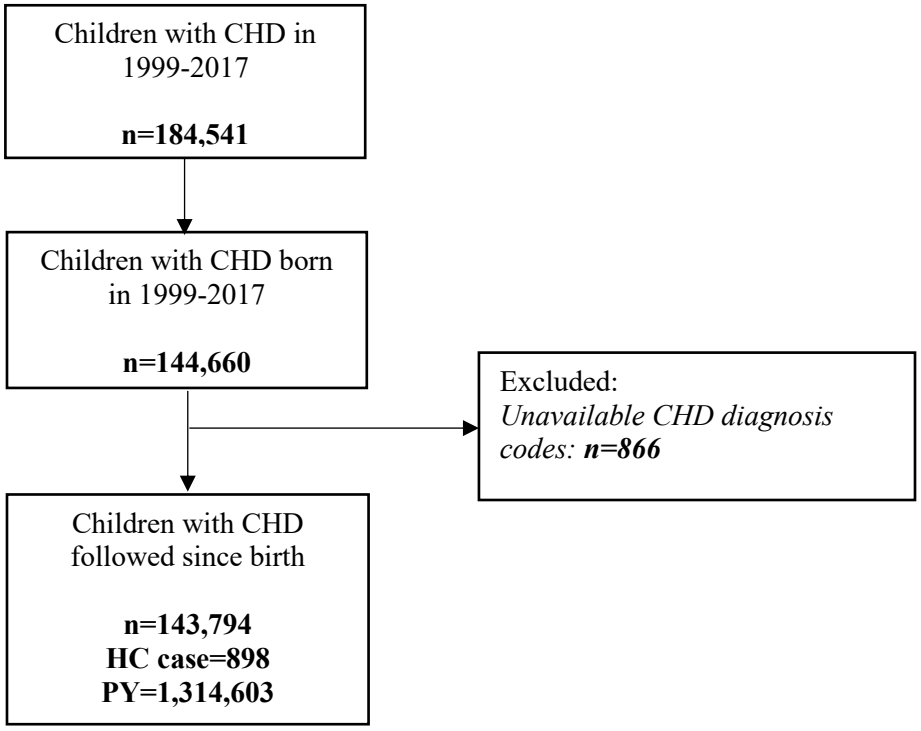


Figure 3. 2 Cumulative incidence of hematopoietic cancer in children with congenital heart disease, by all genetic syndrome, Down syndrome, Noonan's syndrome, and no syndrome

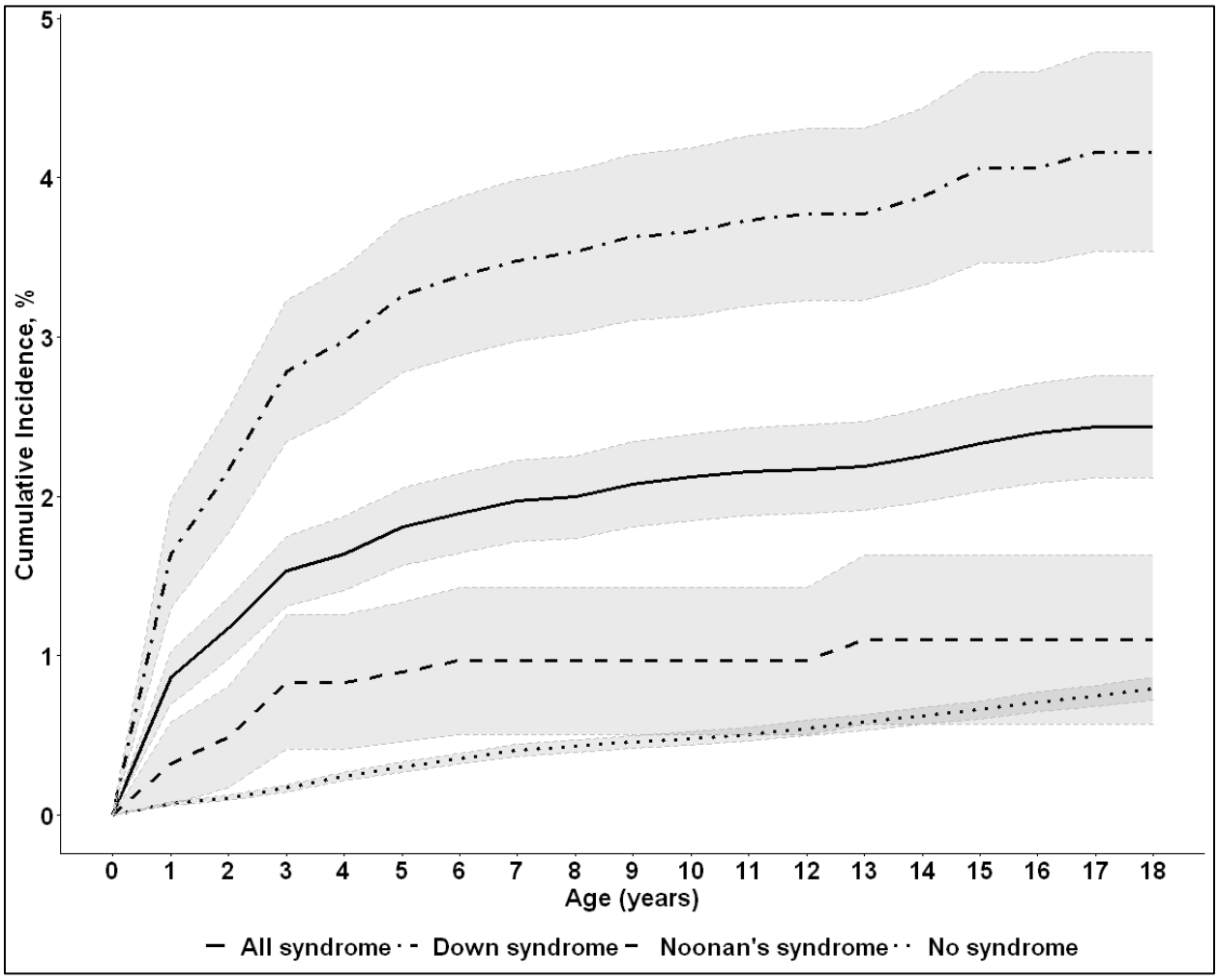


Figure 3. 3 Cumulative incidence of Acute lymphoblastic leukemia (Panel A) and Acute myeloid leukemia (Panel B), by genetic syndrome status

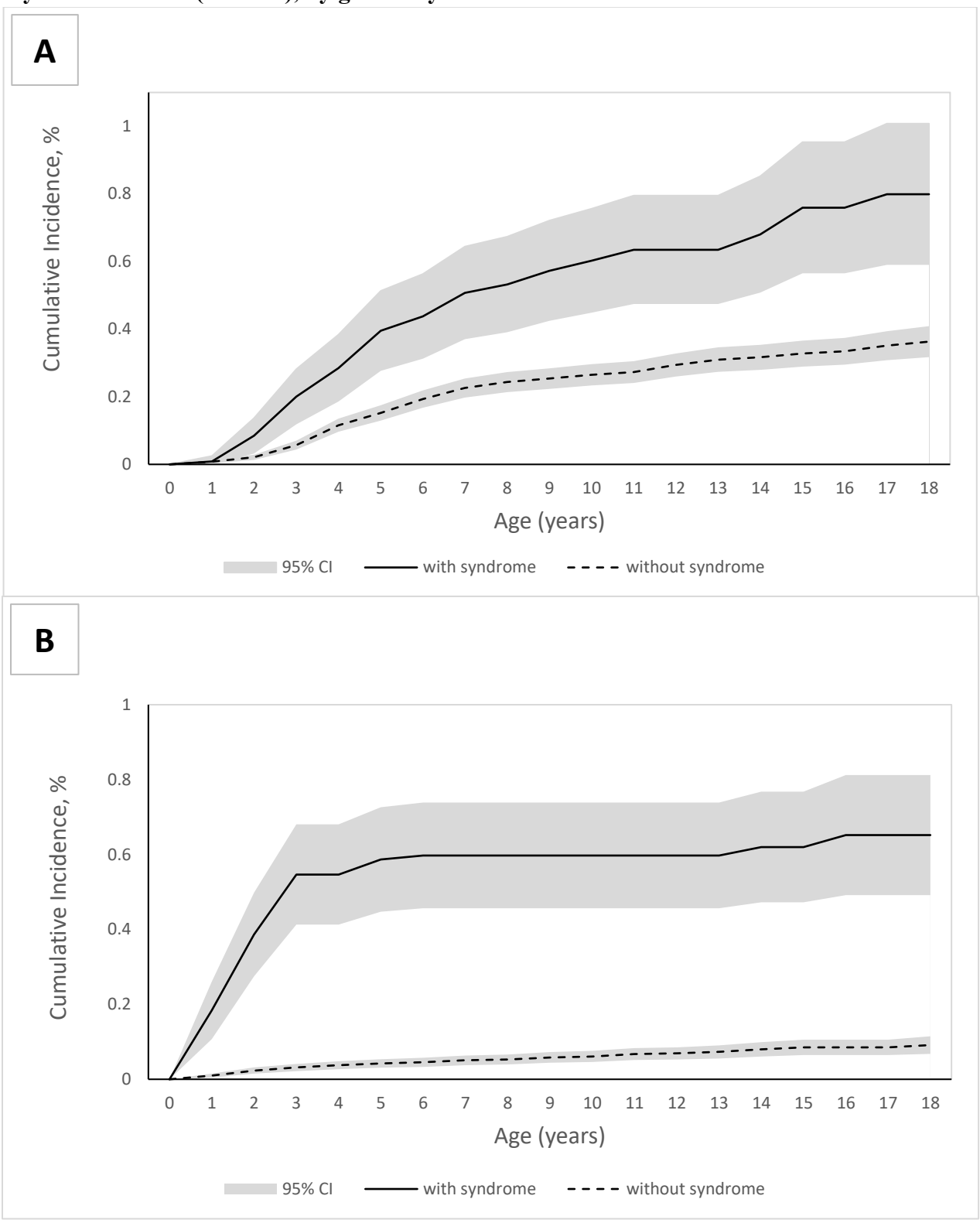
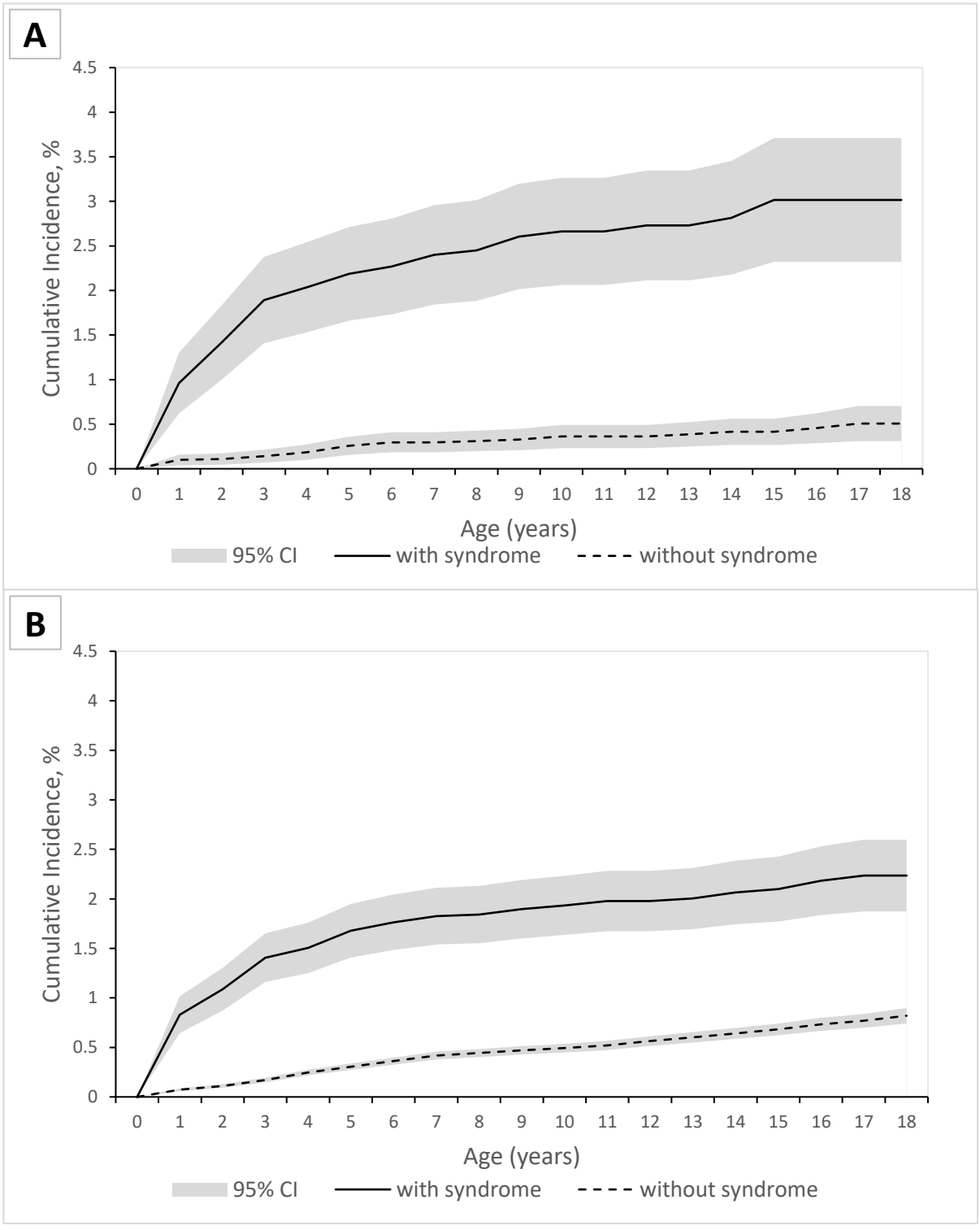


Figure 3. 4 Cumulative incidence of hematopoietic cancer in children with congenital heart disease, by genetic syndrome status. Panel A: Severe CHD lesions and Panel B: Other CHD lesions



SUPPLEMENTAL MATERIALS

Table S3. 1 Cancer definitions by classification system in Canadian Cancer Registry (CCR)

Cancer	ICD-O-3 Site/type	ICD-9	ICD-10
Acute lymphocytic leukemia	Types 9826, 9835, 9836; Types 9811-9818, 9837 for sites C42.0, C42.1, C42.4	204	C91.0
Chronic lymphocytic leukemia	Type 9823 for sites C42.0, C42.1, C42.4	204.1	C91.1
Acute myeloid leukemia	Types 9840, 9861, 9865–9867, 9869, 9871-9874, 9895–9897, 9898, 9910, 9911, 9920	205.0, 207.0, 207.2	C92.0, C92.4-C92.6, C92.8, C94.0, C94.2
Chronic myeloid leukemia	Types 9863, 9875, 9876, 9945, 9946	205.1	C92.1
Hodgkin lymphoma	Types 9650–9667	201	C81
Non-Hodgkin lymphoma	Types 9590–9597, 9670–9719, 9724–9729, 9735, 9737, 9738; Type 9811-9818, 9823, 9827, 9837 for all sites except C42.0, C42.1, C42.4	200, 202.0–202.2, 202.8, 202.9	C82–C86

Table S3. 2 Categories of hematopoietic cancers and their corresponding ICD9 and ICD 10 codes

Categories	ICD 9	ICD 10
ALL	204	C91
AML	205, 206, 238.5, 207.0, 207.2, 207.8	C92, C93, C94
Other unspecified leukemia	208	C95, C96
B cell neoplasms	203, 238.6	C90
Polycythemia vera	238.4, 207.1	D45
MPN & MDS	238.7	D46, D47
Lymphoma	200.1, 200.2, 200.3, 200.4, 200.5, 200.6, 200.7, 200.8, 201 202.0, 202.7, 202.8	C81, C82, C83, C84, C85, C86, C87, C88 (excluding: C88.0, C88.2)

ALL indicates Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; MPN, Myeloproliferative neoplasms; MDS, Myelodysplastic syndrome; ICD, International classification of diseases

Table S3. 3 Description of known genetic syndromes and their corresponding ICD9 and ICD 10 codes

ICD 9 and ICD 10 Codes	Description
Most common syndromes in this study population	
7580, Q900, Q901, Q902, Q909	Down syndrome
7598, Q871, Q870	Noonan's syndrome/Other specified congenital anomalies/Congenital malformation syndromes predominantly associated with short stature & facial appearance
Q878	Other specified congenital malformation syndromes, not elsewhere classified (Alport/Laurence-Moon(-Bardet)-Biedl/Zellweger syndromes)
7583, Q935	Jacobsen syndrome/Autosomal deletion syndromes
2791, D821	Di George's syndrome/Deficiency of cell-mediated immunity
Q447	Alagille's syndrome /Other congenital malformations of liver
7582, Q913	Edwards' syndrome/Trisomy 18, unspecified
7586/Q96	Turner Syndrome/Gonadal dysgenesis
Others	
7587, Q984	Klinefelter's syndrome
7589	Conditions due to anomaly of unspecified chromosome
7595, Q851	Tuberous sclerosis
2377, Q850	Neurofibromatosis
2702, E703	Other disturbances of aromatic amino-acid metabolism/Albinism
7490	Cleft palate
Q872	Congenital malformation syndromes predominantly involving limbs
Q873	Congenital malformation syndromes involving early overgrowth
7560	Anomalies of skull and face bones
7573, Q822	Other specified congenital anomalies of skin/Congenital cutaneous mastocytosis
7581, Q917	Patau's syndrome/Trisomy 13, unspecified
Q910	Trisomy 18, nonmosaicism (meiotic nondisjunction)
Q914	Trisomy 13, nonmosaicism (meiotic nondisjunction)
Q938	William's syndrome/Other deletions from the autosomes
Q980	Klinefelter syndrome karyotype 47, XXY

ICD indicates International classification of diseases

CHAPTER 4: Manuscript 2- Flexible Modeling of the Association Between Cumulative Exposure to Low-Dose Ionizing Radiation from Cardiac Procedures and Risk of Hematopoietic Cancer in Children with Congenital

4.1. Preface

Manuscript 1 demonstrated an increased risk of hematopoietic cancer in the presence of known genetic syndrome among children with CHD. Another potential source of such elevated risk could be exposure to LDIR from cardiac imaging. Hence, leveraging the large CanCHD database, this study assesses the association between cumulative LDIR exposure from cardiac imaging and hematopoietic cancer incidence in children with CHD. A considerable amount of research has been devoted to understanding the association with specific diagnostic or therapeutic modalities, mainly computerized tomography (CT) scan in the general pediatric population or cardiac catheterization among children with a heart defect. Moreover, cumulative exposure to LDIR was not well characterized in terms of time-varying dose and timing. More specifically, they failed to consider the likely effect of exposure not only in terms of cumulative dose of past cardiac imaging encounters but also the recency of the imaging. In this paper, we investigated how flexible extensions of the Cox proportional hazards model could improve our understanding of how LDIR-induced cancer risk may vary depending on the dose and past exposure. The findings can inform the caregivers to be aware of the detrimental carcinogenic effect of LDIR and implement intensive patient surveillance when repeated cardiac imaging is expected.

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4.2. TITLE PAGE

Flexible Modeling of the Association Between Cumulative Exposure to Low-Dose Ionizing Radiation from Cardiac Procedures and Risk of Hematopoietic Cancer in Children with Congenital Heart Disease

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4.3. ABSTRACT

Background: High-dose ionizing radiation is a well-established risk factor for childhood malignancies, including hematopoietic cancers (HC). However, data on the effect of low-dose ionizing radiation (LDIR) from medical imaging are conflicting and scant. Given the concern of cancer in the pediatric population with congenital heart diseases (CHD), where cardiac LDIR exposure is much more common than in the general population, this study aimed to evaluate the association between cardiac LDIR exposure and HC among children with CHD.

Methods: A nationwide population-based cohort study was conducted using the Canadian Congenital Heart Disease (CanCHD) database. The study population included children born between 1999 and 2017 with at least one CHD diagnosis in their medical records. Their cumulative dose of ionizing radiation was quantified based on their records of cardiac diagnostic and therapeutic procedures considering a 6-month exposure lag. The recency-weighted cumulative exposure (WCE) model, a flexible extension of Cox's proportional hazards model, was used to assess the association.

Results: We identified 139,975 children with CHD and followed them for 1,266,034 person-years since birth. In this population, 718 and 602 HC cases were observed, with or without lymphoma, respectively. Compared to children free of HC, children with any HC were exposed to LDIR earlier in life (median age at first exposure: 6 vs. 10 months; p=0.03), had more LDIR procedures (mean number of procedures: 0.4 vs. 0.2; 95% CI for absolute difference: 0.09-0.31) and had higher cumulative doses (mean dose: 2.3 vs. 1.1 mSv; 95% CI for absolute difference: 0.61-1.79 mSv). Similar patterns were observed for HC without lymphoma. We observed an increased risk of HC, with or without lymphoma, depending on the recency of the LDIR

exposure suggesting that the cumulative LDIR doses within five years were associated with an increased risk of HC, with the maximum association magnitude around 2 years.

Conclusion: This is the first large population-based study documenting an increased risk of HC associated with LDIR exposure depending on the recency of the LDIR exposure among children with CHD. Future studies focusing on detecting a threshold effect of LDIR exposure on cancer incidence are needed to help physicians decide the exposure point at which increased surveillance on LDIR exposure should be initiated.

4.4. INTRODUCTION

Children with congenital heart disease (CHD) are subject to repeated cardiac imaging procedures that involve ionizing radiation. The recent trend of increasing use of medical diagnostic and therapeutic procedures with ionizing radiation [47] raises concerns about the potential carcinogenic effect of low-dose ionizing radiation (LDIR) procedures, [61] to which CHD patients are frequently exposed at a progressively younger age.[47]

Understanding how risks change depending on the cumulative dose of LDIR is instrumental in developing a patient-centered surveillance system to ensure radiation safety in children. Excess cancer risk from LDIR procedures among the general children population has been described in recent systematic reviews and meta-analyses.[11, 56, 140] However, studies assessing the cancer risk from low-dose medical imaging among children with CHD reported conflicting findings, owing to inherent and methodological limitations. Most previous studies suffered from insufficient statistical power linked to the small expected risk and short follow-up.[73-75, 97] Studies also failed to account for time-varying radiation exposure, which would be necessary to explore how LDIR exposures received at different times in the past may affect the hazard.[48-52, 54, 73, 75, 78, 94, 97]

Thus, leveraging the extensive pan-Canadian CHD database (CanCHD) we created, the goal of the present study was to apply flexible statistical modeling to gain further insights regarding how risks of hematopoietic cancer (HC) may vary depending on the past cumulative LDIR dose.

4.5. METHODS

Data Sources

We used the Québec CHD database and the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) in this study. The Québec CHD database is created by merging Quebec's medical claims (Régie de l'Assurance Maladie du Québec: 1983-2017), the hospital discharge database (Med-Echo: 1987-2017), and the death registry using the patient's unique scrambled Medicare numbers. The CIHI- Discharge Abstract Database (DAD) database records hospital discharges from all acute and day surgery facilities in all Canadian provinces except Quebec. This database contains all diagnoses, demographic characteristics, and inpatient diagnostic and therapeutic procedures for all hospital encounters of patients with at least one hospitalization record of CHD diagnosis between 1999 and 2017. We combined the Quebec CHD database with the CIHI-DAD to develop the Canadian Congenital Heart Disease Database (CanCHD database). In the database, the diagnosis codes were based on the *International Classification of Diseases, 9th Revision* (ICD-9) and *10th revision* (ICD-10, since 2006), and the treatment codes were based on the *Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures* (CCP), *Canadian Classification of Health Interventions* (CCI, since 2006), and act codes (for Quebec only).

Study population

We included all children patients (0-17 years of age) in the CanCHD database who were born between 1999 and 2017 (Figure 4. 1). Therefore, all the children in the study population had complete hospitalization and day survey records since birth. We excluded patients with unavailable CHD diagnosis codes, sex, or inconsistent data on birth date. We excluded children who had a cancer diagnosis within 6 months (lag-time) following birth. Since chronic

lymphocytic leukemia (CLL) and multiple myeloma (MM) demonstrated low sensitivity to be induced by radiation,[57, 58, 68] children diagnosed with these diseases were not included.

Exposure

Exposure to low-dose ionizing radiation from all cardiac procedures received by each child from birth to 6-months prior to cancer diagnosis, administrative censoring, or death was extracted from the physicians' billing codes (Quebec) and hospitalization service codes (CIHI-DAD). To deal with reverse causality due to protopathic bias (early symptoms of hematopoietic cancers prompted administering the LDIR procedures), we applied a 6-month lag time for assessing LDIR exposure. Since a patient-specific dose is unavailable, we quantified the average or median effective radiation dose for diagnostic and therapeutic cardiac procedures following published literatures: chest CT scans=7mSV; ventriculography =7.8mSV; myocardial perfusion imaging= 15.6mSV; diagnostic cardiac catheterizations=4.6mSV; and interventional catheterization=6.0mSV.[45, 94, 95]

Outcome

The outcome of interest was incident cancer, defined as the first hospitalization with a primary or secondary hematopoietic cancer diagnosis occurring 6 months of age to age 18. We first defined all hematopoietic malignancies as the outcome. We further evaluated the risk for hematopoietic malignancies previously found to be radiogenic.[57, 68] Therefore, the latter excluded lymphoma (NHL and HL) but kept all leukemia (acute, chronic myeloid and lymphoblastic leukemia; other unspecified leukemia), other myeloproliferative malignancies, and myelodysplastic syndrome, resulting in a more etiologically relevant endpoint with respect to ionizing radiation. We set all HC collectively, with or without lymphoma as the outcome for the following reasons. First, previous studies aimed to assess the risk of cancer in children exposed to radiation during cardiac

imaging were unable to differentiate between increased cancer risk due to radiation dose and cancer-predisposing factors owing to the lack of data on an appropriate comparison group with unexposed-to-radiation children with CHD.[72, 74-76] Moreover, these studies reported conflicting findings on cancer risk in children exposed to radiation compared to the general population. Therefore, uncertainty remains regarding the association between LDIR from cardiac imaging and HC, including the subtypes of HC in this patient population. Secondly, with composite outcome definitions, we circumvented the possible overfit bias due to the instability of spline estimates with the number of events around 100 or less across HC subtypes,[141] while preserving the advantages of flexible modelling to establish the temporal relationship of the time-varying LDIR exposure and cancer incidence. In our study with even the pan-Canadian database on CHD, the number of HC incidents was lower than 100 for all subtypes except for ALL (see Table S4. 1 for HC distribution) We ascertained primary specified cancers by ICD-9 codes before 2006 and then by corresponding ICD-10 codes.

Covariates

Covariate measurements were obtained to account for plausible biological confounder variables. Age (continuous) was based on the date of birth and used as a time-varying covariate in regression analyses. Medical comorbidities (congestive heart failure, hypertension, diabetes mellitus, and history of stroke) were measured using diagnosis codes in the database. We applied a 6-months lag time to characterize comorbidities for each subject. Children with CHD were assigned a CHD diagnosis by using a previously described and validated hierarchical algorithm.[16, 105] We classified CHD severity based on anatomic diagnosis[105]: severe defects (tetralogy of Fallot, truncus arteriosus, transposition complex, univentricular heart, hypoplastic left heart syndrome, endocardial cushion defects, and Ebstein anomaly), shunts (atrial or

ventricular septal defects, patent ductus arteriosus, unspecified defects of septal closure), valvular (aortic coarctation, anomalies of the pulmonary artery or valve, congenital tricuspid valve disease, congenital aortic or mitral stenosis, or insufficiency anomalies of great veins), and other CHD lesions (unspecified anomalies of the heart or aorta). Genetic syndromes were defined as a binary indicator (yes/no), having a hospital discharge diagnosis of any genetic syndrome during the observation period. Sex and birth year were also included in regression analyses as time-fixed covariates.

Statistical analysis

We hypothesized that the impact of LDIR exposure might depend not only on the past cumulative dose but also on how recently the exposures occurred. Therefore, we assessed the potential association between cumulative LDIR dose (effective dose in mSv) from cardiac diagnostic and therapeutic procedures and hematopoietic cancer incidence with the recency-weighted cumulative exposure (WCE) model, a flexible extension of the Cox proportional hazards (PH) model with a time-varying exposure.[142] The WCE model has the advantage of modeling the cumulative effect of a time-varying exposure at a given time during follow-up as a weighted sum of past doses.[141] In contrast to the conventional (unweighted) metrics of the cumulative sum of all past doses, the time-varying WCE metrics assign differential weights to past exposures/doses. The resulting weight function, modeled with cubic regression B-splines, reflects the relative importance of the timing of the exposure assigned in the past to the current risk of cancer incidence. Because of the uncertainty associated with the estimated weight function in terms of (1) the number of interior knots of splines (1, 2, or 3 knots) (2) the time window over which the past cumulative exposure may be associated with the current hazard of incident cancer (3, 6, 9 and 12 years), and (3) which exposure measure, actual effective dose or

log-transformed effective dose yield better fit, we performed several sensitivity analyses to inform the best-fitted model. As for our analyses, we divided the follow-up time into 6-month time units and constrained our models to the right, assuming that past exposure beyond the etiologically relevant time window does not affect current cancer incidence. The model with a minimum Akaike Information Criterion (AIC) was considered the best-fitted model. We considered any difference in AICs larger than 10 points to represent a more significant improvement in model fitting.[143] The pointwise 95% confidence interval around the estimated weight function was estimated using a Monte Carlo procedure.[144] We estimated exposure weight functions of past cumulative effective dose for all HC, with or without lymphoma. To further examine the robustness of our fitted model, we performed sensitivity analysis extending the exposure lag to 1-year, excl uding the children with known genetic syndrome from the study population, and censoring patients at the time of heart transplant. All the WCE analyses were performed using the "`WCE`" package in R statistical software.[144]

4.6. RESULTS

In total, 139,975 children were included in the birth cohort. Of them, 718 children were hospitalized with an HC diagnosis during the follow-up period, yielding an incidence rate of 5.7/10,000 person-years (95% CI, 5.3-6.1). The incidence rate of HC excluding lymphoma (602 cancer cases) was 4.8/10,000 person-years (95% CI, 4.4-5.2). Table 4. 1 represents the basic characteristics of the study population by their cancer status. Children with HC, with or without lymphoma, were exposed to LDIR earlier in life and had more procedures than those without cancer. The mean dose they received was also higher than their counterparts. They had more

known genetic syndromes, were more severe regarding CHD lesions, and had more cardiac comorbidities compared to patients without cancer.

In our preliminary WCE models with the alternative number of interior knots (1, 2, or 3 knots) over the entire time window of 18 years, 3-knots WCE model yielded the minimum AIC (AIC=15654). However, we finally selected the most parsimonious model with 1-knot (AIC=15663), recalling the pre-specified 10-unit benchmark. Next, we selected an appropriate time window for our WCE model. Among the four unlagged, 1-knot unconstrained WCE model alternatives, the 9-year model yielded the lowest AIC (see APPENDIX 4.1). Finally, our comparison of the AICs with two alternative exposure measures resulted in selecting the log-transformed cumulative dose, which systematically improved our model fit, whether constrained to the right or not (see APPENDIX 4.2). Thus, we presented our findings based on 6-months lagged 1-knot right-constrained WCE model, with cumulative LDIR exposure defined as the weighted sum of log-doses received in the past 9 years.

The estimated weight function for the final best-fitting models, with and without lymphoma and the corresponding pointwise 95% confidence interval is shown in Figure 4.2 A and Figure 4.2 B, respectively. As depicted in both instances, the LDIR exposure from the past 1 to 5 years was associated with an increased risk of current cancer incidence. Exposure beyond 5 years, suggested no unambiguous evidence of an association.

Figure 4.3 illustrates the implications of the WCE model for assessing the relative risks of all HC in hypothetical scenarios of past LDIR exposures with different doses and timing. For instance, in Panel A: scenario I, a child (patient B) who underwent two diagnostic cardiac catheterizations (4.6 mSv) around 2 years ago, is estimated to have almost 3 times higher risk (HR 2.70; 95% CI: 1.96-3.75) than a child without any diagnostic cardiac catheterization during

the same point in time (patient A). With a diagnostic modality of higher dose, interventional cardiac catheterization= 6.0 mSv and CT scans=7.0 mSv, the risk is higher, patient C: HR 3.22 (95% CI: 2.20-4.72) and patient D: HR 3.56 (95% CI: 2.35-5.40), respectively. In contrast, Panel B: scenario II describes the increase in risk associated with the timing of exposure, the dose being the same. For example, a child (patient E) who underwent two diagnostic cardiac catheterizations (4.6 mSv) around 5 years ago has 37% higher risk (HR 1.37; 95% CI: 0.99-1.97) than a child without any exposure (patient A) whereas the risk is 3 times higher for a child who was exposed to the same dose around 2 years ago (patient B). Similar patterns were observed for HCs without lymphoma, with HR point estimates further away from the null and relatively wider confidence intervals. For example, a child with a similar exposure history to patient B (Panel A, Figure 4.3) had an HR of 3.02 (95% CI: 2.09-4.22) for HC excluding lymphoma, compared to a child without any diagnostic cardiac catheterization during the same time point. Similarly, a child with a comparable exposure pattern to patient E (Panel B, Figure 4.3) had an HR of 1.53% for HC excluding lymphoma (95% CI: 1.05-2.17) than a child without exposure. Additionally, we estimated the hazard ratios associated with the empirical dose histories in our cohort. We identified the hazard ratios corresponding to the 50th, 75th, 90th, and 95th percentile of the distribution and sampled an exposure pattern corresponding to that HR, with or without lymphoma (see Table S4. 2 in the data supplement). The 1st row of Table S4. 2 shows the median HR = 1.32 for all HCs, which corresponds, for example, to the magnitude of the association with two LDIR exposure of 4.6 mSv received about 4 years ago. Similarly, the 4th row shows that a patient who underwent a diagnostic cardiac catheterization and ventriculography procedure about 2.5 years and two diagnostic cardiac catheterization procedures about 4.5 years ago has an adjusted HR = 3.04, corresponding to the 95th percentile

of all HRs estimated in our cohort. The percentiles of HRs for HC without lymphoma and the corresponding empirical dose histories follow similar interpretations.

To demonstrate the robustness of our findings, we present hazard ratios corresponding to the 50th, 75th, 90th and 95th percentile of the distribution for our primary analysis, with or without lymphoma and sensitivity analyses in Figure S4. 1. We noted similar results in our sensitivity analysis in which we excluded all cardiac LDIR procedures in the 1 year before hematopoietic cancer. The risk estimates without lymphoma moved away from the null with relatively wider confidence interval. Analyses based on the study population without any known genetic syndrome or censoring patients on heart transplants yielded similar findings. (Figure S4. 1)

4.7. DISCUSSION

This is the first nationwide study in a pediatric CHD population to evaluate the association between LDIR exposure from cardiac procedures and HC incidence using a recency-weighted flexible modeling approach. We demonstrated an association between cumulative LDIR dose from the previous 5 years and risk of HC, with or without lymphoma, with the maximum association magnitude around 2 years regarding the timing of the LDIR exposure. Our model enabled us to estimate hazard ratios subject to different exposure patterns in the past.

Recent decades have been marked by growing use in medical imaging involving low-dose ionizing radiation, [44, 61] including cardiac imaging.[95, 145, 146] Our group previously documented increasing numbers of cardiac procedures emitting LDIR and exposures occurring at progressively younger ages in patients with CHD.[47] In this study, children with incident hematopoietic cancer were exposed to LDIR earlier in life and accumulated higher cumulative doses than those without cancer. The association of age at exposure in the setting of radiation has

been indicated to increase the risk for cancer.[51, 56, 147] Risk of childhood leukemia was found to be higher at a younger age at exposure among Japanese A-bomb survivors.[148] Due to rapid cell division and longer life expectancy, infants and young children are more susceptible to ionizing radiation.[149-152]

Several recent epidemiological studies on the general pediatric population have assessed the risk of cancer following CT exposure in childhood and reported increased risks of lymphohematopoietic malignancies [53, 77, 78], while others found no significant increased risk for leukemia.[48, 153] A more recent cohort study among youths in South Korea reported an increased risk of both solid and lymphohematopoietic cancers due to exposure to diagnostic LDIR.[49] Considerably detailed analysis of the subtypes of lymphohematopoietic malignancies in A-bomb survivors demonstrated a radiation-associated excess risk for leukemias other than chronic lymphocytic leukemia or adult T-cell leukemia, but weak or no excess risks for non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma.[154] Based on a UK pediatric CT-scan cohort, Gonzalez et al. found an association between radiation and leukemia/myelodysplasia,[55, 116] but no association for HL.[70] In a recent pooled analysis of nine historical cohort studies, Little and colleagues [57] reported an increased risk of AML, ALL, and AML and MDS combined, among individuals younger than 21 years at the time of first irradiation.[57] With the same nine historical cohorts, another pooled analysis found no radiation-associated excess risks for NHL, HL and MM or CLL.[67] However, a borderline significant increase in risk was observed for NHL, CLL and NHL+CLL, when the exposure was lymphatic tissue dose, instead of active bone marrow (ABM) dose.[67] Similar findings of no association between lymphoma and post-natal exposure to diagnostic x-rays in a cohort of over 90 000 German children were reported.[62, 65, 66]. A recent case-control study also found no evidence of an association between lymphoma risk and

self-reported lifetime medical x-ray exposure.[63] These findings contrast with those in a case-control study led by Rajaraman [64] in which an increased risk of all lymphoma and especially NHL following exposure to diagnostic x-ray in infancy was reported.[64] Similarly, a raised incidence rate ratio (IRR) was reported for NHL in a Korean cohort of children exposed to diagnostic x-ray.[49] However, the study found no association for HL.[49] On the contrary, Mathews and colleagues reported a raised IRR for all lympho-haematological cancer types combined, and HL among 680 000 Australians receiving CT scans before 19 years of age, while no association for other lymphoma or lymphoid leukemia.[53] In the model of children with CHD, however, the evidence is scant and conflicting. Using cytogenetic biomarkers in peripheral lymphocytes, studies on children with CHD reported an association between cardiac imaging with long-term somatic chromosomal damage, an intermediate endpoint of carcinogenesis.[91, 92] A limited number of epidemiological studies compared the cancer incidence in children exposed to LDIR during cardiac catheterization procedures to the general population.[72-76] However, these studies suffered from the limitation of not having data on unexposed children with CHD. The absence of such a comparison group in these studies restricted the assessment of whether the increased cancer risk was independently associated with radiation exposure or was due to other cancer-predisposing factors. Moreover, these studies reported conflicting findings: In a Canadian single-center study of 3,915 children who had procedures between 1950 and 1965, 67% of whom had only 1 procedure, no significant increase in any cancer or leukemia incidence was observed during a mean follow-up of 21.7 years.[74] On the other hand, in a study of 674 Israeli children, 71% of whom also had 1 procedure from 1950-1970, an increased risk of cancer including lymphoma was documented compared to population-based standardized risk ratios.[75] However, no dose-response association was observed.[75] A retrospective cohort study focusing on the

cancer incidence following childhood or early adulthood exposure to cardiac fluoroscopically guided cardiac catheterization procedures reported an elevated risk for leukemia, and lymphoma including both NHL and HL, compared to the general population.[73] Transplantation was reported to be the larger contributor to the increased cancer risk in this patient population, likely due to associated immunosuppression.[73] More recently, a single-center observational study among children who underwent cardiac catheterization reported an increased cancer risk in the first year of life.[76] However, no association was reported between cancers and effective radiation dose.[76] Similarly, in a multicenter cohort study, increased risks for all cancer, leukemia, and lymphoma were reported among children (<16 years) with CHD compared to the general population, without a dose-response analysis.[72]

This present study reported an increased risk of hematopoietic cancers, with or without lymphoma, among children with CHD due to increased LDIR dose and recency, based on a large population-based cohort in Canada. Our estimated point estimates of HRs for all HC were closer to the null than those excluding lymphoma. However, the degree of overlap in their confidence intervals was substantial. The apparent dilution of risk estimates for all HC including lymphoma compared to excluding lymphoma could be due to a weak or no association between radiation and lymphoma. This is consistent with the literature that lymphoma might not be radiogenic.[67]

Our study benefitted from the application of weighted cumulative exposure effects (WCE) models, which allows us to examine the importance of the timing of exposure on the incidence of hematopoietic cancer among children with CHD. Studies assessing the association between cumulative exposure to LDIR and cancer incidence mostly used a single cumulative quantity (total number of procedures or total doses) as the exposure metric.[74, 75, 97] Failure to accurately model such time-varying exposure, however, could dilute the effect estimate affecting

the validity of the findings.[155, 156] To this end, our flexible WCE model enabled us to assess how LDIR exposures received at different times in the past may influence the current hazard.[156] Furthermore, our recent findings on an increased risk of incident cancer due to increased cumulative LDIR dose from the previous 2–6 years among the adult CHD (ACHD) population,[157] reassure the application of this spline-based WCE modeling approach in our present settings.

Studies on cancer risk from low-dose ionizing radiation exposure are subject to indication bias,[77], which can be suspected when cancer-predisposing factors [77, 158] induce the indication of the imaging procedure.[159] Patients with genetic syndromes can manifest both CHD and a tumor predisposition due to possible common underlying pathways.[10, 32, 160-162] For instance, patients with Down syndrome are known to have a higher risk of CHD and 10- to 20- fold higher risk of childhood leukemia compared to the general population.[32] Other established syndromes include 22q11.2 deletion syndrome,[10] Noonan syndrome [112, 161] and other RAsopathies. Another cancer-predisposing factor is organ transplantation. A higher risk for a range of malignancies, including hematopoietic cancers, is among the major complications of post-transplantation immunosuppression.[163] Moreover, we have previously published that LDIR exposure from cardiac procedures differs significantly across baseline characteristics of the CHD population, including age, year of birth, CHD severity, and comorbidities.[47] We, therefore, dealt with the indication bias by including these relevant variables in our model *a priori*. However, we conducted sensitivity analyses excluding children with known genetic syndromes and censoring the patients at the date of heart transplants, an approach undertaken by some CT studies with medical information available.[50, 54, 77, 158] Our results yielded increased risk estimates in the same range obtained in the entire cohort, corroborating previous findings, and ruling out the potential

bias linked to predisposing conditions to cancer.[11] Despite our efforts, residual confounding due to the presence of unknown genetic syndromes is still a possibility, and thus our findings should be interpreted with caution.[164]

Another potential source of bias is reverse causality, which could occur whenever LDIR exposures to imaging procedures are indicated due to the early symptoms of undetected cancers.[165] CT studies employed various lag periods, ranging from 3 months to 24 months for lymphohematopoietic malignancies, to deal with such bias.[11] A pooled analysis of nine historical cohort studies showed a latency period of 2-5 years for most leukemia and myeloid malignancies, especially for ALL, justifying a lag of 2 years to be more relevant.[57] However, for AML, the excess risk is indicated to be within 0-2 years.[57] In a separate study on the same nine cohorts, Little and colleagues [67] reported few indications of change in results when the lag period was shorter than 2 years for lymphoma.[67] An increased risk of leukemia and lymphoma was suggested among patients who were examined because of congenital malformations, using a 6-month exposure lag.[166] Recently, Lee et al. reported comparable risk estimates with varying lag ranging from 6-months to 5-years for hematologic malignant neoplasms among patients who underwent appendectomy.[167] In our study, we applied an a priori chosen weighted-cumulative dose lag of 6-month lag period and extended it to 1 year. Since the hematopoietic cancer genesis is brief and the diagnosis is not assessed by cardiac imaging procedures,[157] our choice of a conservative lag period is unlikely to bias the association estimated. Moreover, our sensitivity analysis in which we excluded all cardiac LDIR procedures in the 1 year prior to hematopoietic cancer diagnosis showed similar results.

Our results suggest that LDIR exposures from the previous 5 years before the cancer diagnosis increases the cancer risk with a maximum magnitude around 2 years. Our findings of a

2-5 years latency is consistent with studies that reported, using different analytical methods, a minimum latency period of 2 years for hematopoietic cancers.[11, 52, 54, 56] One possible explanation for the possible shorter latency period in our study could be surveillance bias. Since our CHD population underwent frequent medical examinations leading to increased diagnoses of cancers than the general population, [168] they might be diagnosed with cancer at an earlier stage. However, our use of inpatient data to define primary specified hematopoietic cancers could minimize such bias due to the use of more robust diagnostic criteria during hospitalization.[135] In addition, our regression model included the severity of CHD lesions and comorbidities as covariates for the purpose of controlling the potential surveillance bias. Our estimated WCE curve corroborates previous findings manifesting a temporal 'wave'[56], that the radiation-induced hematopoietic cancer risk peaks to a higher level after the minimum latency period, and thereafter, as the time since exposure increases, the risk decays to zero.[56, 148]

As far as we could establish, this is the first large population-based study documenting an increased risk of HC associated with increased dose and recency of the LDIR exposure among children with CHD. We merged multiple databases to harness detailed longitudinal information on each hospital encounter of CHD children across Canada in order to overcome the limitation of insufficient power in previous studies. Moreover, our use of novel modeling techniques to measure time-varying LDIR exposure and the methodological approaches to account for different biases pertinent to radiation-cancer studies could improve the internal validity of our study.

Limitations

There are, however, some inherent limitations in our study. Firstly, this study used an administrative database, and thus the findings depend on the completeness and accuracy of the

recorded data. To this end, our use of inpatient data to define cancer may be less subject to misclassification due to its high data quality.[169] However, some cancer cases not requiring hospitalization may be underreported. We defined a composite outcome with or without lymphoma in the current study. Our data-driven, flexible WCE modeling approach was subject to overfit bias due to the instability of spline estimates, especially with a limited number of events of around 100 or less.[141] Evaluation of the putative mechanisms linking radiation to the risk of various subtypes of lymphohematopoietic malignancies with our empirical data was not feasible and, thus, remains a limitation. Procedure-specific data on doses delivered were not available in our database, and thus, similar to other studies,[47, 94, 95, 97, 135, 157] this study relies on effective doses reported in the literature.[170, 171] Since the effective dose is not a physical parameter that can be directly measured or verified, a true gold standard "correct" value for the effective dose from an examination is difficult to define[172] and, therefore, should be interpreted with caution. We cannot rule out the possibility of residual confounding due to heterogeneity in exposure intensity across calendar time,[173, 174] type of equipment and imaging strategies, training of the operator, and site or procedure complexity.[175] Our data on death were not complete as we had information only on in-patient deaths for patients who were outside Quebec. However, it is reasonable to believe that most deaths in children with CHD are recorded in hospitalizations.

Radiation from cardiac imaging, often referred to as a double-edged sword,[176] can be used to diagnose and treat children with CHD effectively, but it can also cause subsequent cancers. Our study suggested an increased cancer risk associated with cardiac imaging among this patient population. This association necessitates monitoring radiation doses among children with frequent cardiac imaging. A patient-centered surveillance system may be helpful for better management of doses delivered during each cardiac imaging procedure and, thus, ensure

radiation safety in children with CHD. Future data with more cancer cases to aid the risk assessment of the sub-types of lymphohematopoietic malignancies in this patient population. Nonetheless, future studies focusing on detecting a threshold effect of LDIR exposure on cancer incidence are needed to help physicians decide the exposure point at which increased surveillance on LDIR exposure should be initiated.

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DISCLOSURES

All authors declare no conflict of interest.

TABLES

Table 4. 1 Baseline characteristics of a birth cohort of pediatric patients with congenital heart disease in Canada, 1999-2017

Characteristics	Children with Hematopoietic Cancer†	Children with Hematopoietic Cancer excluding Lymphoma‡	Children without Hematopoietic Cancer
	n=718	n=602	n=139, 257
Male, n (%)	386 (53.8)	323 (53.7)	73237 (52.6)
Median age at 1st Cancer (IQR), years	4.4 (2.5, 7.7)	3.8 (2.2, 6.0)	-
Median age at 1st LDIR (IQR), months	6 (3, 23)	6 (3, 23)	10 (4, 42)
Total person-years	4060	2908	1261974
With cardiac LDIR procedures, n (%)	93 (12.9)	78 (13.0)	13117 (9.4)
Mean number of LDIR procedures (Std)	0.4 (±1.5)	0.4 (±1.4)	0.2 (±0.7)
Mean doses(mSv)(Std)	2.3 (±8.1)	2.2 (±7.6)	1.1 (±4.7)
Known genetic syndromes, n (%)	141 (19.6)	138 (22.9)	11330 (8.1)
CHD lesions, n (%)			
Severe	96 (13.4)	88 (14.6)	12723 (9.1)
Shunt	230 (32.0)	203 (33.7)	90875 (65.25)
Valve	45 (6.3)	40 (6.6)	12549 (9.0)
Other	347 (48.3)	271 (45.0)	23110 (16.6)
Comorbidity*, n (%)	69 (9.6)	63 (10.5)	7094 (5.1)
History of cardiac surgery, n (%)	88 (12.3)	80 (13.3)	20066 (14.4)

†All hematopoietic cancers, including leukemia (AML, CML, ALL, and other unspecified leukemia), other myeloproliferative neoplasms (MPN), and myelodysplastic syndromes (MDS), and lymphoma (NHL, and HL)
‡Excluding NHL, and HL
*Comorbidities include congestive heart failure, hypertension, diabetes mellitus, and history of stroke

FIGURES

Figure 4. 1 Derivation of the study population. CHD indicates congenital heart disease; HC, hematopoietic cancers

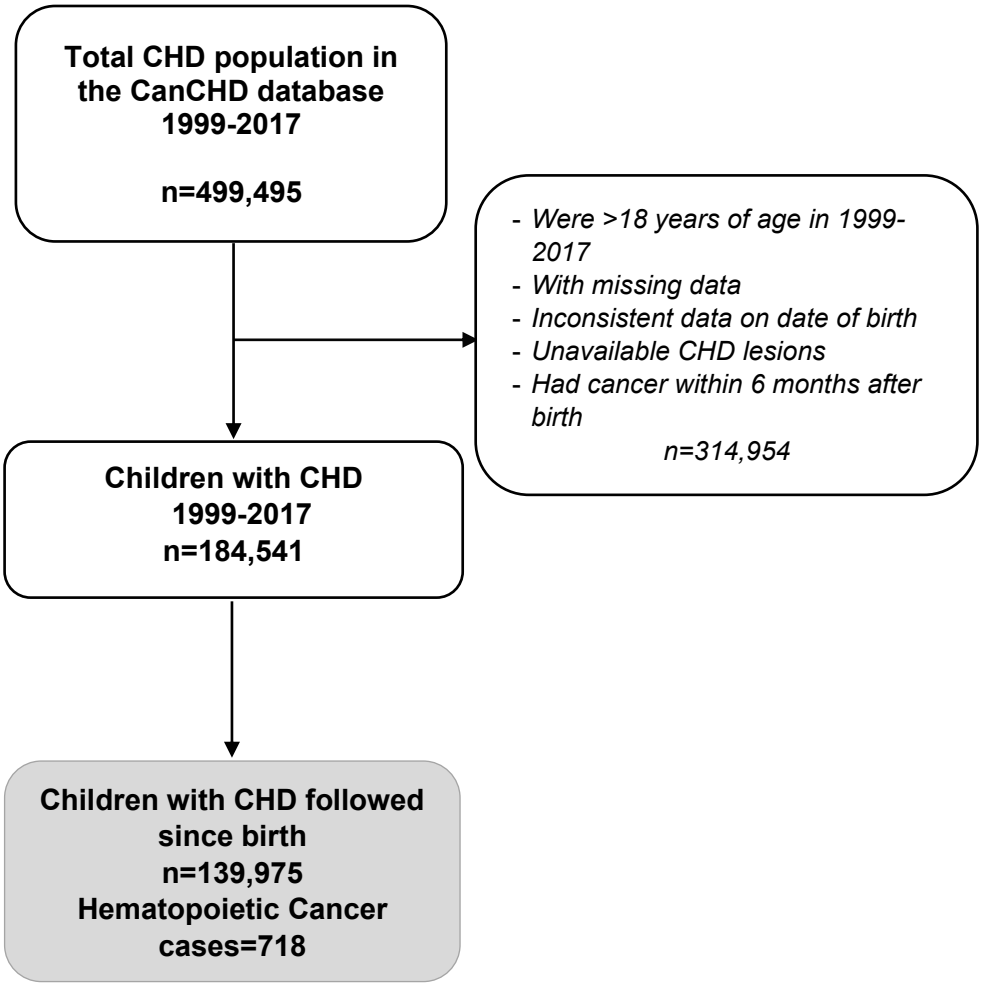


Figure 4.2 A. Estimated weight function (solid line) and pointwise 95% bootstrap confidence interval (shaded areas) for the association between the logarithms of past doses of low-dose ionizing radiation exposure and any HC incidence among children with CHD

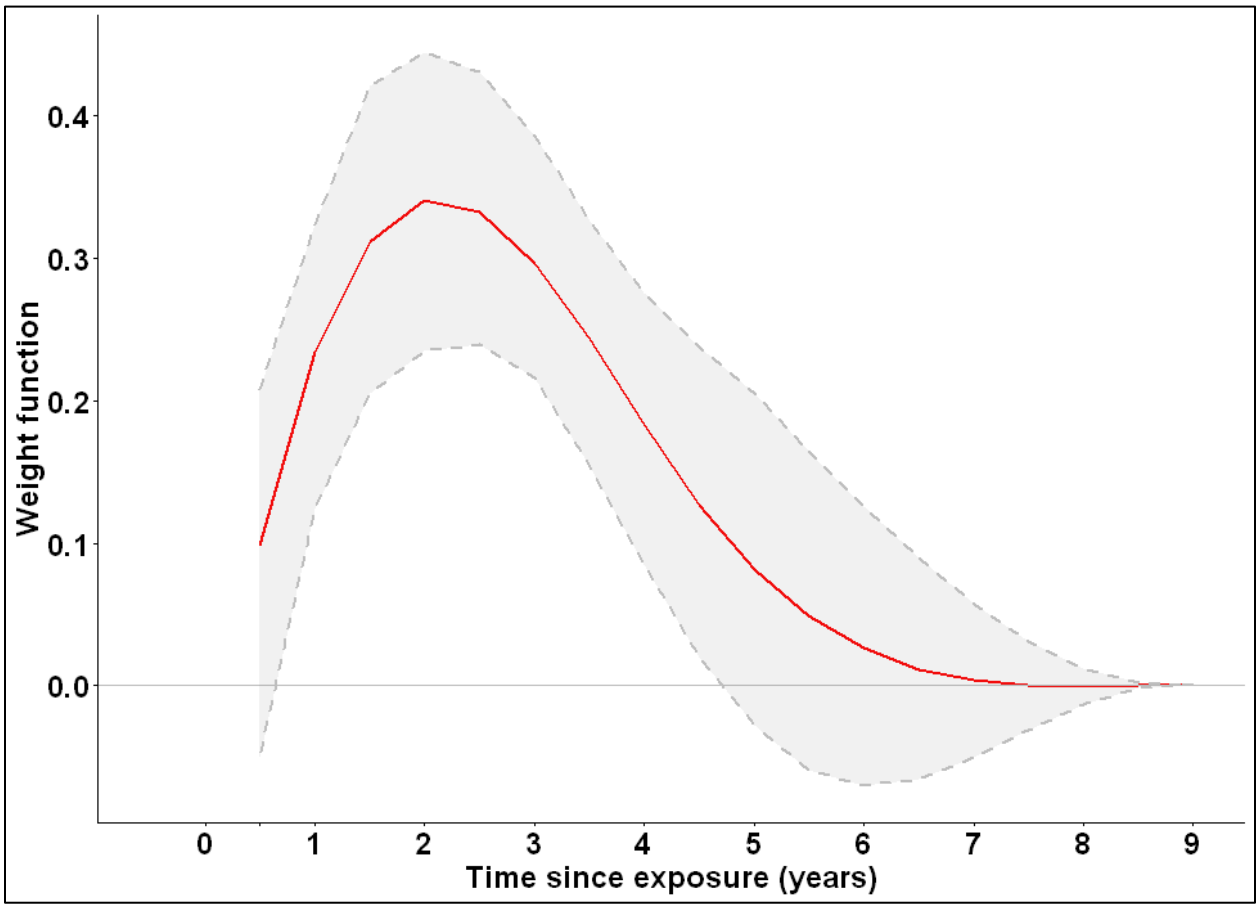


Figure 4.2 B. Estimated weight function (solid line) and pointwise 95% bootstrap confidence interval (shaded areas) for the association between the logarithms of past doses of low-dose ionizing radiation exposure and HC (excluding lymphoma) incidence among children with CHD

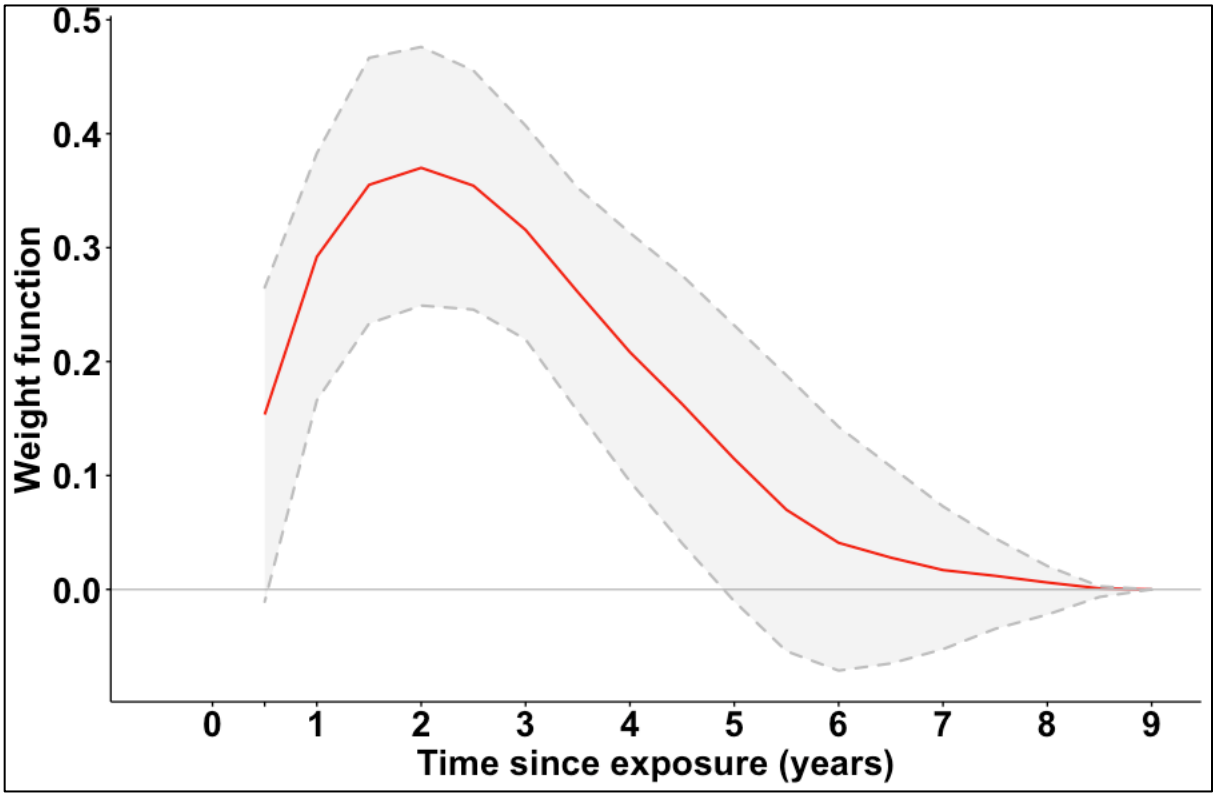
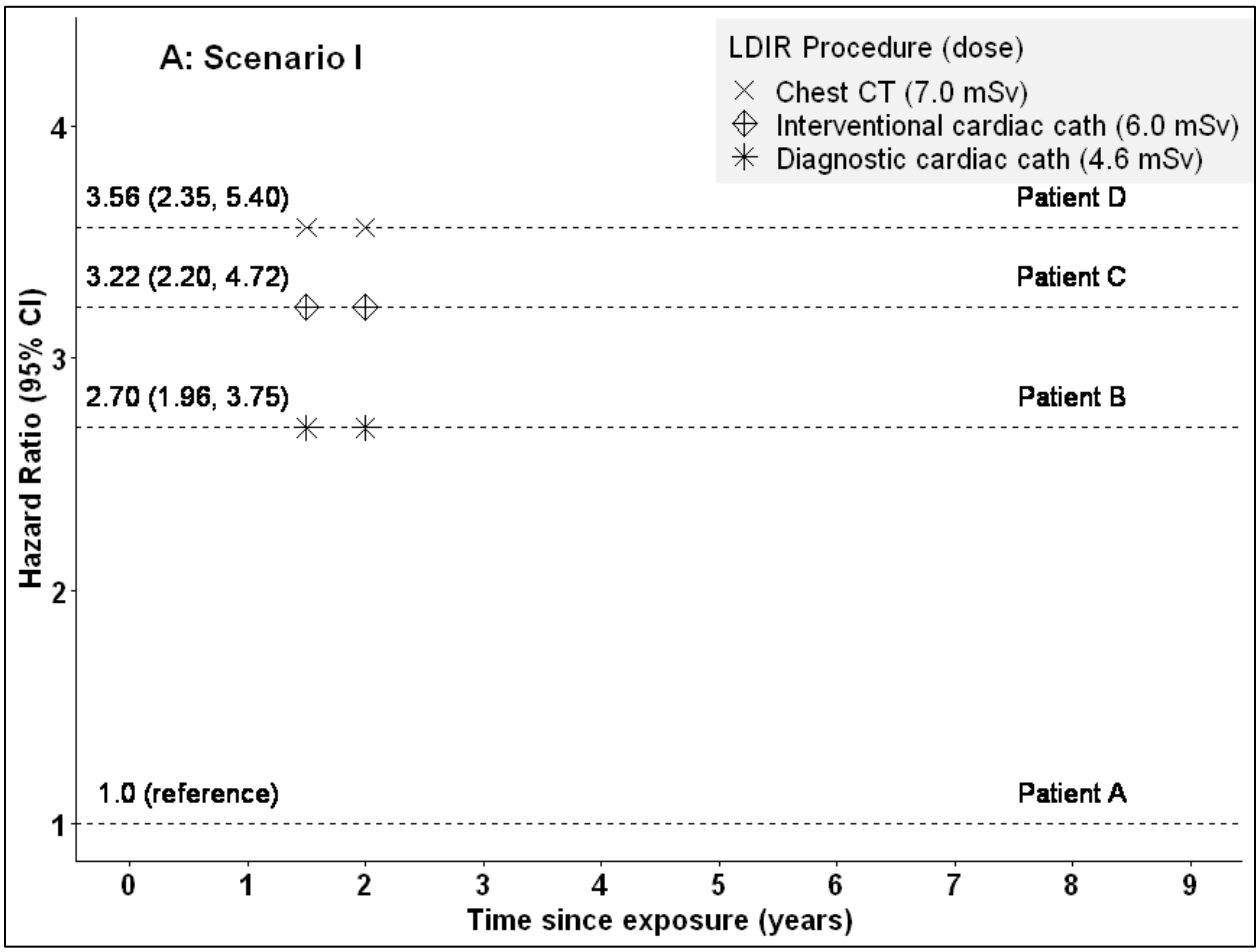
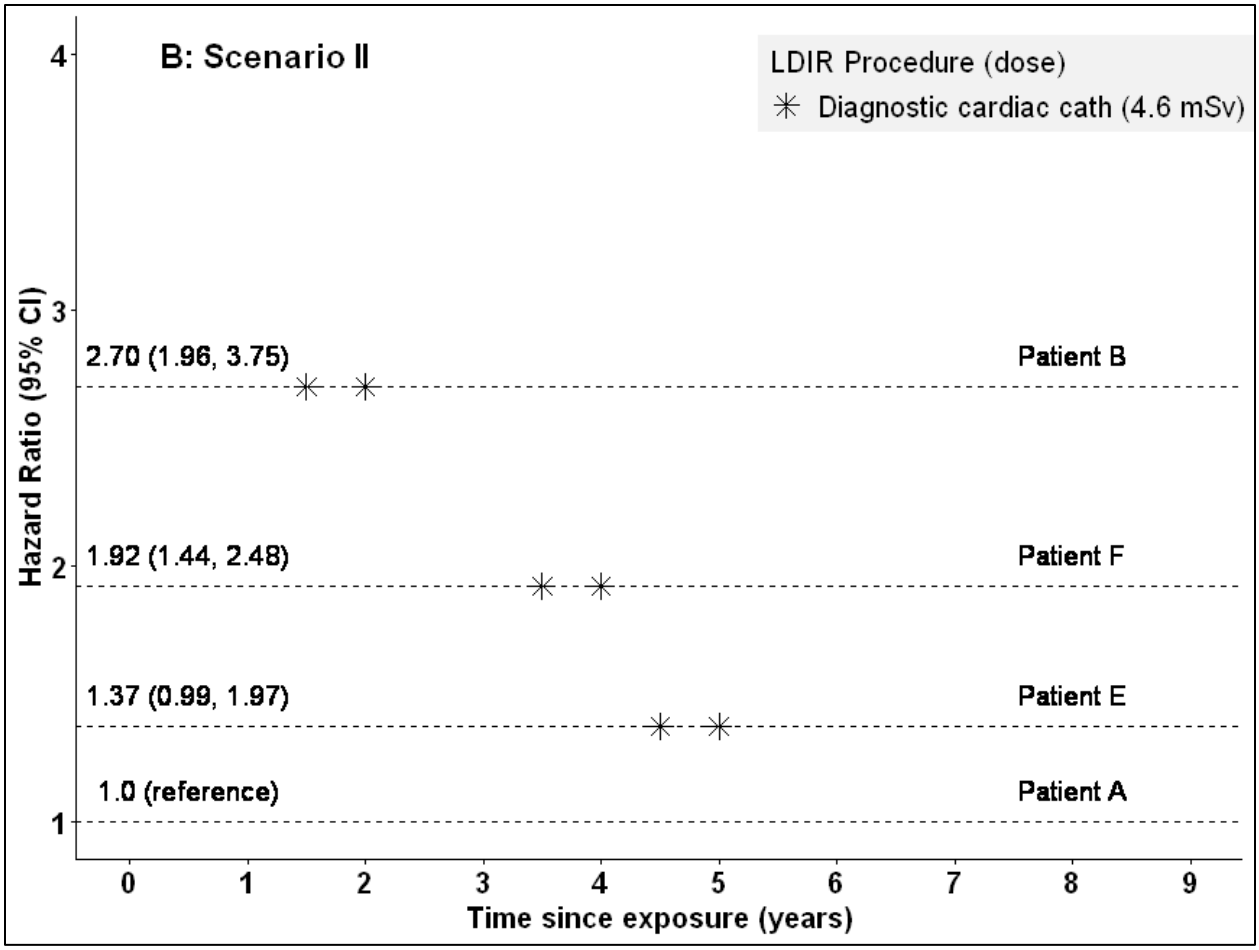


Figure 4.3 Adjusted hazard ratios from the final model (6-months-lagged analysis of associations between the logarithms of past doses of low-dose ionizing radiation (LDIR) exposure and all hematopoietic cancer incidence) for selected hypothetical scenarios of LDIR




B: Scenario II
LDIR Procedure (dose)
Diagnostic cardiac cath (4.6 mSv)
Hazard Ratio (95% CI)
4
3
2
1
2.70 (1.96, 3.75)
Patient B
1.92 (1.44, 2.48)
Patient F
1.37 (0.99, 1.97)
Patient E
1.0 (reference)
Patient A
0
1
2
3
4
5
6
7
8
9
Time since exposure (years)

SUPPLEMENTAL MATERIALS

Table S4. 1 Categories of hematopoietic cancers, their corresponding ICD 9 and ICD 10 codes, and distribution by exposure to at least one cardiac imaging modality involving LDIR

Categories	ICD 9	ICD 10	Exposed/Unexposed	Total
AML/CML	205, 206, 238.5, 207.0, 207.2, 207.8	C92, C93, C94	4/86	90
ALL	204	C91	15/324	339
Other unspecified leukemia	208	C95, C96	12/49	61
Polycythemia vera	238.4, 207.1	D45	6/4	10
MPN/MDS	238.7	D46, D47	41/61	102
NHL	200.1, 200.2, 200.3, 200.4, 200.5, 200.6, 200.7, 200.8, 202.0, 202.7, 202.8	C82, C83, C84, C85, C86, C87, C88 (excluding: C88.0, C88.2)	9/69	78
HL	201	C81	6/32	38

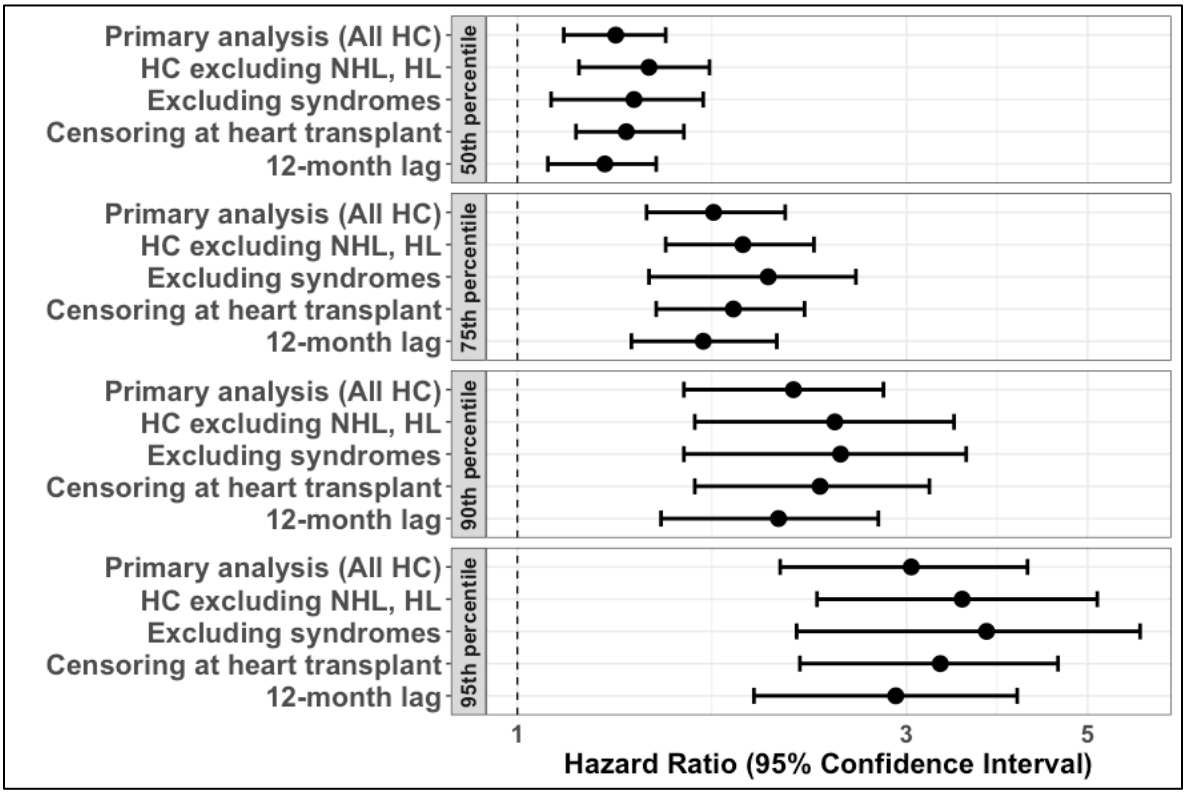
ALL indicates Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CML, Chronic myeloid leukemia; MPN, Myeloproliferative neoplasms; MDS, Myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; ICD, International classification of diseases

Table S4. 2 Estimated adjusted HRs associated with selected dose histories observed in the cohort, relative to patients with the same values of all covariates and who were not exposed to LDIR in the past 9 years.

Percentile of HR Distribution	Dose History (mSv) According to Time Since Exposure (years)																		
	All HC																		
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9
50% HR=1.32									4.6										
75% HR=1.74				6.0															
90% HR=2.18					7.0							4.6	4.6						4.6
95% HR=3.04						12.4				9.2									
	HC excluding lymphoma																		
50% HR=1.45										6.0									
75% HR=1.89				6.0															
90% HR=2.45									4.6	4.6			4.6	6.0					
95% HR=3.51				7.0				6.0											

CT Scans=7 mSv; Ventriculography=7.8 mSv; Myocardial perfusion imaging=15.0 mSv; Diagnostic cardiac catheterizations=4.6 mSv and Interventional cardiac catheterizations=6 mSv

Figure S4. 1 Percentiles of estimated adjusted hazard ratio distribution associated with primary and sensitivity analyses. The primary analysis includes 6-month exposure lag, adjusting for age, sex, birth year, medical comorbidities, CHD lesions, cardiac surgery and genetic syndromes

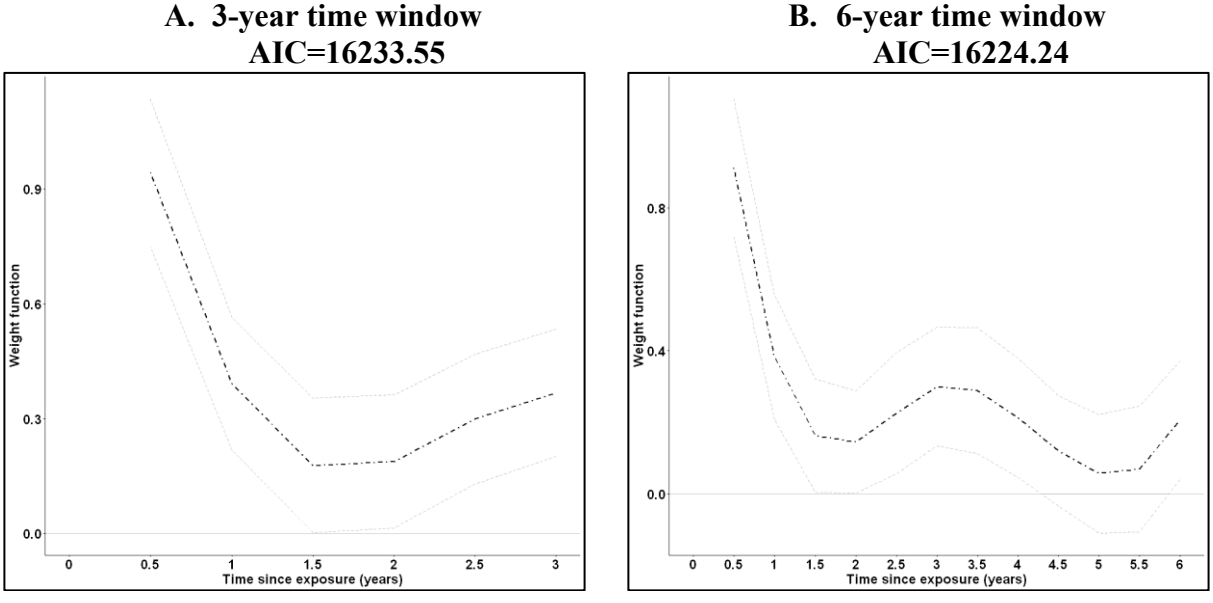


APPENDICES

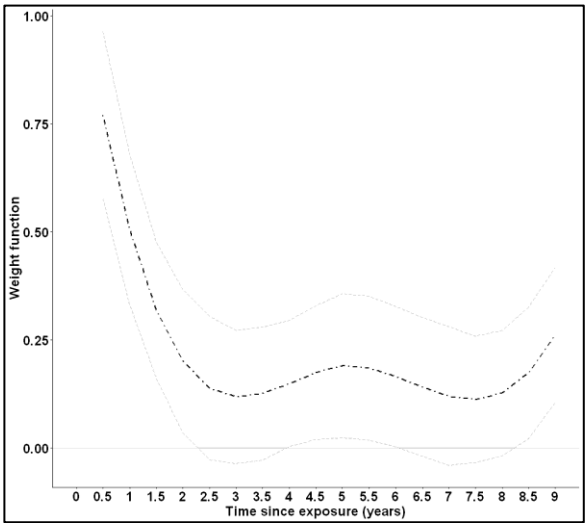
APPENDIX 4.1. Selection of an appropriate time window

In order to select an appropriate time window for our WCE model, we estimated alternative unconstrained and unlagged 1-knot WCE models, with log dose, for time windows [0, *a*] with *a* = 3, 6, 9, and 12 years. The purpose of this sensitivity analysis was to assess the behavior of weight estimates close to the end of the corresponding exposure time window (*a* year ago).[157] The region of the estimated weights systematically higher than 0 would indicate the importance of the exposures that occurred more than *a* year on the current hazard. Since the unconstrained cubic spline estimates in the upper tail are notoriously unstable,[142] we took both visual assessment and AIC values into account. Accordingly, the 9-year model with the lowest AIC were selected as an appropriate time window in our main analysis.

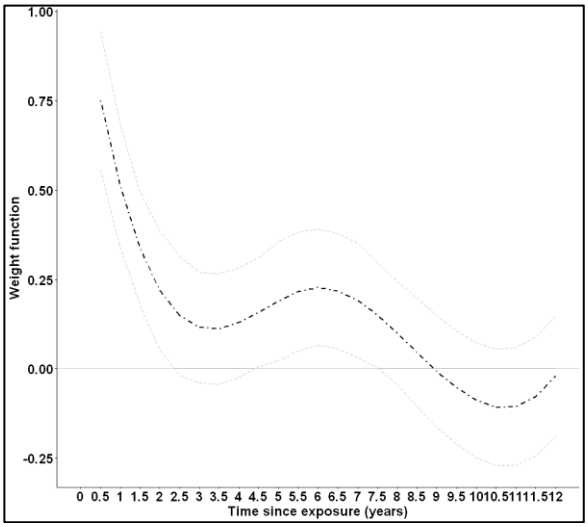
Figure A4. 1 Estimated weight functions and pointwise 95% bootstrap confidence intervals for the associations between LDIR exposures and hematopoietic cancer incidence for the A) 3-year, B) 6-year, C) 9-year, and D) 12-year time window



C. 9-year time window
AIC= 16221.50



D. 12-year time window
AIC= 16229.68



APPENDIX 4.2. Selection of an appropriate exposure metric

We compared two alternative exposure metrics (1) effective dose (2) the logarithm of the effective dose of all corresponding procedures. Table A1 shows the corresponding Akaike Information Criterion (AIC) values of the fitted WCE models. The WCE models used 6-month lagged exposure (actual effective dose or log-transformed dose) and were constrained to the right with a 9-year time window. As presented, all the models with log-transformed dose improved the WCE model's fit the data relative to the actual dose. We, therefore, represented our results in the main article with a log-transformed effective dose.

Table A4. 1 Comparison of 2 alternative exposure metrics

Exposure definition	Model	AIC
Dose	Constrained-lag	16260.83
	Unconstrained-lag	16261.76
Log(dose)	Constrained-lag	**16226.15**
	Unconstrained lag	**16221.50**

CHAPTER 5: Manuscript 3-Threshold Effect of Low-dose Ionizing Radiation from Cardiac Imaging on Hematopoietic Cancer incidence in Children with Congenital Heart Disease

5.1. Preface

Manuscript 2 demonstrated that the elevated hematopoietic cancer risk is associated with increased dose and how recent the cardiac diagnosis or therapeutic procedure was performed. However, the issue of how much radiation is too much to induce a carcinogenic effect remains. This question is particularly relevant in children with CHD due to their repeated exposure to various imaging modalities used to treat their condition. Hence, Manuscript 3 aimed to determine a threshold effect of LDIR exposure from cardiac imaging on HC in children with CHD, if one exists. We employed a non-parametric smoothing spline modeling approach to identify thresholds and estimate their locations. Using a restricted search algorithm, potential thresholds in a neighborhood identified a measure of local curvature in the flexible curve. We performed an analysis of deviance to compare the fitted threshold model or a simpler alternative model and determine if a threshold association exists. The findings can inform clinicians to be aware of the threshold dose at which radiation surveillance should be intensified.

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5.2. TITLE PAGE

Threshold Effect of Low-dose Ionizing Radiation from Cardiac Imaging on Hematopoietic Cancer incidence in Children with Congenital Heart Disease

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5.3. ABSTRACT

Background: Cancer risk associated with low-dose ionizing radiation (LDIR) from medical imaging has become a public health concern. The risk is demonstrated to be substantial, particularly among patients with congenital heart disease (CHD). However, the existence of a threshold level of radiation exposure from cardiac imaging at which the carcinogenic effect starts to rise is not well-explored. This study aimed to explore the threshold association between cardiac LDIR exposure and hematopoietic cancer (HC) among children with CHD.

Method: A nationwide population-based cohort study was conducted using the Canadian Congenital Heart Disease (CanCHD) database. The study population included children with CHD between 1999 and 2017 exposed to at least one cardiac imaging procedure involving LDIR. The cumulative dose of ionizing radiation was quantified based on their records of cardiac diagnostic and therapeutic procedures considering a 6-month exposure lag. A generalized Additive Model (GAM) with a smoothing spline was used to detect and estimate the threshold dose of LDIR.

Results: There were 13 210 children with CHD identified with cardiac imaging exposure. Of them, 93 had HC and 78 had HC other than lymphoma. Children with any HC had more LDIR procedures (mean number of procedures: 3.2 vs. 1.7; CI for absolute difference: 0.93-2.06) and had higher cumulative doses (mean dose: 18.0 vs. 11.5 mSv; CI for absolute difference: 3.44-9.55 mSv) than those without HC. Similar patterns were observed among HC cases without lymphoma. The generalized additive model (GAM) suggested a threshold dose of 6 mSv at which the LDIR exposure starts to have a carcinogenic effect. However, the most parsimonious HC dose-response is supported by a non-linear function of dose with no threshold.

Conclusion

The findings provide inconclusive evidence in favor of the threshold effect of LDIR on the HC incidence among children with CHD, possibly due to the small number of patients in the low-dose range. Large epidemiologic studies with support from studies on biomarkers of exposure effect should provide credible insights into a threshold dose.

5.4. INTRODUCTION

The possible carcinogenic effect of low-dose ionizing radiation (LDIR) from imaging procedures is an emerging public health concern. Trends of increasing use of medical imaging modalities involving LDIR have been accompanied by marked increases in radiation-induced malignancies. [47, 61] The association may be more pronounced in children with higher radiosensitivity than adults [177], especially with congenital heart disease (CHD). For the potentially deleterious effect of LDIR, the 'linear, no threshold' (LNT) dose-response model for radiation-induced cancer is adopted by the national and international regulatory and advisory bodies based on the principle that there is no safe level of radiation. [68, 178-180] This LNT assumption is widely debated for its potential to overestimate or underestimate the true low-dose risk. [82, 181, 182] Moreover, there is a difference between using a LNT model for radiation protection and whether a biological non-linear dose-response or threshold exists at low doses.[86] Indeed, evidence suggests non-linear dose-response relationship for cancer risk based on the A-bomb survivor cohort. These studies indicated non-linear dose-response for leukemia and leukemia subtypes, namely acute lymphatic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML), with weak evidence on the existence of a threshold dose.[86-88, 181-183] However, data on the threshold effect of LDIR in medically exposed patient populations, including children with CHD, who are at higher risk of developing hematopoietic cancer than the general pediatric population are largely absent. Therefore, further evaluation of the potential non-linear association between radiation exposure on hematopoietic cancer risk, including the threshold effect, is warranted.

Thus, the goal of the present study was to investigate the threshold effect of LDIR exposure from cardiac imaging on hematopoietic cancer risk in children with CHD.

5.5. METHODS

Data Sources

We combined the Quebec CHD database with the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) to develop the Canadian Congenital Heart Disease (CanCHD) Database. In Quebec, Canada, a unique Medicare number is assigned to every individual at birth to link all medical services delivered during the life course systematically. Using this unique healthcare number, we developed a population-based cohort of CHD patients from 1983 to 2017, linking the province's three administrative databases- the hospital discharge database (Med-Echo), the medical service claim database (RAMQ), and the vital status database.[105] Thus, the resulting Quebec CHD database contains comprehensive longitudinal information on all demographic, diagnostic, and therapeutic records for all Quebec residents with CHD between January 1, 1983, and March 31, 2018, inclusive.

CIHI-DAD database includes data on admission and discharge date, demographic variables, comorbidities, diagnostic and therapeutic procedures, and discharge disposition for all patients admitted to acute and day surgery facilities in all Canadian provinces except Quebec. This study included patients with at least one hospitalization record of CHD diagnosis between 1999 and 2017 in DAD. Similar to the Quebec CHD database, unique IDs can be obtained for each patient to link different hospitalization records in these databases. From them, records on patients with at least one diagnosis of CHD were extracted and combined with the Quebec CHD database to develop the Canadian Congenital Heart Disease Database (CanCHD database) for the overlapping years (1999-2017). The pooled CanCHD database thus provided longitudinal information of all hospital encounters of CHD patients across Canada for two decades. In the database, the diagnosis codes were based on the *International Classification of Diseases, 9th*

Revision (ICD-9) and *10th revision* (ICD-10, since 2006), and the treatment codes were based on the *Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures* (CCP), *Canadian Classification of Health Interventions* (CCI, since 2006), and act codes (for Quebec only).

Study population

Our study population included all patients in the CanCHD database who were born between 1999 and 2017 (Figure 5. 1) and were exposed to at least one cardiac LDIR imaging procedure. Patients with unavailable CHD diagnosis codes, sex, or inconsistent data on birth date were excluded. We also excluded children who had a cancer diagnosis within 6 months (lag-time) following birth. Due to lack of evidence on chronic lymphoblastic leukemia (CLL) and multiple myeloma (MM) to be radiogenic, [57, 58, 68] children with these cancer diagnoses were excluded.

Exposure

A 6-months lag time for assessing LDIR exposure was applied to deal with reverse causality due to protopathic bias (early symptoms of HC prompted administering the LDIR procedures).[11] Thus, records on all cardiac imaging procedures received by each child from birth to 6-months prior to the earliest cancer diagnosis, administrative censoring, or death were extracted from the CanCHD database. Since a patient-specific dose of the LDIR exposure from the procedures was unavailable, we quantified the average or median effective radiation dose for diagnostic and therapeutic cardiac procedures for children following published literatures: chest CT scans=7mSv; ventriculography =7.8mSv; myocardial perfusion imaging= 15.6mSv; diagnostic cardiac catheterizations=4.6mSv; and interventional catheterization=6.0mSv. [45, 94, 95] Cumulative LDIR doses were calculated for each subject.

Outcome

We defined our outcome of interest, incident cancer, as the first hospitalization with a primary or secondary HC diagnosis occurring 6 months to age 18, during the observation period from January 1, 1999, to March 31, 2018. We first defined all hematopoietic malignancies as the outcome. We further evaluated the risk for hematopoietic malignancies previously found to be radiogenic.[57, 68] Therefore, the latter excluded lymphoma (NHL and HL) but kept all leukemia (acute, chronic myeloid and lymphoblastic leukemia; other unspecified leukemia), other myeloproliferative malignancies, and myelodysplastic syndrome, resulting in a more etiologically relevant endpoint with respect to ionizing radiation. We set all HC collectively, with or without lymphoma as the outcome for the following reasons. First, previous studies aimed to assess the risk of cancer in children exposed to radiation during cardiac imaging were unable to differentiate between increased cancer risk due to radiation dose and cancer-predisposing factors owing to the lack of data on an appropriate comparison group with unexposed children with CHD.[72, 74-76] Moreover, these studies reported conflicting findings on cancer risk in children exposed to radiation compared to the general population. Therefore, uncertainty remains regarding the association between LDIR from cardiac imaging and HC, including the subtypes of HC in this patient population. Secondly, with composite outcome definitions, we circumvented the possible overfit bias due to the instability of spline estimates with the number of events around 100 or less across HC subtypes,[141] while preserving the advantages of flexible modelling to establish the temporal relationship of the time-varying LDIR exposure and cancer incidence. In our study with even the pan-Canadian database on CHD, the number of HC incidents was lower than 100 for all subtypes except for ALL. Primary specified cancers were ascertained by ICD-9 codes before 2006 and then by corresponding ICD-10 codes.

Covariates

Measurements were obtained for the following covariates to account for plausible biological confounders in our regression analyses: Age (continuous and time-varying), medical comorbidities (congestive heart failure, hypertension, diabetes mellitus, and history of stroke). We applied a 6-months lag time to characterize comorbidities for each subject. Children with CHD were assigned a CHD diagnosis by using a previously described and validated hierarchical algorithm.[16, 105] We classified CHD severity based on anatomic diagnosis[105]: severe defects (tetralogy of Fallot, truncus arteriosus, transposition complex, univentricular heart, hypoplastic left heart syndrome, endocardial cushion defects, and Ebstein anomaly), shunts (atrial or ventricular septal defects, patent ductus arteriosus, unspecified defects of septal closure), valvular (aortic coarctation, anomalies of the pulmonary artery or valve, congenital tricuspid valve disease, congenital aortic or mitral stenosis, or insufficiency anomalies of great veins), and other CHD lesions (unspecified anomalies of the heart or aorta). Genetic syndromes were defined as a binary indicator (yes/no), having a hospital discharge diagnosis of any genetic syndrome during the observation period. Sex, age at first exposure, and year of birth were also included in the regression analyses as time-fixed covariates.

Statistical Analysis

A generalized additive model (GAM) with a binomial link was used to identify the threshold association for the effect of LDIR on the incidence of cancer among children with CHD.[184, 185] We used a spline smoothing with 4 degrees of freedom to fit the potential non-linear dose-response association, which has been validated and used in several studies to identify and estimate threshold association.[184, 186-188] We fitted 4-df GAM models for all HC, with or without lymphoma.

Epidemiological evidence on prolonged exposure to low-dose ionizing radiation suggests an increased cancer risk above 50 mSv.[80, 93] Due to high radiosensitivity among children,[177] we hypothesized that the range for potential threshold dose for our study population might be much lower than 50 mSv. Moreover, it has been estimated that the lifetime exposure dose from cardiac catheterization of a contemporary young adolescent with CHD is about 20 mSv.[92, 189] We, therefore, applied our search algorithm for cumulative doses less than 50 mSv. Using the restricted search,[184] we searched for potential thresholds in a neighborhood of doses rather than the entire exposure range. We identified the neighborhood based on a measure of local curvature in the GAM curve, a numerical second derivative.[184] The neighborhood where the mean numerical second derivative of the estimated GAM curve is more than one standard deviation away from zero across the entire range of the LDIR dose is of our interest (See APPENDIX 5.1). A Chi-square test comparing the deviances of the fitted threshold model and a simpler alternative model was used as the criterion for determining if a threshold association exists.

This GAM-derived threshold was validated using piecewise regression.[186] The use of piecewise regression aided us in determining whether the GAM-derived threshold represents the meaningful split of the data. With a meaningful threshold, the relationship between LDIR exposure and cancer incidence would differ between the regions separated by the threshold. In order to gauge the stability of the shape of the GAM curve, we conducted sensitivity analyses changing the degrees of freedom (df) to 3. We also varied the span in calculating the numerical second derivative (Δ=0.02 and 0.05) and the number of points at which the threshold model is estimated (n or n/2). Lastly, we performed a simulation study to examine how much precision we

had for estimating a threshold effect given the distribution of exposure among cases in the study population (see APPENDIX 5.2). All Statistical analyses were performed using R.

5.6. RESULTS

In total, 93 children were hospitalized with any HC diagnosis during the follow-up period of up to 18 years of age, yielding an incidence rate of 6.5/10 000 person-years (95% CI, 5.3-8.0). The corresponding incidence rate of 78 HC cases without lymphoma is 5.5/10 000 person-years (95% CI, 4.3-6.8). Table 5. 1 presents the basic characteristics of the study population by cancer status. Children with hematopoietic cancer, with or without lymphoma, had more procedures than those without cancer. The mean dose they received was also higher than their counterparts. They had more known genetic syndromes, were more severe regarding CHD lesions, and had more cardiac comorbidities than patients without cancer.

In our preliminary analyses, we fit three generalized linear models (GLM) with logit links corresponding to linear, linear-quadratic [87-89, 183, 190] and log-transformed cumulative dose. The model with log-transformed cumulative dose yielded the minimum AIC and maximum positive deviance from linearity (Table S5. 1). Thus, our subsequent findings were based on the exposure metric defined as 6-months lagged log-transformed cumulative LDIR dose. Figure 5.2 A and Figure 5.2 B show the estimated 4-df GAM curves for the associations between cumulative dose and HC incidence, with or without lymphoma, respectively. Wider confidence intervals for cumulative doses of more than 3.5 mSv could reflect low statistical power as only a few children had exposure around that higher dose range. Using the estimated GAMs, our restricted neighborhood search algorithm identified a local curvature at 6 mSv, with or without lymphoma, indicating a possible threshold dose. We noted comparable probability of HC on logit scale, with

or without lymphoma, owing to limited exposed lymphoma cases (Figure S5. 1). The vertical line in Figure 5.3 indicates the location of the estimated 'change-in-effect threshold, [184] suggesting that the risk of HC starts to increase as the cumulative effective dose exceeds a threshold of 6.0 mSv. However, the fitted threshold model and the simpler model with log-transformed cumulative dose (downward-curving) provided an equivalent fit to the data suggesting that the association might be non-linear but without a threshold (Figure 5.3).

Comparison between the linear and the final downward-curving non-linear model suggested that the linear representation of the cumulative dose would have underestimated the risk in this low-dose range (Figure 5.3). Our sensitivity analyses noted no difference from our primary analyses (Figure S5. 2 and Figure S5. 3). Our simulation study suggested that the power for the chi-square test increased as the number of exposed individuals (n=1000 vs. 13000) increased. However, the power decreased as the location of the true threshold moved away from the 10th percentile of the exposure distribution (Table A5. 1).

5.7. DISCUSSION

This is the first nationwide study in a pediatric CHD population to evaluate the possible threshold effect of LDIR exposure from cardiac procedures and hematopoietic cancer incidence. We demonstrated that the risk of hematopoietic cancer starts to increase as the cumulative effective dose exceeds a threshold of 6.0 mSv, which corresponds to an additional risk of fatal cancer in 1 of 700 patients exposed at less than 1 year of age.[92, 149-151] However, comparing the fitted threshold model and the simpler model with log-transformed cumulative dose indicated that the association might be non-linear but without a threshold.

The cancer risk associated with low-dose ionizing radiation and the corresponding shape of the dose-response curve is central to setting standards in radiological protection. Epidemiological evidence supports an increased cancer risk above 50 mSv of protracted exposure.[80] However, the shape of the dose-response curve below 50 mSv is uncertain.[80] Large epidemiological studies based on Life-Span Study (LSS) cohort demonstrated an absence of evidence of a significant departure from a linear dose-response in the low-dose region (<0.2 Sv) for solid cancer incidence.[87, 88, 183, 190] For leukemia incidence, a non-linear dose-response model fitted the data reasonably well.[86-88, 183, 190] Separate analyses for leukemia subtypes, namely acute lymphatic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML) also suggested a linear-quadratic dose-response model.[183] Concerning lymphoma, however, the evidence of an association with ionizing radiation exposure has been inconclusive.[62] It is noteworthy that A-bomb survivor follow-up data for radiation carcinogenesis in humans involve radiation doses 1 to 2 orders of magnitude greater than those encountered in diagnostic imaging studies, on the order of 1 Sv (1000 mSv) and more.[191] Concerning the dose-response curve for hematopoietic cancers associated with LDIR, our data supported a non-linear fit, similar to LSS leukemia incidence.[86-88, 183, 190] The number of exposed cases of lymphoma diagnosed in our study population was too low (n=15, accounting for only 16% of the exposed HC cases), and their inclusion into the analysis did not alter the non-linear fit. Our result suggested a downwardly curving (decreasing slope) dose-response relationship among children with CHD. This indicated that with a linear-no-threshold (LNT) assumption, the LDIR-induced cancer risk at the low-dose range in our study population would be underestimated. A possible explanation for such downward curving could be the presence of a subpopulation of children hypersensitive to radiation.[192] Since all the hypersensitive exposed individuals would have

developed cancer as the doses increase, even a modest fraction of such individuals (only 0.25% of the population) could lead to the downward sloping of the dose-response for the entire study population.[80] Another explanation is the manifestation of the "bystander effect" phenomenon.[80, 193] This refers to radiation-induced oncogenic damage to the bystander cells adjacent to directly irradiated cells. [194] With a relatively higher dose, all relevant cells subject to radiation damage get affected, resulting in a saturation of bystander effect and, thus, the downward dose-response curve.[80, 189, 195] Indeed, using γ-H2AX foci in peripheral blood lymphocytes as a biomarker for the assessment of individual DNA radiation damage in pediatric CHD patients undergoing cardiac catheterization, Beels and Colleagues suggested that the in vivo dose-response does not support LNT assumption, rather a hypersensitivity is observed at the low-dose range, owing to the bystander effect and the associated reactive oxygen species formation. [195] With an estimated median effective dose of 6.4 mSv, the authors demonstrated that the risk estimates according to the LNT hypothesis might be underestimated in the pediatric CHD population.[195]

We found evidence of non-linearity in the relationship between radiation dose as a continuous variable and cancer risk, a condition necessary for the existence of a threshold effect.[184] Previous studies exploring the threshold effect of low-dose ionizing radiation demonstrated the presence of threshold dose in the low-dose range of 0.01-0.10 Sv, notably in the leukemia incidence data among A-bomb survivors.[86-88, 183] Hoel and Li showed that a "threshold-like response" up to 0.15 Sv range is equivalent to or better than a no-threshold model for leukemia.[86] The authors reported a linear dose-response function for CML and ALL but linear-quadratic for AML.[86] An improvement in model fit was observed for a threshold model than a no-threshold model for CML and total leukemia.[86] Accounting for uncertainties in radiation dose, Little and Muirhead reported a central estimate of a threshold being 0.11 Sv (95%

CI: 0.003, 0.27) for leukemia incidence data.[89] The statistical significance of the threshold effect for leukemia incidence, however, disappeared when the assumed dosimetric geometric standard deviation was increased from 35% to 45%, indicating weak evidence of a dose threshold.[89] Separate analyses by leukemia subtypes suggested strong evidence of a dose threshold (best estimate 0.30Sv, 95% CI: 0.08, 0.60) for AML, borderline levels of statistical significance for CML, and a positive but insignificant dose threshold for ALL.[183] However, the linear-quadratic dose-response model improved the model fit compared to a linear-threshold model across all leukemia subtypes.[183] The authors conclude that the current evidence on the biological mechanisms does not support the existence of a low threshold.[88, 89] In line with these findings, our study showed a threshold dose of 6mSv for hematopoietic cancer incidence among children with CHD, yet suggested that the threshold model is equivalent to the non-linear model with no threshold.

Major challenges for epidemiologic radiation dose-response studies have been to achieve statistical power and precision, especially in the low-dose range.[81, 196] Statistical power and precision are in good part a function of the number of persons at risk and person-time at risk, the number of minimally exposed cases with the health outcome of interest, follow-up time, dose range, and distribution in the study population, and the magnitude of the radiation effect.[81] Our inconclusive findings regarding the threshold effect could be a reflection of low statistical power as only a few exposed children had hematopoietic cancer in the low-dose range during the observation period. It was demonstrated that it would require a sample size of approximately 5 million to document the carcinogenic effect of a radiation dose of 10mSv or less. [80, 196, 197] Studies in children would require a larger sample size to achieve reasonable power due to low exposure levels and limited cancer cases.[198] Indeed, our simulation study also indicated that we

had limited statistical power to detect a threshold dose, albeit our study was based on the largest pan-Canadian birth cohort of children with CHD.

There has been a paucity of observational research examining the threshold effect of low-dose ionizing radiation from medical imaging and cancer incidence. Existing data on the large CT studies [53, 55] are of limited use in evaluating linear no-threshold assumptions owing to the dosimetric limitations and likely epidemiologic biases, namely, reverse causality and indication bias.[81] Our study's strength is its ability to use a unique database with extended follow-up time on a large birth cohort of children with CHD. It enhances internal validity by providing opportunities to adjust potential confounders and other inherent biases. In this study, we applied a 6-month lag time for assessing LDIR exposure to deal with reverse causality due to protopathic bias. Our choice of the lag period is unlikely to bias the findings as the hematopoietic cancer genesis is brief, and diagnosis is typically not assessed by cardiac imaging procedures.[157] Moreover, several covariates, including sex, age at first LDIR exposure, birth year, CHD severity, and syndromes, were taken into account to control for indication bias. Our use of the flexible data-driven GAM modeling to identify a potential threshold dose enabled us to assess the non-linearity of the dose-response association. Unlike most studies that resorted to visual inspection of the GAM curve to identify a threshold,[186-188] we used a more robust restricted neighborhood searching approach, which has been validated and previously used for estimating threshold associations.[184]

Limitations

Some limitations of our work need to be mentioned. We used an administrative database, and critical clinical information, including but not limited to the reason a cardiac imaging procedure was performed, for instance, was not available. Regarding the outcome ascertainment, our use of

inpatient data to define cancer may be less subject to misclassification due to its high data quality.[169] However, since we used only inpatient data, some cancer cases not requiring hospitalization may be underrepresented. Assessment of threshold dose by HC subtypes was not feasible due to the small number of exposed cases. Moreover, procedure-specific data on delivered doses were unavailable in our database; thus, similar to other studies,[47, 94, 95, 97, 135, 157] this study relies on effective doses reported in the literature.[170, 171] Since the effective dose is not a physical, measured quantity but a single 'whole-body equivalent' dose estimate, using it as a proxy for the actual delivered dose can induce measurement error in exposure [172] and, therefore, should be interpreted with caution. We cannot disregard the possibility of residual confounding due to heterogeneity in exposure intensity across calendar time,[173, 174] type of equipment and imaging strategies, training of the operator, and site or procedure complexity.[175]

Exploring the presence of a threshold effect of LDIR exposure on cancer risk against the linear no-threshold dose-response model is crucial for radiologic protection policy. In patients with CHD, where repeated radiation exposure is expected throughout the entire lifespan, the threshold association will help identify the point of exposure at which increased surveillance should be initiated. Our findings indicated that the most parsimonious dose-response model for HC among children with CHD is a non-linear model without a threshold. These results indicated the difficulty of distinguishing between a threshold and a non-linear association in a setting where only a fraction of children with CHD born between 1999 and 2017 and followed since birth was exposed (9.4% in Figure 5. 1). However, simply because a 'nonlinear-no threshold' model fits the data does not imply that biologically a low-dose threshold is non-existent. Future studies with sufficient power, extended follow-up time, improved dosimetry, and appropriate methodology to control for potential sources of bias should permit credible insights into a

threshold dose. Moreover, evidence synthesis from the large epidemiological studies and studies with biomarkers of exposure effects (γ-H2AX foci), disease risk, and susceptibility are necessary to better understand radiation-induced carcinogenesis at low dose.[189]

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None

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DISCLOSURES

All authors declare no conflict of interest.

TABLES

Table 5. 1 Clinical characteristics of the study population, by cancer status

Characteristics	Children with Hematopoietic Cancer†	Children with Hematopoietic Cancer excluding Lymphoma ‡	Children without Hematopoietic Cancer
	n=93	n=78	n=13117
Male, n (%)	46 (49.5)	36 (46.2)	6951 (53.0)
Median age at 1st Cancer (IQR), years	4.6 (3.0, 8.4)	4.5 (2.9, 7.7)	-
Median age at 1st LDIR (IQR), months	6 (2, 22)	6 (2, 22)	7 (2, 36)
Total person-years	587	452	141759
Mean number of LDIR procedures (Std)	3.2 (±2.8)	2.9 (±2.6)	1.7 (±1.5)
Mean doses(mSv)(Std)	18.0 (±15.0)	17.0 (±14.4)	11.5 (±10.5)
Known genetic syndromes, n (%)	22 (23.7)	21 (26.9)	2189 (17.0)
CHD lesions, n (%)			
Severe	45 (48.4)	38 (48.7)	4952 (37.8)
Shunt	29 (31.2)	26 (33.3)	5362 (40.9)
Valve	5 (5.4)	4 (5.13)	1726 (13.2)
Other	14 (15.1)	10 (12.8)	11077 (8.2)
Comorbidity*, n (%)	41 (44.1)	36 (46.2)	2908 (22.2)
History of cardiac surgery, n (%)	55 (59.1)	47 (60.3)	7801 (59.5)

†All hematopoietic cancers, including leukemia (AML, CML, ALL, and other unspecified leukemia), other myeloproliferative neoplasms, and myelodysplastic syndromes, and lymphoma (NHL, and HL)
‡Excluding NHL, and HL
*Comorbidities include congestive heart failure, hypertension, diabetes mellitus, and history of stroke

FIGURES

Figure 5. 1 Derivation of the study population. CHD indicates congenital heart disease; HC, hematopoietic cancers; and LDIR, low-dose ionizing radiation

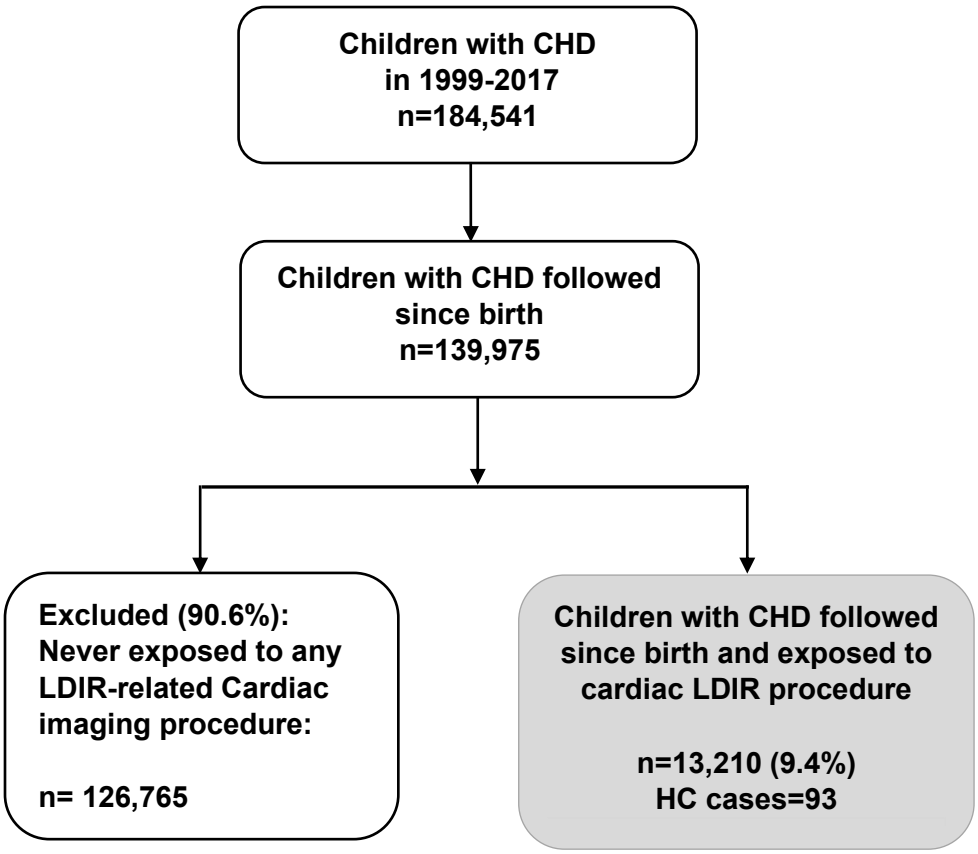


Figure 5.2 A. Estimated 4-df GAM curve (95% CI) for the associations between all HC incidence and cumulative LDIR dose (log-transformed). The restricted neighborhood searching algorithm was employed on this estimated GAM curve to identify the threshold dose using Δ=0.02 and *n/2* additional number of points at which the threshold model was estimated.

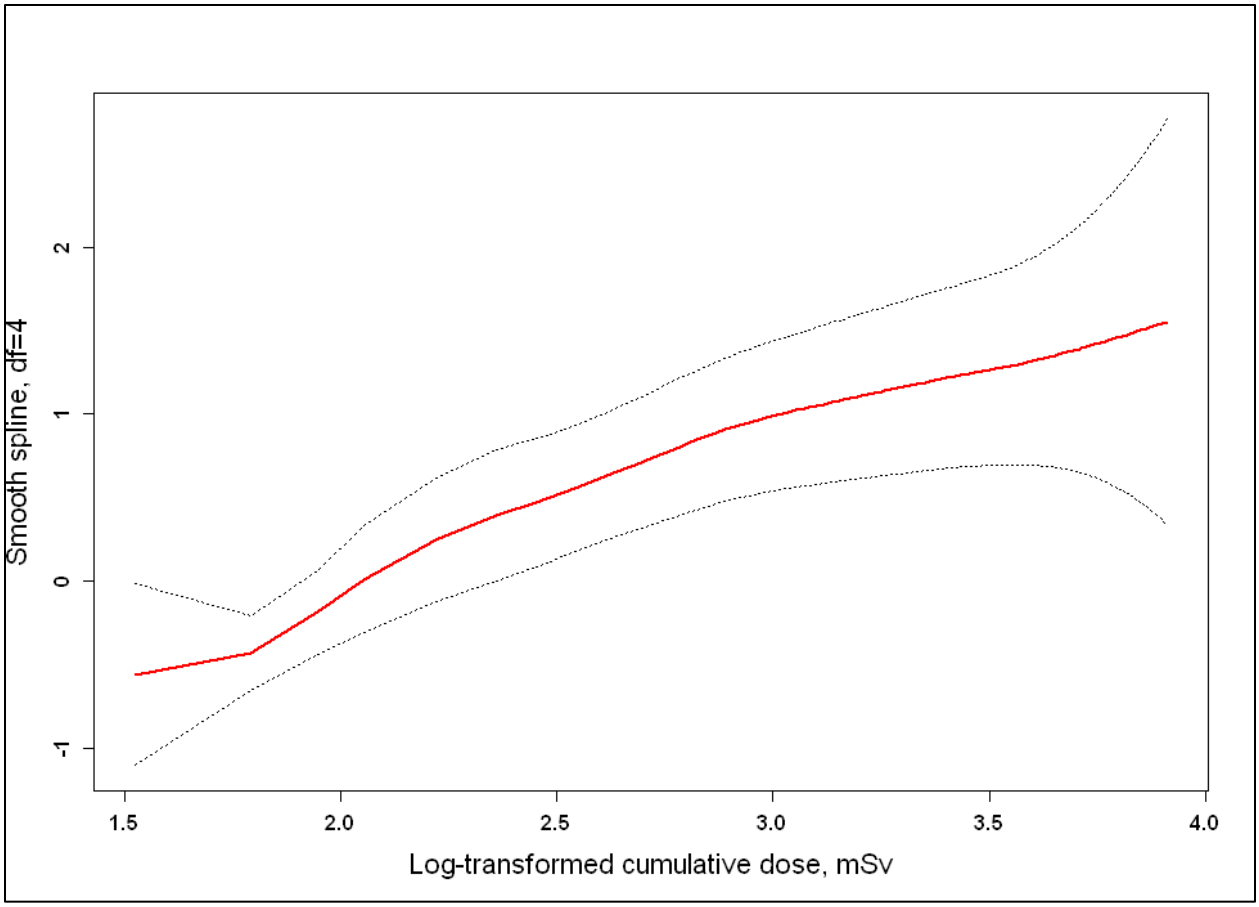


Figure 5.2 B. Estimated 4-df GAM curve (95% CI) for the associations between HC incidence (excluding NHL, HL) and cumulative LDIR dose (log-transformed). The restricted neighborhood searching algorithm was employed on this estimated GAM curve to identify the threshold dose using Δ=0.02 and *n/2* additional number of points at which the threshold model was estimated.

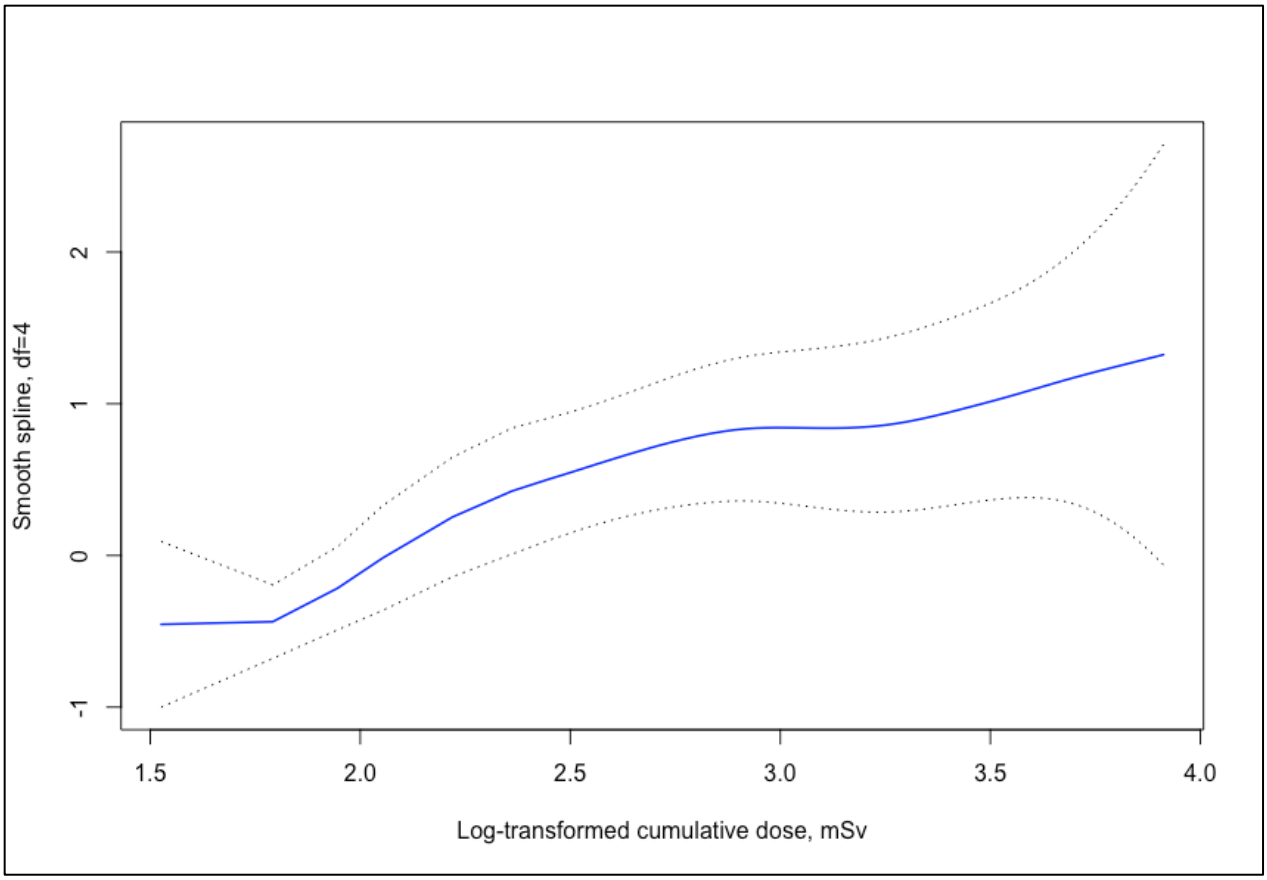
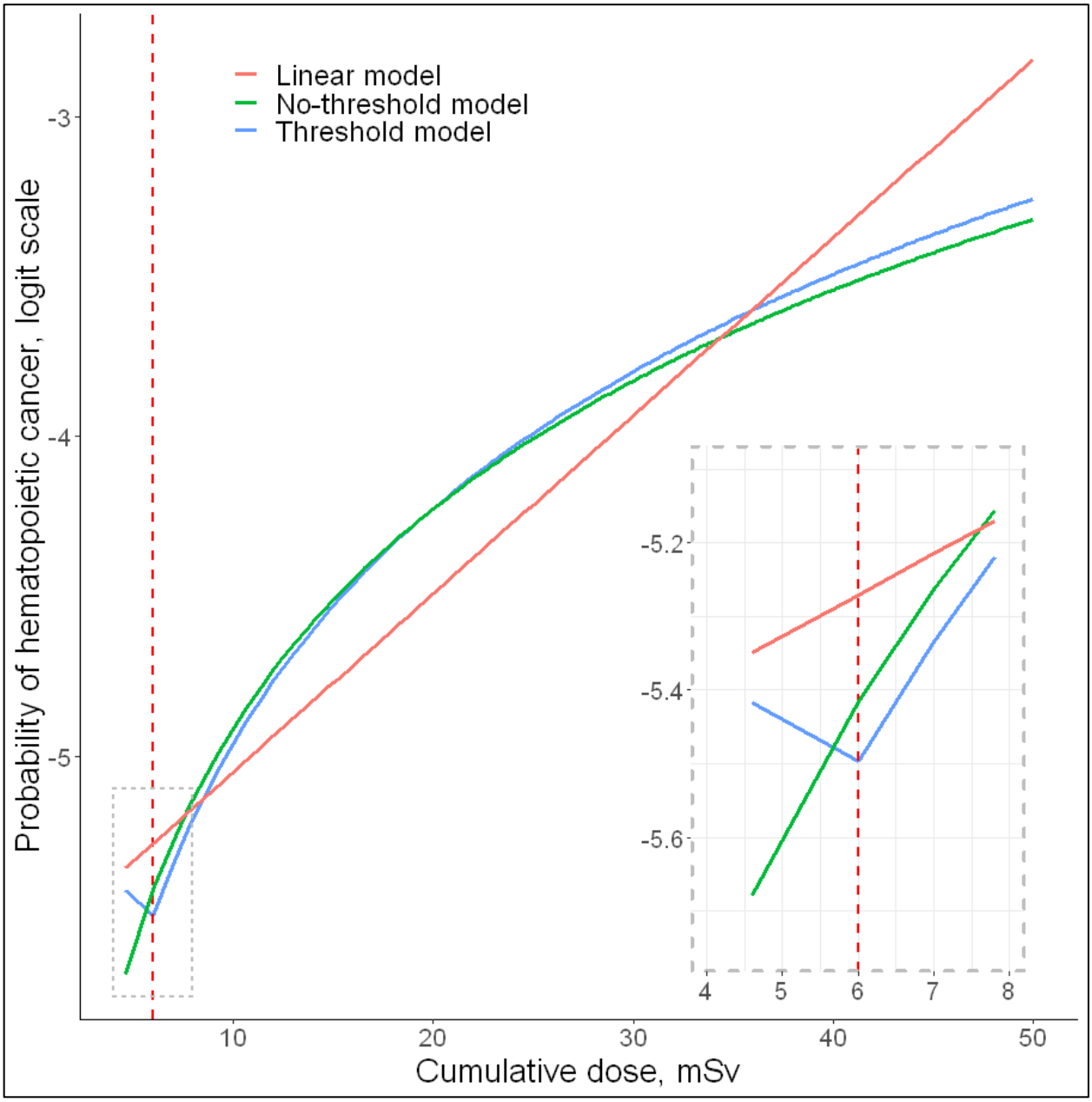


Figure 5.3 Probability of HC (logit scale) using a non-linear (i) threshold model (solid blue) and (ii) no-threshold model (solid green) and (iii) a linear model (solid red). The vertical (dashed red) line indicates the location of the GAM-identified threshold (6 mSv)



SUPPLEMENTAL MATERIALS

Table S5. 1 Result of three logistic regression models, corresponding to linear, linear-quadratic, and log-transformed representation of cumulative dose. The positive maximum deviance difference and minimum AIC indicates a model which fits better than a straight line

Model	Representation of dose	AIC[a]	Deviance	Deviance Difference[b]
1	Linear	1068.3	1064.3	-
2	Linear-quadratic	1064.2	1058.2	6.1
3	Log-transformed	1061.6	1057.6	6.7
Best model	**Log-transformed**	**1061.6**	**1057.6**	**6.7**

[a] AIC, Akaike Information Criteria
[b] Compared with the linear model (Model 1)

Figure S5. 1 Probability of HC (logit scale), with or without lymphoma, using a non-linear threshold model. The vertical (dashed red) line indicates the location of the GAM-identified threshold (6 mSv)

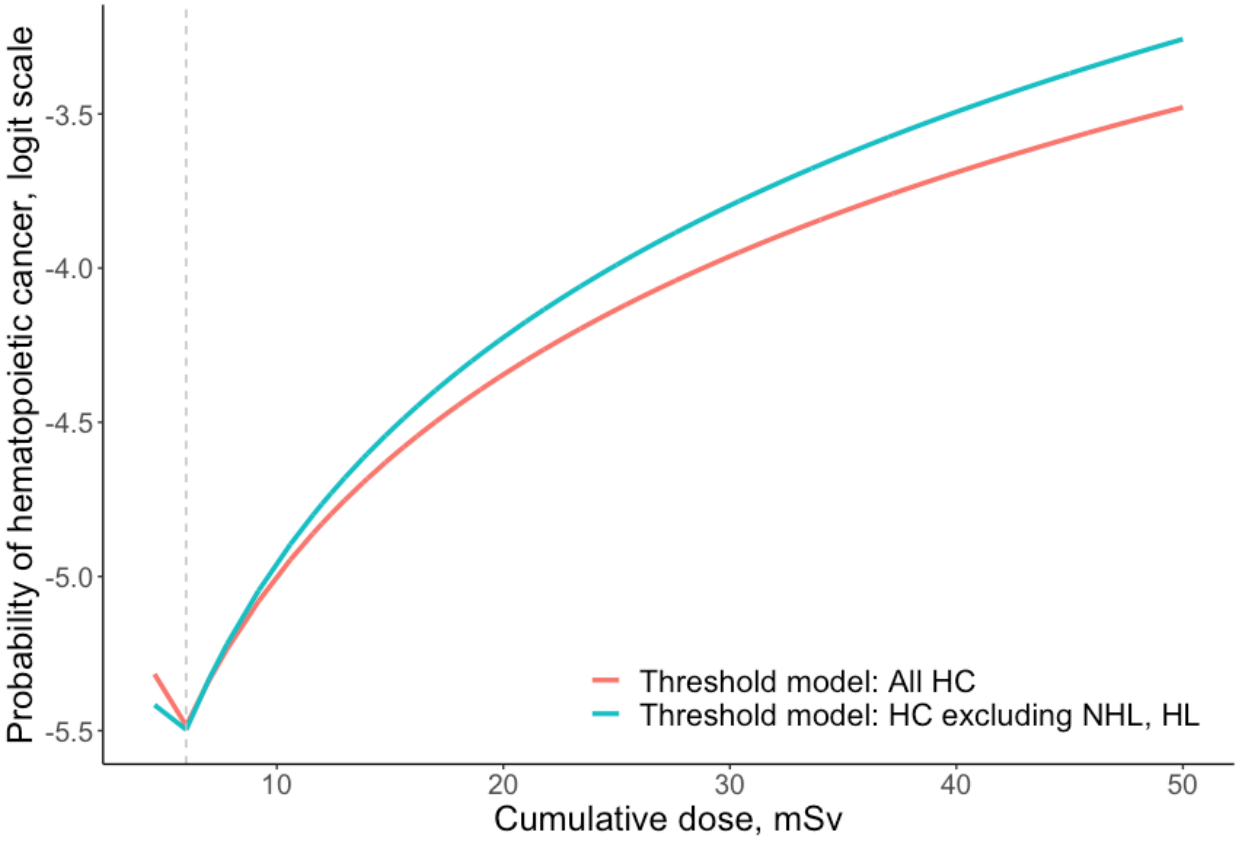


Figure S5. 2 Estimated 3-df GAM curve (95% CI) for the associations between all HC incidence and cumulative LDIR dose (log-transformed).

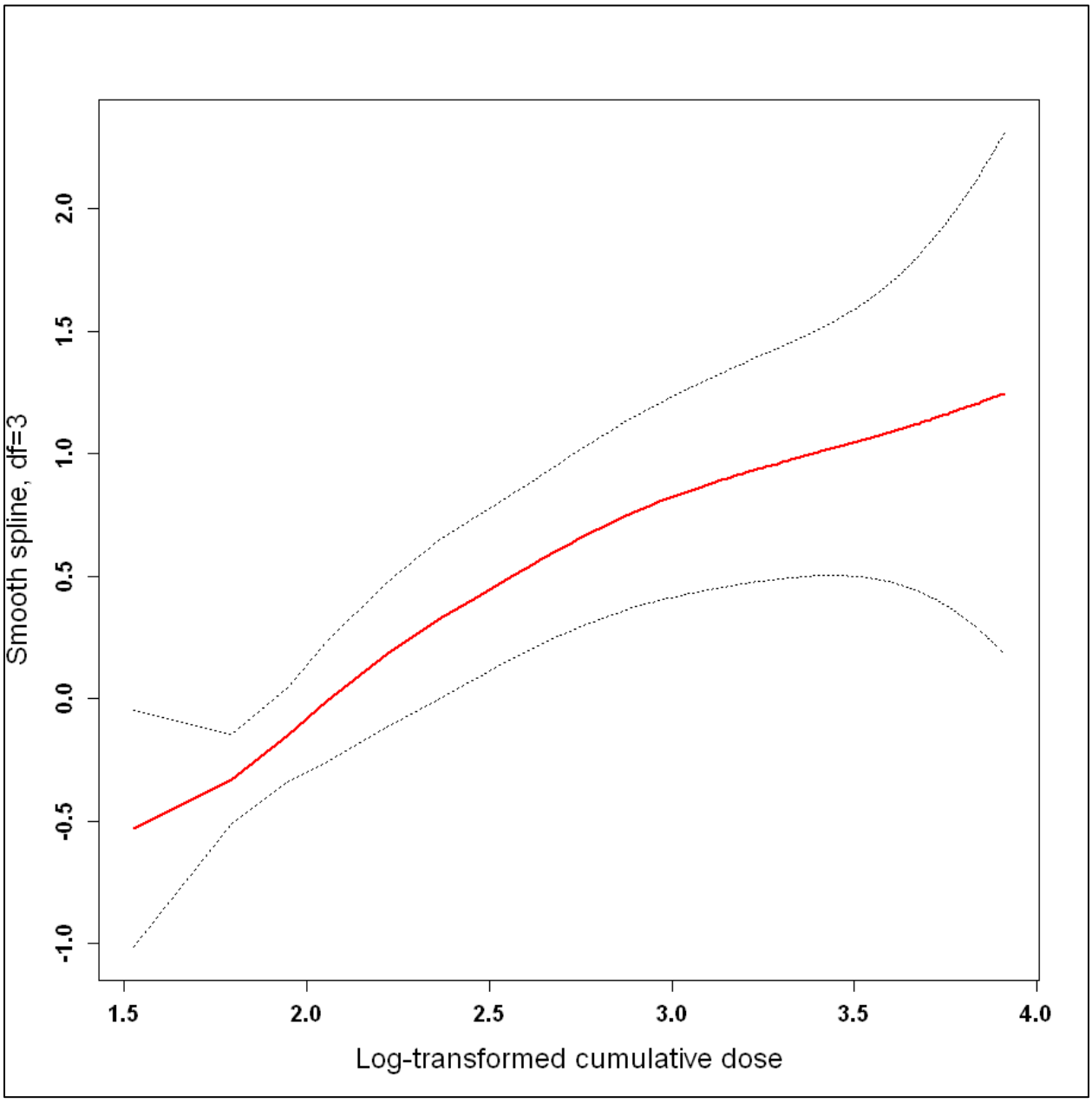
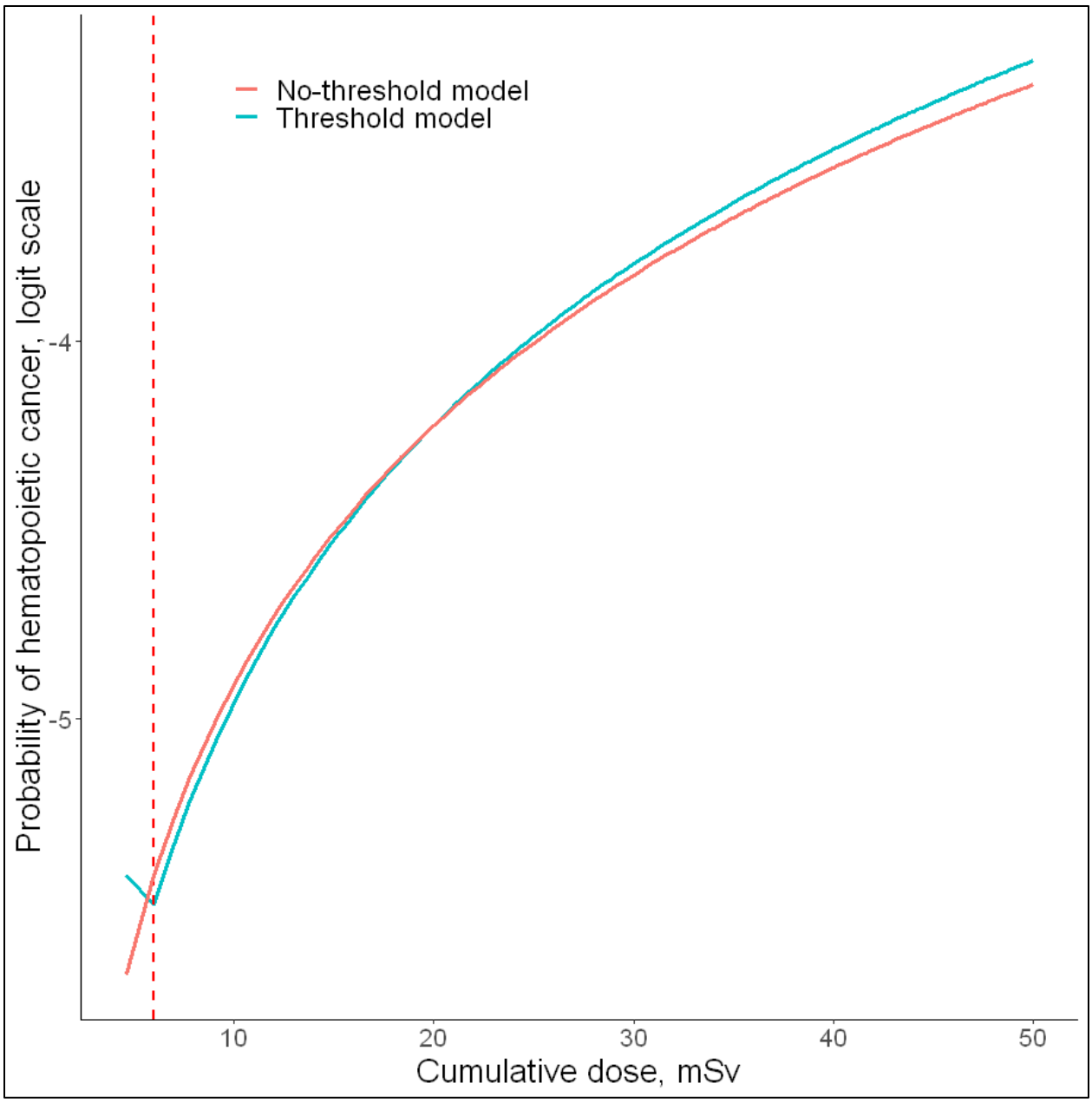


Figure S5. 3 Sensitivity Analysis: The restricted neighborhood searching applied to 3-df GAM curve, Δ=0.05 and *n* additional number of points at which the threshold model is estimated. The curves are the probability of all HC (logit scale) using a non-linear (i) threshold model (solid blue) and (ii) no-threshold model (solid green). The vertical (dashed red) line indicates the location of the GAM-identified threshold (6 mSv).



APPENDICES

APPENDIX 5.1. Steps to identify a threshold, estimate, and determine if a threshold exists [184] (primary analysis)

STEP 1: Fit a generalized additive model (GAM) with 4-df to the data.

STEP 2: Calculate the numerical second derivative based on the following finite difference formula

$$\frac{\big(S_4(x+\Delta)-S_4(x)\big)-(S_4(x)-S_4(x-\Delta))}{\Delta^2}$$

where, $S_4(x)$ is the GAM estimate at x. Δ=0.02, the smoothing parameter based on the 1% of the range of the empirical exposure distribution (log-transformed).

STEP 3: Identify a suspicious neighborhood of potential thresholds consisting of all points at which the quantity in STEP 2 > 1SD away from 0.

STEP 4: At each potential point identified in STEP 3, t, fit logit(P(Y=1) =b_0+b_1X+b_2t; The location t with the lowest Akaike Information Criterion (AIC) was chosen as the threshold.

STEP 5: To determine if a threshold exists, we tested H_0: logit(P(Y=1) = b_0+b_1X using LRT.

STEP 6: We declared a threshold model exists if the final threshold model fitted better than a 4-df GAM based on AIC.

APPENDIX 5.2. Simulation study design

Data generation

We evaluated our precision for estimating a threshold effect given the exposure distribution among cases in the study population. To this end, we generated the exposure variable from a skewed normal distribution with mean=2.09, standard deviation=0.54, skewness=1.22, and kurtosis=3.74. These values of the parameters were obtained from the empirical exposure distribution in our study population. The exposure distribution from the skewed normal distribution and that from the empirical data represented in Figure A5. 1. We hypothesized that the true model is a "change-in-effect" model with the following coefficients:

$$Logit(P(Y = 1)) = a + bX + c(X - t)_{t+}$$

where, a= log(0.007), b=log(1.1) and c=log(2.5)

$$(X - t)_{t+} = x - t \; if \; x \geq t \; and \; (X - t)_{t+} = 0 \; if \; x < t$$

The "change-in-effect" model refers to the dose-response curve where the effect is assumed to change (increase) after reaching the threshold. Following the data generation, we applied the restricted neighborhood search algorithm (APPENDIX 5.1) to the simulated data. We assumed that the threshold (t) located at the 10th, 25th, 50th, 75th or 90th percentile of the true distribution of the exposure. Precision and bias of the estimated threshold using GAM-based searching with exposed sample sizes, n=1000 and 15000 (similar to that of the study population) were presented in terms of empirical power, relative bias, variability and mean squared error (MSE).

Figure A5. 1 Overlayed density of the empirical distribution of log-transformed cumulation dose and simulated dose from skewed-normal distribution

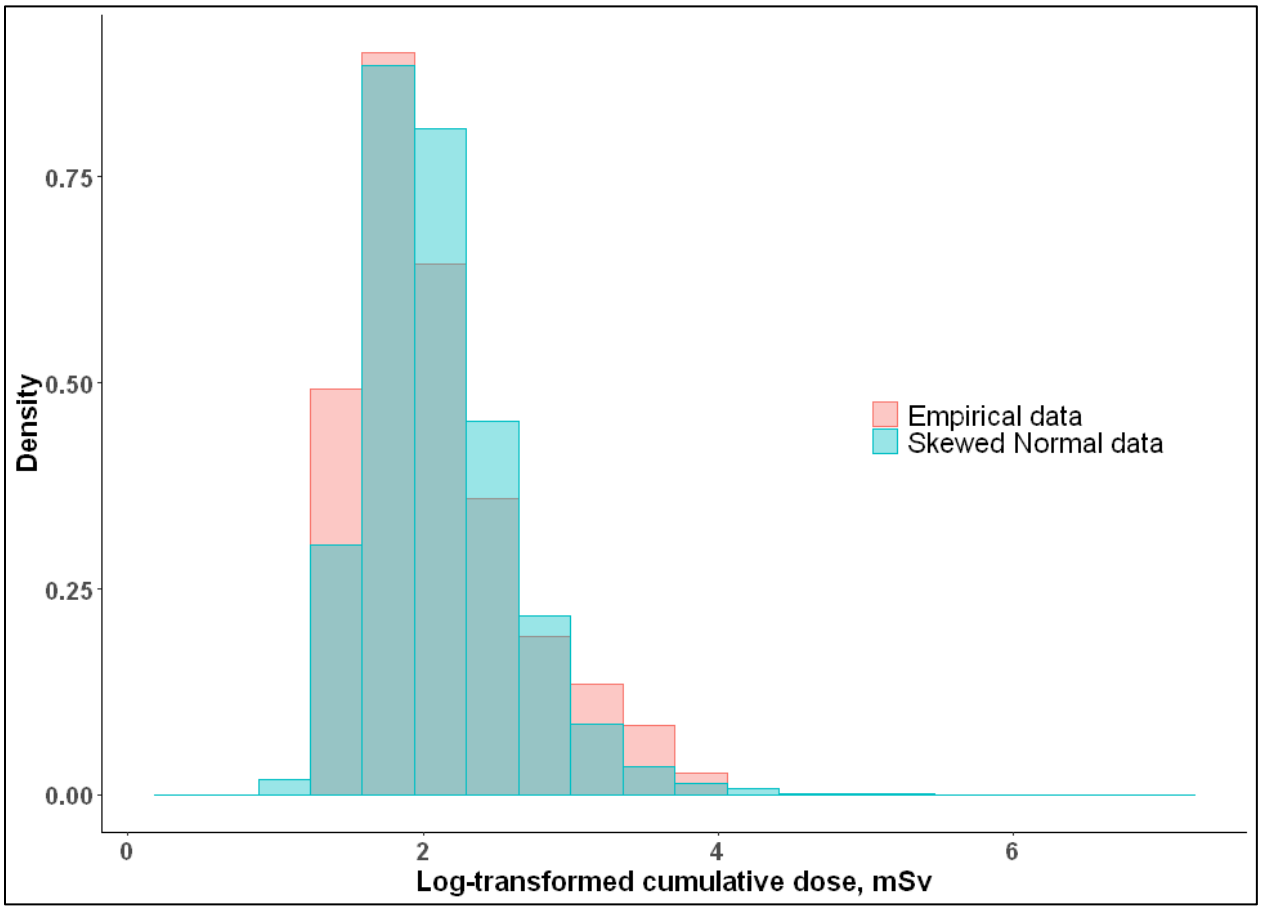


Table A5. 1 Empirical power, Bias, Variability and Mean squared error (MSE) of the estimated model for Skewed Normal exposure and binary outcome by location of true threshold (500 simulations)

True model	Searching for	Number of Exposed individuals	Criteria	Position of the threshold (percentiles)				
				10	25	50	75	90
Threshold Change-in-effect	Threshold: Change-in-effect	n=1000	Power (%)	26.8	25.1	22.0	21.3	20.4
			Relative Bias	82.4	48.5	32.3	5.5	-3.8
			Variance	2.3	2.1	2.1	2.0	2.3
			MSE	3.9	2.8	2.5	2.0	2.3
			# of outcome	18	15	12	10	9
		n=13000	Power (%)	48.6	48.0	46.4	46.6	47.4
			Relative Bias	79.7	55.1	39.2	10.1	3.7
			Variance	3.3	3.3	3.5	3.2	3.1
			MSE	4.8	4.2	4.1	3.3	3.2
			# of outcome	89	89	89	89	88

CHAPTER 6: DISCUSSION

Improved survivorship among children with CHD results in a longer time window to express carcinogenesis. Therefore, characterizing the multifactorial mechanism of cancer predisposition in children with CHD remains compelling. The findings from this research elucidate the shared genetic and environmental risk factors of HC among children with CHD. Knowledge gained from this series of studies is expected to help efficiently manage the CHD population and improve their prognosis and quality of life.

6.1. Summary of findings

In the first manuscript (Chapter 3), I estimated the overall and sub-type specific HC incidence with or without genetic syndromes in children with CHD. I compared the risk of HC in our study population to the general pediatric population in Canada. Overall, the risk of HC is found to be 13-fold higher in children with known genetic syndromes compared to the general population. I found that the cumulative incidence of HC is higher in children with known genetic syndrome compared to children with the genetic syndrome (2.44% vs. 0.79%). The findings from the manuscript showed that the overall HC incidence was higher in the first six years of life than in the subsequent 6-year intervals up to adulthood. In addition, HC subtype analyses demonstrated that Acute myeloid leukemia (AML) had a higher cumulative incidence during early childhood than acute lymphoblastic leukemia (ALL). Given the importance of early cancer detection to improve long-time survival, these results highlighted the need to be especially vigilant for possible symptoms and choose therapeutic approaches for CHD patients with genetic syndromes as early as necessary.

The second manuscript (Chapter 4) used a population-based cohort of children with CHD born between 1999 and 2017 to assess the association between LIDR from cardiac imaging and

cancer risk. In Manuscript 2, using the novel method of modeling time-varying exposures, I investigated how radiation-related cancer risk may vary depending on the current and past LDIR dose. Overall, the results indicated that the risk of HC, with or without lymphoma is mostly associated with the LDIR dose in the past 5 years, with a maximum risk for continuous exposure in the last 2 years. The limitations in the existing literature on the association between LDIR and cancer incidence were highlighted, including insufficient statistical power and follow-up time, reverse causality, and indication bias. This study demonstrated how careful analyses accounting for time-varying exposure and timing of past exposures might improve the model's fit to data and enhance our understanding of the mechanism underlying the potential carcinogenic effect of LDIR exposure.

Manuscript 3 (Chapter 5) explored the existence of a threshold dose of LDIR exposure, beyond which the exposure results in an increased risk of HC. I defined a cohort of children with CHD who were exposed to LDIR from cardiac imaging. I used a generalized additive model (GAM) with smoothing splines, therefore, with no *a priori* assumptions on the functional form of the dose-response relationship, to identify the threshold and estimate its location. The restricted neighborhood searching algorithm identified a threshold dose of 6 mSv for HC incidence, with or with lymphoma. However, a non-linear function of dose without a threshold improved the model fit to the data more than a threshold. This study underscored the necessity of sufficient statistical power, extended follow-up time, and improved dosimetry in identifying a threshold effect of LDIR from cardiac imaging on cancer incidence.

6.2. Main contributions

Manuscript 1 strengthened the evidence base of the shared genetic component of CHD and cancer, especially HC. The role of known genetic syndromes on the incidence of overall and

subtypes of HC was explored. The finding that an increase in the risk of HC associated with genetic syndromes among children with CHD highlighted the necessity of a better understanding of the possible common underlying pathways of CHD and cancer and evaluating if there is a need for cancer screening in this vulnerable patient population.

Accurate modeling of time-varying exposure is paramount towards avoiding biases in estimating the association under study. In Manuscript 2, we used the novel modeling approach, which allowed us to account for the time-varying nature of LDIR exposure. The flexible WCE modeling offered additional insights regarding the importance of the cumulative effect and the timing of exposure on the incidence of HC among children with CHD.

Radiation-induced cancer risk estimates at the low-dose level are mostly based on the linear no-threshold hypothesis, which extrapolates the risk at the high dose of radiation to the low doses. However, the question of a potential threshold level of radiation from medical imaging before which there is no carcinogenic effect is of prime interest and virtually unanswered. Leveraging the large CanCHD database, Manuscript 3 explored the threshold dose of LDIR exposure from cardiac imaging on HC incidence among children with CHD. The findings and methodological approaches in this study helped to advance our understanding of the possible non-linear dose-response of LDIR exposure on the risk of radiation-induced hematopoietic cancer incidence, a critical component for developing and improving guideline recommendations for radiological protection for children with CHD.

6.3. Generalizability

The Quebec CHD database is a well-characterized population-based database that includes comprehensive longitudinal information on all demographic, diagnostic, and therapeutic records for all Quebec residents with CHD with an extended follow-up time (1983-2017). The CIHI-

DAD database, on the other hand, contains diagnoses, demographic characteristics, and in-patient diagnostic and therapeutic procedures for all hospital encounters between 1999 to 2018 in all other provinces and territories in Canada. The combined Canadian CHD (CanCHD) database used in this thesis thus generated the largest population-based cohort of children with CHD across Canada. Therefore, the results from this database are expected to be generalizable to Canada, the US, and similar other developed countries. The findings from this thesis will not be generalizable to solid cancers. Adults are not the subjects of this research; thus, the findings are not generalizable to adult CHD (ACHD) populations.

6.4. Implication and future directions

This thesis draws attention to several key issues and directions for future research in children with CHD and cancer. Manuscript 1 highlighted the need for cancer surveillance for early detection of HC among children with CHD and known genetic syndromes. To date, there is no standardized screening recommendation for HC. Cancer surveillance in patients with RASopathies and other genetic disorders has been recommended.[199] More recently, a proposal for cancer screening in adults with Down syndrome has been made.[200] However, no screening recommendation exists for children with Down syndrome. Therefore, physicians should be aware of the increased risk of cancer among this vulnerable patient population and assess the clinical symptoms promptly. More research to structure tailored surveillance recommendations is warranted.

Manuscript 2 informed the increased cancer risk associated with an increased dose of LDIR and the timing of the exposure. Caregivers must be aware of the LDIR-cancer association and avoid any unwarranted cardiac imaging procedure. The findings of this research justify the "as low as reasonably achievable" (ALARA) principle, which promotes dose reduction for a

given imaging or therapeutic procedure and the selection of non-LDIR-related imaging if medically indicated.[47] The ALARA principle is essential when patient care management combines surgical and interventional techniques.[195] Therefore, every effort should be made to justify the indication and optimize the dose delivered without compromising the quality of care.[10, 189] Currently, no regulation exists to monitor radiation exposure for patients but health care workers. The need for developing an electronic and portable "patient passport", potentially a mobile application, for patients with CHD with an overview of their CHD history and cumulative lifetime exposure has been emphasized.[13] However, with the current setting, the practitioners need to step forward to avoid the "friendly fire" of unjustified imaging.[189] Nonetheless, only more aggressive research initiatives, as urged in the new consensus study report from the National Academies of Science, Engineering, and Medicine (NASEM)[201] would allow tailored surveillance recommendations for this vulnerable patient population.

Manuscript 3 demonstrated a non-linear dose-response association between LDIR exposure and HC incidence. The results emphasized the need for epidemiological data with a large patient population to be followed for several decades. In addition, improved dosimetry is particularly important for detecting and quantifying cancer risk at a low dose range. Our findings from this research underscored the importance of future studies with biomarkers of exposure effects (γ-H2AX foci), disease risk, and susceptibility to support and integrate the epidemiological evidence on radiation-induced carcinogenesis at low dose.[189]

6.5. Conclusion

This doctoral thesis, comprised of three manuscripts involving multiple research methods and approaches, enriches the knowledge pool of cancer predispositions in children with CHD. Intensified surveillance should be commenced to detect cancer as early as possible in this high-

risk patient population. The findings from this thesis will encourage physicians to become more vigilant about this cancer predisposition, make judicious choices towards CHD management and therefore curb the associated risk.

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