CESP – Inserm – UMR 1018
Équipe: Cancer et radiations

Directeur
Florent de Vathaire
Tel : 01 42 11 54 57
florent.devathaire@gustaveroussy.fr

Assistante
Françoise Terrier
Tel : 01 42 11 41 40
Fax : 01 42 11 53 15
francoise.terrier@gustaveroussy.fr

CR Inserm
Carole Rubino
Tel : 01 42 11 62 33
carole.rubino@gustaveroussy.fr
Nadia Haddy
Tel : 01 42 11 62 33
nadia.haddy@gustaveroussy.fr

IR Inserm
Ibrahima Diallo
Tel : 01 42 11 49 18
ibrahim.diallo@gustaveroussy.fr

Médecins
Cécile Thomas-Teinturier
Tel : 01 42 11 41 14
cecile.teinturier@bct.aphp.fr
Brice Fresneau
Tel : 01 42 11 42 21
Brice.FRESNEAU@gustaveroussy.fr

Chercheurs Gustave Roussy
Agnès Dumas
Tel : 01 42 11 66 26
Agnes.DUMAS@gustaveroussy.fr
Rodrigue Allodji
Tel : 01 42 11 54 98
rodrigue.allodji@gustaveroussy.fr

Post-doctorants
Neige Journy
Tel: 01 42 11 54 27
Neige.journy@gustaveroussy.fr

Doctorants
Monia Zidane
Tel : 01 42 11 54 27
Monia.ZIDANE@gustaveroussy.fr
Imene Mansouri
Tel: 01 42 11 62 33
Imene.MANSOURI@gustaveroussy.fr

Ingénieurs
Cristina Veres
Tel : 01 42 11 51 60
cristina.veres@gustaveroussy.fr
Vincent Souchard
Tel : 01 42 11 41 29
Vincent.SOUCHARD@gustaveroussy.fr
Giao Vu-Bezin
Tel : 01 42 11 55 79
MAI-QUYNH-GIAO.BEZIN@gustaveroussy.fr

Techniciens
Isao Kobayashi
Tel : 01 42 11 41 14
isao.kobayashi@gustaveroussy.fr
Martine Labbé
Tel : 01 42 11 51 69
martine.labbe@gustaveroussy.fr
Amel Boumaraf
Tel : 01 42 11 53 85
AMEL.BOUMARAF@gustaveroussy.fr

Projet: "PanRadLeuk"

Titre:

Collaborative international analyses on long-term risk of leukemia after treatment for childhood cancer: Incidence of leukaemia in PanCareSurFup data and pooled analysis RadLeuk

Cordinateur : Dr Rodrigue S. Allodji (PI)

Adresse :
Radiation Epidemiology, clinical cancer epidemiology and cancer survivorship
CESP - Unit 1018 INSERM
Institut Gustave Roussy
B2M, 114, rue Édouard Vaillant
94805 Villejuif Cedex

Email : rodrigue.allodji@gustaveroussy.fr
Tel : 01 42 11 54 98

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Problématique scientifique

Des études épidémiologiques sur les personnes exposées à des doses de rayonnements modérées et élevées, il ressort que la leucémie infantile est particulièrement associée aux rayonnements ionisants (Wakeford 2013). Cependant, la plupart des données disponibles chez les survivants de cancers pédiatriques suggère qu'il n'existe quasiment pas de risque de leucémie après radiothérapie, pendant que le risque de leucémie associé à certains agents de chimiothérapie est très important (Haddy et al 2006). La concomitance quasi systématique avec les agents de chimiothérapie est l'une des principales limites de la plupart des études publiées.

Rappel des objectifs du projet PanRadLeuk

L'objectif du projet PanRadLeuk est d'améliorer notre compréhension sur le risque de survenue de leucémie secondaire chez les enfants survivants de cancer, en utilisant les données de la grande cohorte PanCareSurFup et en réalisant une analyse poolée (RadLeuk) de toutes les études épidémiologiques pour lesquelles des estimations individuelles des drogues de chimiothérapie et des estimations individuelles de la dose radiation reçue à la moelle osseuse avaient été faites. Par l'étude poolée RadLeuk, la puissance statistique sera augmentée et il alors sera possible de quantifier la relation dose-réponse pour la leucémie secondaire en fonction de l'exposition à des groupes spécifiques de médicaments cytotoxiques et tout en prenant en compte l'hétérogénéité de la distribution de dose de radiations à la moelle osseuse active.

Etat d'avancement des travaux

Le tableau ci-dessous rappelle les étapes clés du projet RadLeuk.

	key steps	schedule *(nb. of months from T0)*	Justification
D1.1	Periodic report – year 1	12	GR / U1018 Inserm
D1.2	Periodic report – year 2	24	GR / U1018 Inserm
D1.3	Final Report.	36	GR / U1018 Inserm

D2.1	Report on incidence of subsequent leukaemia from PanCareSurFup data	24	GR / U1018 Inserm
D2.2	Report on the potential risk factors of subsequent leukemia	36	GR / U1018 Inserm
D3.1	Report on cross-validation study comparing dose reconstruction performed by MD Anderson Hospital and INSERM/IGR dosimetry groups	24	GR / U1018 Inserm
D4.1	Report on the dose-response relationship for secondary leukemia in relation to exposure to specific groups of cytotoxic drugs	24	GR / U1018 Inserm

Au cours du projet PanRadLeuk, nous avons donc travaillé sur l'étude d'incidence des leucémies secondaires après un cancer durant l'enfance dans la Cohorte Européenne PanCareSurFup et mais également sur l'étude collaborative internationale (RadLeuk).

Projet collaboratif international sur l'étude du risque de leucémie secondaire chez les enfants survivants de cancer

Le nombre de cas d'évènement iatrogènes à long terme des traitements anticancéreux, dans la plupart des études épidémiologiques est souvent relativement faible. Dans l'objectif d'augmenter la puissance statistique de ces études en vue de rendre plus robustes les estimations de risque des effets iatrogènes après radiothérapie la mise en place de projets collaboratifs internationaux est indispensable.

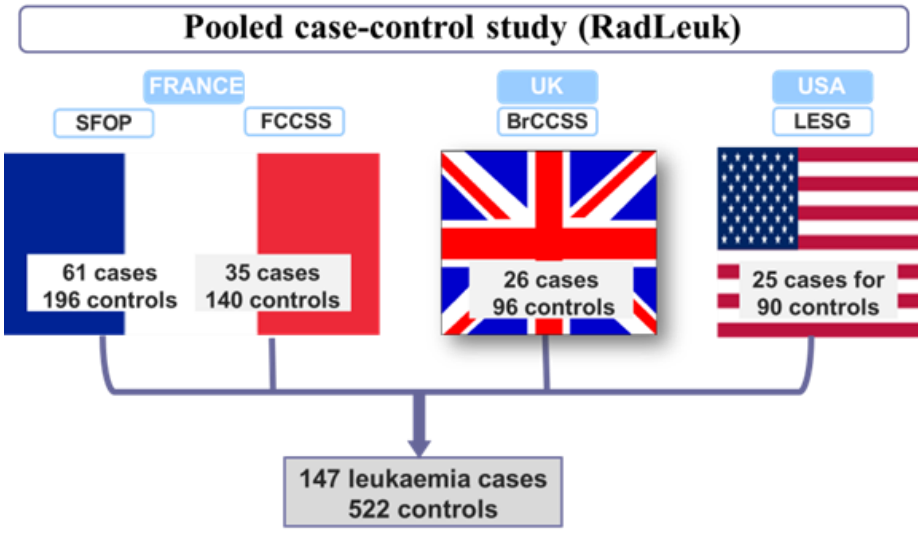
Etude du risque de leucémie secondaire après un cancer durant l'enfance dans la Cohorte Européenne PanCareSurFup

Au cours de cette deuxième année, le protocole de l'étude sur l'incidence des leucémies secondaires après un cancer durant l'enfance dans la grande cohorte Européenne PanCareSurFup a été accepté par le comité scientifique de PanCareSurFup. Ainsi, après été déclaré comme collaborateur scientifique du 'Centre for Childhood Cancer Survivor Studies' de l'Université de Birmingham, qui a la charge de la gestion pratique de ces données, nous avons eu accès aux données de cette très large cohorte pan-européenne qui comprend environ 100.000 sujets de 12 pays européens (France, Suisse, Grande-Bretagne, Italie, Pays-Bas, Slovénie, Finlande, Danemark, Norvège, Suéde, Islande, et Hongrie). Cette très large cohorte offre une occasion unique d'évaluer

le risque de leucémie secondaire dans une grande population de survivants de cancer de différents pays européens.

Les analyses ont été effectuées et le manuscrit est en révision par les co-auteurs pour une soumission au premier trimestre 2019 au journal : Journal of the National Cancer Institute (JNCI) ou The Lancet Haematology (Voir en annexe 1).

RADLEUK : méta-analyse internationale sur le risque de leucémie secondaire après un cancer durant l'enfance



Quatre études cas-témoins ont été sélectionnées comme éligibles à l'inclusion dans la méta-analyse proposée, à savoir les données de la LESG avec 25 cas et 90 témoins, fournies par le NCI/USA (Tucker et al 1987), celles de la BrCCSS-UK avec 26 cas et 96 témoins (Hawkins et al 1989), et pour la France : l'étude SIOP avec 61 cas et 191 témoins (Ledeley et al 2003) et la cohorte FCCSS avec 35 cas et 140 témoins (Allodji et al 2015). Cette méta-analyse d'environ 147 cas de leucémie est la plus grande étude à ce jour dans le domaine.

Les analyses pour cette méta-analyse ont été refaites pour prendre en compte les nouveaux commentaires et modifications apportés par les co-auteurs partenaires du projet. Les modifications apportées ont permis de corriger les erreurs de données observées dans les précédentes analyses. Il a été également proposé par les co-auteurs partenaires, d'approfondir les recherches sur la prise en compte de la combinaison des drogues de chimiothérapies administrées au cours du traitement du cancer de l'enfant. Ces travaux en cours de finalisation avec le Dr Peggy Tucker du NCI, feront

l'objet d'un manuscrit spécifique qui aura pour objectif de comparer l'apport de la prise en compte de la combinaison des drogues de chimiothérapies en comparaison avec celle basée sur les groupes pharmacologiques couramment utilisée dans la littérature. Le manuscrit de l'étude poolée a donc été révisé pour prendre en compte pour prendre en compte les commentaires et modifications apportés par les co-auteurs partenaires du projet.

Il a été soumis au Blood journal et sera resoumis très prochainement au JNCI: Journal of the National Cancer Institute (Voir en annexe).

RADLEUK : comparaison des approches dosimétriques

L'étude de comparaison des approches dosimétriques de deux groupes (Inserm/IGR vs Anderson Hospital: MDACC) ayant travaillé sur la reconstruction dosimétrique, a été finalisée. Des discussions sont toujours en cours, sa publication éventuelle.

Positionnement par rapport aux objectifs initiaux et perspectives

La totalité des objectifs prévus dans projet PanRadLeuk a été atteint. Toutefois, quelques mois supplémentaire seront nécessaires, pour la publication des différentes études dans les revues indiquées ci-dessus. Le tableau ci-dessous présente le positionnement par rapport aux objectifs initiaux.

	key steps	schedule *(nb. of months from T0)*	Justification	Statut
D1.1	Periodic report – year 1	12	GR / U1018 Inserm	Fait
D1.2	Periodic report – year 2	24	GR / U1018 Inserm	Fait
D1.3	Final Report.	36	GR / U1018 Inserm	Présenté ici
D2.1	Report on incidence of subsequent leukaemia from PanCareSurFup data	24	GR / U1018 Inserm	Finalisé – Soumission à

				The Lancet Haematology pour sa valorisation
D2.2	Report on the potential risk factors of subsequent leukemia	36	GR / U1018 Inserm	Finalisé – Soumission à *The Lancet Haematology* pour sa valorisation
D3.1	Report on cross-validation study comparing dose reconstruction performed by MD Anderson Hospital and INSERM/IGR dosimetry groups	24	GR / U1018 Inserm	Finalisé – discussion pour sa valorisation
D4.1	Report on the dose-response relationship for secondary leukemia in relation to exposure to specific groups of cytotoxic drugs	24	GR / U1018 Inserm	Finalisé – Resoumission au *Journal of the National Cancer Institute* pour sa valorisation

Publications en cours dans le cadre du projet (articles, abstracts congrès etc.)

Allodji R. S., Hawkins MM, Bright JC, Winter DL, Vu-Bezin G, et al. *Risk of subsequent leukaemias among 69,460 5-year Survivors of Childhood Cancer in Europe*. To be submitted to The Lancet Haematology.

Allodji R. S., Morton L, Hawkins MM, Le Deley MC, Tucker P, Veres C, Weathers R, Howell R, winter D, Haddy H, Diallo I, Little MP, and de Vathaire F. *A Pooled Analysis of Subsequent Leukaemia after a Solid Tumour in Childhood: late side effect of Radiation dose to the Bone Marrow and Chemotherapy drugs*. To be resubmitted to JNCI: Journal of the National Cancer Institute.

Annexes

Annexe 1 : *Etude du risque de leucémie secondaire après un cancer durant l'enfance dans la Cohorte Européenne PanCareSurFup*

Annexe 2 : *RADLEUK : méta-analyse internationale sur le risque de leucémie secondaire après un cancer durant l'enfance*

Annexe 3 : *RADLEUK : comparaison des approches dosimétriques*

Annexe 1 : Etude du risque de leucémie secondaire après un cancer durant l'enfance dans la Cohorte Européenne PanCareSurFup

Risk of subsequent primary leukaemias among 69,460 5-year Survivors of Childhood Cancer in Europe

Rodrigue S Allodji[1,3], Mike M Hawkins[1], Chloe J Bright[1], David L Winter[1], Daniela Alessi[2], Giao Vu-Bezin[3], Carole Rubino[3], Brice Fresneau[3,4], Vera Morsellino[5],Edit Bárdi[6,7], Andrea Bautz[8], Julianne Byrne[9], Elizabeth AM Feijen[10], Miranda M Fidler[1], Stanislaw Garwicz[11], Desiree Grabow[12], Thorgerdur Gudmundsdottir[8,13], Joyeeta Guha[1], Momcilo Jankovic[14], Peter Kaatsch[12], Melanie Kaiser[12], Rahel Kuonen[15], Helena Linge[11], Monica Muraca[5], Neige Journy[3], Damien Llanas[3], Cristina Veres[3], Hilde Øfstaas[16], Ibrahima Diallo[3], Cecile M Ronckers[10], Roderick Skinner[17], Jop C Teepen[10], Monica Terenziani[18], Finn Wesenberg[19], Thomas Wiebe[11], Carlotta Sacerdote[2], Zsuzsanna Jakab[20], Riccardo Haupt[5], Päivi Lähteenmäki[21], Lorna Zadravec Zaletel[22], Claudia E Kuehni[15,23], Jeanette F Winther[8], Leontien C Kremer[10,24], Lars Hjorth[11], Nadia Haddy[3], Florent de Vathaire[3], Raoul C Reulen[1]

Affiliations:

[1]Centre for Childhood Cancer Survivor Studies, Institute of Applied Health Research, Robert Aitken Building, University of Birmingham, Birmingham, UK.

[2]Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin and AOU Città della Salute e della Scienza di Torino, Italy.

[3]Cancer and Radiation Team, Center for Research in Epidemiology and Population Health, INSERM U1018, University Paris Saclay, Gustave Roussy, Villejuif, France.

[4]Department of Pediatric oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France

[5]Epidemiology and Biostatistics Section, Gaslini Children Hospital, Via Gerolamo Gaslini, 5, 16148, Genova, Italy.

[6]2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary.

[7]Kepler Universitätsklinikum, Linz, Austria.

[8]Danish Cancer Society Research Center, Survivorship Unit, Copenhagen, Denmark. .

[9]Boyne Research Institute, Drogheda, Ireland.

[10]Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands.

[11]Lund University, Skane University Hospital, Department of Clinical Sciences, Paediatrics, Lund, Sweden.

[12]German Childhood Cancer Registry (GCCR), Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center, Mainz, Germany.

[13]Children´s Hospital, Landspitali University Hospital, Reykjavik, Iceland.

[14]Foundation MBBM, Hemato-Oncology Center, University of Milano-Bicocca, via Cadore 38, 20900 Monza (MB), Italy.

[15]Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Switzerland.

[16]Norwegian National Advisory Unit on solid tumors in children, Norway.

[17]Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, and Northern Institute of Cancer Research, Newcastle University, Newcastle upon Tyne, UK.

[18]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori , Milano, Italy.

[19]Norwegian Cancer Registry and Dept. of Pediatric Medicine, Oslo University Hospital and Institute of Clinical Medicine, Faculty of medicine, University of Oslo, Norway.

[20]Hungarian Childhood Cancer Registry, 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary.

[21]Turku University and Turku University Hospital, Department of Pediatric and Adolescent Medicine, Turku, Finland.

[22]Institute of Oncology, Ljubljana, Slovenia.

[23]Department of Paediatrics, University Children's Hospital of Bern, University of Bern, Switzerland

[24]Department of Pediatric Oncology, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands.

Corresponding author: Dr Rodrigue S. Allodji, Radiation Epidemiology Group / CESP - Unit 1018 INSERM, Gustave Roussy, B2M, 114, rue Édouard Vaillant 94805 Villejuif Cedex, Tel 01 42 11 54 98 / Fax 01 42 11 56 18 E-mail: rodrigue.allodji@gustaveroussy.fr / Centre for Childhood Cancer Survivor Studies, Institute of Applied Health Research, Robert Aitken Building, University of Birmingham, Birmingham, B15 2TT; Tel: +44 (0)121 414 4946; Email: A.Rodrigue@bham.ac.uk

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Conflicts of Interest

No conflicts of interest declared.

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Key words: Subsequent primary leukaemias, Childhood cancer, Europe

Abbreviations: PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup); standardized incidence ratio (SIR); absolute excess risk (AER); relative risk (RR); subsequent primary neoplasm (SPN); first primary neoplasm (FPN).

Word Count: xxx of xxxx; Abstract: xxx of xxx

Abstract

Background: Survivors of childhood cancers are at risk of developing subsequent primary leukaemias (SPLs), but the long-term risks after 20 years following treatment are still unclear. We investigated the risk of SPLs in 5-year childhood cancer survivors using a large-scale pan-European (PanCareSurFup) cohort and evaluated variations in the risk by cancer and demographic factors.

Patients and methods: This largest-ever assembled cohort comprises 69,460 5-year childhood cancer survivors from 12 European countries. Standardized incidence ratios (SIRs) and absolute excess risks (AERs) were calculated. Cumulative incidence was calculated accounting for competing risk of death.

Results: 115 survivors developed a SPL including 31 occurring beyond 20 years from first cancer diagnosis. Compared with the general population, childhood cancer survivors had a 4-fold increased risk (SIR = 3.7; 95%CI: 3.1-4.5) of developing leukaemia, and 8 leukaemias per 100,000 person-years (AER = 7.5; 95%CI: 6-9.2) in excess of that expected. The risks remained significantly elevated beyond 20 years from first primary malignancy. Overall, the risk of myeloid leukaemias (SIR = 5.8; 95%CI: 4.6-7.1) was higher than that for all other SPL combined.

Conclusions: We demonstrate that beyond 20 years after childhood cancer diagnosis survivors experienced an excess risk for SPL compared to that expected from the general population. Our findings should inform evidence-based surveillance of survivors of childhood cancer for the development of SPL.

Keywords: Childhood cancer survivors, second cancers, subsequent primary leukaemia.

Introduction

The outcome for children with cancer has improved significantly over the past 60 years, with more than 80% of individuals diagnosed recently becoming 5-year survivors [1]. Despite this progress, significant treatment late effects continue to impact the majority of children who survived cancer, and one of the most devastating sequelae of cancer treatment is the occurrence of subsequent primary neoplasms (SPNs) [2-8]. Given that the number of childhood and adolescent cancer survivors continues to increase, it is imperative that studies are undertaken to improve understanding of the risks and causes of late effects of treatments for cancer in order to produce an evidence base to inform clinical guidelines for follow-up.

Subsequent primary leukaemias (SPLs) are a concern for long-term survivors of childhood cancer [5], previous investigations reported that the cumulative incidence of SPLs plateaus between 10 and 15 years after first primary therapy, but the risk of developing a SPLs after 20 years remains scarce information. To our knowledge, no previous study had adequate statistical power and follow-up duration to investigate the risks of SPLs satisfactorily. Among 14,358 five-year survivors from the North American Childhood Cancer Survivor Study (CCSS) cohort, 43 developed a SPLs of which only 13 were diagnosed after 15 years from the original cancer diagnosis [5]. Due to small numbers of SPLs in the previous studies [5-8], the pan-European cohort of survivors of childhood and adolescent cancer (PanCareSurFup) offers a unique opportunity to evaluate the risk of SPL in a large population of survivors with a variety of first primary malignancies and a long follow-up into adulthood from several European countries [9-13].

The principal aim of the current study was to investigate the risk of occurrence of SPLs in 5-year survivors of childhood cancer using the large-scale pan-European

(PanCareSurFup) cohort and evaluate variations in the risk by cancer and demographic factors.

Methods

PanCareSurFup cohort

The PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) consortium pools data from 13 European cohorts, within 12 countries, to establish the largest ever collaborative study to comprehensively investigate adverse health outcomes in long-term survivors of childhood and adolescent cancer. The PanCareSurFup cohort comprises data from both population-based cancer registries and major treatment centers. More details of establishing of this cohort were reported by Grabow et al [11]. Ethical approval was obtained separately for each cohort from the appropriate bodies within each specific country.

A total of 69,460 5-year survivors of cancer diagnosed before the age of 20 years between 1940 and 2008 were included in this cohort as previously described [12,13].

Identification and ascertainment of subsequent primary leukaemias (SPLs)

The main characteristics of the PanCareSurFup cohort are described in Table 1. First primary neoplasms (FPN) were grouped according to the International Classification of Childhood Cancer (ICCC) [14]. Leukaemia events were coded using the International Classification of Diseases for Oncology Editions 1, 2 and 3 [14-16], consistent with other publications analysing such data [6-8,19,20] as described in Supplementary Table S1. These SPLs were ascertained and validated by each data provider mostly using pathology reports [12,13].

Statistical analyses

To compare the observed number of SPLs with that expected from the general population, general population leukaemia incidence rates were classified according to the adolescent and young adult (AYA) cancer classification based on ICD-O morphology. Incidence rates by ICD-O morphology were available for the UK (years 1971-2006: England and Wales, only) [21] and were used as general population rates also for France, Hungary, Italy, Netherlands, Slovenia and Switzerland. Similarly, Finnish incidence rates by ICD-O morphology (years 1953-2011) [22] were used for Denmark, Norway, Sweden and Iceland. When the range of calendar-years for the general population cancer rates did not extend to cover the entire follow up period, rates from the closest available calendar year were used.

Standardized incidence ratios (SIRs) were calculated as the observed SPLs divided by the expected number of leukaemias. The expected number was calculated by accumulating person-years in the cohort by strata defined by single calendar-year, sex and 5-year age groups and multiplying by the corresponding general population leukaemia incidence rates. Absolute excess risks (AERs) were calculated as the observed minus the expected number of leukaemias, divided by person-years at risk and multiplied by 100,000. The AER can be interpreted as the number of excess leukaemias observed beyond that expected per 100,000 persons per year. AERs are reported throughout per 100,000 persons per year unless otherwise specified. The 95% confidence intervals (CIs) were calculated assuming that the observed number of SPLs followed a Poisson distribution. SIRs and AERs were stratified by country, sex, type of childhood cancer, age at (and decade of) childhood FPN diagnosis, attained age, and years of follow-up. Relative risks (RR) of developing SPLs associated with these potential explanatory factors were estimated using univariate and multivariable Poisson regression [23]. Lastly, cumulative incidence curves relating

to the first occurrence of a SPL, adjusting for death as a competing risk, were calculated and Gray's test was used to evaluate hypotheses of equality of cumulative incidence functions between subgroups where relevant [24. All statistical analyses were conducted in SAS software, version 9.4. A 2-sided p-value <0.05 was considered statistically significant.

Results

Cohort characteristics

Of the 69,460 5-year survivors in the PanCareSurFup cohort, 115 developed a SPL. The most commonly observed SPLs were myeloid leukaemias (86 events including 45 Acute myeloid leukaemias, 10 chronic myeloid leukaemias and 31 unspecified/other myeloid leukaemias), lymphoid leukaemias (17 events including 5 Acute lymphoid leukaemias, 4 chronic myeloid lymphoid leukaemias and 8 unspecified/other lymphoid leukaemias) and others type of leukaemias (12 events including 5 acute undifferentiated leukemias, 2 hairy cell leukemia, 1 acute biphenotypic leukemia, and 4 unspecified/other leukaemias (Supplementary Tables S1 & S2, online only). Demographic and cancer characteristics of the study cohort are shown in Tables 1 and 2. Entry to risk was date of 5-year survival. Exit from risk was the first of: date end of follow-up; date of death from SPL; date of death from other causes (competing risk); date lost to follow-up. These individuals accrued 1,126,272.6 person-years. Female survivors accounted for 40.9% of 5-year survivors who developed a SPL (Table 1) and their mean attained age at study exit was 23.6 years (range, 6.4 to 65.3 years. Of those survivors who developed a SPL, 24 (20.9%) were originally diagnosed with childhood cancer before 1970, while it was 12.9% in the all

5-year-survivors. There were 31 (26.9%) SPLs diagnosed beyond 20 years after the FPN and 15 SPLs diagnosed beyond age 40 years (Table 1).

Characteristics of survivors with a subsequent primary leukaemia (SPL) with regard to the first primary neoplasm (FPN)

The characteristics of the 115 5-year survivors who developed a SPL are summarised in Table 2. Among 22 patients treated for central nervous system (CNS) cancer, the median age at FPN diagnosis was 9.3 years (range 1.6–15.9 years), age at diagnosis of SPL was 19.6 years (range 8.2–65.3 years), 50% were treated after 1990 and 36.4% had developed SPL beyond 10 years from the original childhood CNS cancer diagnosis. For these patients, the median time to occurrence of SPL was 9.7 years (range = 5.1–50.5 years), while it was 8.5, 9.2, 9.5, 10.1, 10.5, 10.5, 17 and 37.2 years for soft tissue sarcoma, leukaemia, Hodgkin lymphoma, bone sarcoma, non-Hodgkin lymphoma, neuroblastoma, Wilms tumor, and retinoblastoma, respectively.

Overall risk of subsequent primary leukaemia (SPL)

Compared to that expected from the general population, survivors had an almost 4-fold risk (SIR = 3.7; 95%CI: 3.1-4.5) of developing leukaemia, and almost 8 additional leukaemias per 100,000 person-years (AER = 7.5; 95%CI: 6-9.2) in excess of that expected (Table 3). The cumulative incidences for development of SPL is steadily increased with the years from FPN diagnosis, from 0.1% (95%CI: 0.1 to 0.2) at 20 years to 0.6% (95%CI: 0.4 to 0.9) at 50 years (Figure 1a). FPNs were stratified in 4 tumor types (leukaemia, lymphoma included also the non Hodgkins, CNS and others). The cumulative incidence at 20 years was at 0.3% (95%CI: 0.2 to 0.4) (Figure 1b) among lymphoma survivors.

All survivors of each specific type of primary childhood cancer—except retinoblastoma and bone sarcoma—had both a statistically significantly increased multiplicative (SIR)

and absolute (AER) excess risk of developing a SPL, the greatest excess risks were among Hodgkin lymphoma survivors (SIR = 7.8, 95%CI: 4.7–12.1; AER = 18.9, 95%CI: 11.7–30.6) (table 3). SIRs appeared to be significantly higher among survivors diagnosed in more recent decades (P-trend<0.001), but this was not confirmed by multivariable analyses (P-trend=0.32) (tables 3 & 4). SIRs decreased significantly with increasing attained age (P-trend<0.001), but were still 2-fold elevated beyond 30 years of age (SIR= 2) (table 3). SIR was particularly high in the first 20 years and then declined but remained significantly elevated (SIR = 2.3; 95%CI: 1.6-3.3) more than 20 years after childhood cancer treatment (table 3). The multivariable analysis revealed that SIRs varied substantially with follow-up (P for heterogeneity = 0.0064), (Table 4). AERs were particularly high between 5-9 years of follow-up (AER = 15.2; 95%CI: 11.4-20.2) and then declined substantially to around 3 to 5 between 10 to 39 years, and then increased sharply (AER = 12.2; 95%CI: 4.5-33.3) more than 40 years. There is evidence of excess risk in both multiplicative and absolute terms across all durations of follow-up (Table 3).

Risks of subsequent primary myeloid leukaemias (SPML) and subsequent primary lymphoid leukaemias (SPLL)

Differences in the cumulative incidences of subsequent primary myeloid leukaemias (SPML) and subsequent primary lymphoid leukaemias (SPLL) were observed (Figure 1d). The cumulative incidences for development of SPML is steadily increased with the years from FPN diagnosis, while for SPLL, this increase steadily only began at 35 years after FPN diagnosis (Figure 1d).

Overall, survivors had significantly and substantially elevated risks for myeloid neoplasms, with increased risk 6-fold (SIR = 5.8; 95%CI: 4.6-7.1), and 6 additional myeloid leukaemias per 100,000 person-years (AER = 6.3; 95%CI: 5-8) in excess of

that expected (Table 5). In contrast, the SIR did significantly elevated for lymphocytic leukemia (SIR = 1.2; 95%CI: 0.7-2.0) and the AER of developing a SPLL was only 0.3 per 100,000 person-years (Supplementary Tables S3). Survivors of each specific type of childhood cancer—except retinoblastoma and bone sarcoma—had both a statistically significantly increased multiplicative (SIR) and absolute (AER) excess risk of developing a SPML, Hodgkin lymphoma survivors experienced the greatest multiplicative and absolute excess risk (SIR = 12.1, 95%CI: 6.9–19.6; AER = 16.8, 95%CI: 10.0–27.9). SPML AERs varied with age at diagnosis, those diagnosed at ages 0 to 4 and 15 to 19 years experienced an excess of 4 SPMLs, while those diagnosed at ages 5 to 14 experienced an excess of 8 to 10 SPMLs (Table 5). Most myeloid leukaemia were diagnosed under the attained age of 30 years (81.4%) and 76.7% occurred within 20 years of FPN diagnosis.

Discussion

Main findings

In this largest ever cohort study investigating the risk of SPL in survivors of childhood cancer we showed that the risk of developing SPL does not appear to plateau after 15 years from diagnosis and remains elevated for at least 30 years. This large collaborative study allowed us to expand on and address the main limitation of previous individual studies that had very small number of cases in assessing SPL risk among childhood cancer survivors from the UK [8], France [6], Nordic countries [19] and United States [5,20]. The largest previous study addressing this topic which did not contribute data to PanCareSurFup is the North American Childhood Cancer Survivor Study (CCSS) [5], which included 43 SPL compared to our 115 in this study.

More importantly, the CCSS study reported 13 observed SPL beyond 15 years from diagnosis [5], whilst in this PanCareSurFup study it was 40.

Comparison with other studies

The overall SIR was 3.7 for SPL, which was slightly lower, but not inconsistent, than that reported in a previous CCSS publication with 14,358 survivors showing 6-fold increased risk (SIR = 6.3; 95% CI, 4.6-8.5) [5] and two previous European papers: a British cohort of 16,422 including childhood cancer patients diagnosed between 1962 and 1983 who survived at least one year (SIR = 8) [8] and the French-British Euro2K cohort including 4,204 3-year survivors of childhood cancer diagnosed between 1947 and 1986 (SIR = 7.8). However, our SIR was slightly higher than the SIR from the previous Nordic countries study with 30,880 childhood cancer patients diagnosed between 1943 and 1987 (SIR = 2.8) [19]. This difference could be explained, in part, because the latency of at least 5 years in the present study was higher than the 0 to 3 years reported in the previous European studies. Indeed, as in the CCSS [5], the PanCareSurFup study only includes 5-years survivors; therefore all SPL occurring in the first 5 years after treatment were not considered in the present study. The excess absolute risk ≥ 20 years in our study (EAR = 4.8 events per 100,000 person-years of follow-up) has also risen from that a previous analysis ≥ 15 years in CCSS survivors (EAR = 2 per 100,000 person-years [5]). Previous reports have indicated that the risk of SPL reaches a plateau at approximately 10 years [25,26-36], we reported a median latency between primary childhood cancer diagnosis and SPL of 8.9 years, which was very close to that in the previous study from the CCSS [3].

Furthermore, consistent with previous studies [28-31], the highest SPL risks (SIR and AER) were found in Hodgkin lymphoma survivors in this study, mainly in their early teens (5-19 years), which is consistent with previous studies [32,33]. Therefore, the

awareness of this risk remains crucial for survivors of Hodgkin's lymphoma [34]. Statistically significant risks (SIRs or AERs) of SPL were found after leukeamia, soft-tissue sarcoma, CNS tumors, non-Hodgkin's lymphoma, neuroblastoma, and Wilms tumor survivors. Clinicians should be aware of these risks during long-term follow-up of these survivors. Overall, it has been shown that both chemotherapy (alkylating agents and/or topoisomerase II inhibitors) and radiation therapy can increase the risk of SPL following treatment [5-8,35,36].

Study limitations and sensitivity analyses

The main advantage of the current study is its large size with nearly 70,000 survivors; however, an inherent limitation of large scale cohort studies is that it is often not feasible to collect detailed information on exposures. The main limitation of our study is the lack of detailed treatment information on cumulative radiation dose (dose to active bone marrow), bone marrow transplantation (BMT) and cumulative chemotherapy dose exposures given as treatment for the childhood cancer; and as a result we were unable to look specifically at the effect of treatment protocols on the risk of SPL. However, separately and in parallel we are currently conducting an international pooled study of all existing cohort and case-control studies relating to leukaemia after childhood cancer (RadLeuk project). Although smaller in size than the current study, this study will have available cumulative doses of individual cytotoxics and cumulative doses of radiation to the active bone marrow for each individual included [7,8,20,38]. The RadLeuk study should address the risks associated with cumulative radiation and chemotherapeutic doses and development of SPL.

We also performed SIR or AERs sensitivity analyses to determine if the risk estimates reported were not sensitive to the general population rates applied, in which we used only UK or Finnish rates for all countries. These additional analyses revealed

that excess risk estimates were very similar regardless of the general population rates applied (Online Tables S4 and S5).

Conclusions

We demonstrate that the cumulative incidence of SPL does not reach plateau by 20 years but continues to increase and compared to the general population childhood cancer survivors face an increased risk for SPL beyond 20 years after their treatment. More efforts are still needed to collect information on the long-term risk of SPL in the increasingly large and ageing population of childhood cancer survivors. A thorough understanding of the epidemiology of SPL is essential for helping target surveillance of survivors of childhood cancer for the development of SPL.

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Table 1: Characteristics of all 69,460 5-year survivors of childhood cancer of the European PCSF study, 115 survivors who developed a subsequent primary leukaemia and 7099 survivors who died.

Factor	All 5-year survivors, No. (%) or Mean (Range)	Survivors who developed a subsequent leukaemia, No. (%) or Mean (Range)	Survivors who died, No. (%) or Mean (Range)
Country			
Norway	3783 (5.4)	2 (1.7)	329 (4.6)
France	3138 (4.5)	9 (7.8)	539 (7.6)
Hungary	4885 (7)	11 (9.6)	350 (4.9)
Italy	8966 (12.9)	9 (7.8)	527 (7.4)
Netherlands	6044 (8.7)	13 (11.3)	491 (6.9)
Denmark	4840 (7)	4 (3.5)	597 (8.4)
Sweden	7709 (11.1)	13 (11.3)	610 (8.6)
Finland	6229 (9)	9 (7.8)	679 (9.6)
Iceland	275 (0.4)	1 (0.9)	20 (0.3)
Slovenia	1252 (1.8)	3 (2.6)	146 (2.1)
Switzerland	4379 (6.3)	7 (6.1)	279 (3.9)
UK	17960 (25.9)	34 (29.6)	2532 (35.7)
Sex			
Male	37738 (54.3)	68 (59.1)	4125 (58.1)
Female	31722 (45.7)	47 (40.9)	2974 (41.9)
Type of Childhood Cancer			
Soft Tissue Sarcoma	4501 (6.5)	8 (7)	453 (6.4)
Leukemia	16595 (23.9)	25 (21.7)	1776 (25)
Hodgkin Lymphoma	6000 (8.6)	19 (16.5)	692 (9.7)
Non-Hodgkin Lymphoma	3350 (4.8)	6 (5.2)	196 (2.8)
Central Nervous System	14096 (20.3)	22 (19.1)	2338 (32.9)
Neuroblastoma	3169 (4.6)	6 (5.2)	251 (3.5)
Retinoblastoma	2578 (3.7)	3 (2.6)	87 (1.2)
Wilms Tumor	4756 (6.8)	8 (7)	228 (3.2)
Bone Sarcoma	3147 (4.5)	3 (2.6)	401 (5.6)
Other and not classifiable	11268 (16.2)	15 (13)	677 (9.5)
Age at Diagnosis			
Mean (range)	8.3 (0-20)	8.1 (0.3-18.6)	8.9 (0-20)
0–4 years	26793 (38.6)	39 (33.9)	2232 (31.4)
5–9 years	15702 (22.6)	30 (26.1)	1842 (25.9)
10–14 years	15483 (22.3)	34 (29.6)	1890 (26.6)
15–19 years	11482 (16.5)	12 (10.4)	1135 (16)
Decade of Diagnosis			
Mean (range)	1984.3 (1940-2008)	1980.3 (1948-2006)	1976.5 (1940-2008)
<1970	8993 (12.9)	24 (20.9)	1989 (28)
1970-1979	13479 (19.4)	27 (23.5)	2204 (31)
1980-1989	20900 (30.1)	34 (29.6)	1858 (26.2)
1990–1999	19260 (27.7)	21 (18.3)	869 (12.2)
≥ 2000	6828 (9.8)	9 (7.8)	179 (2.5)
Attained Age at exit			
Mean (range)	29.5 (5-79.4)	23.6 (6.4-65.3)	22.5 (5.3-75.8)
5–19 years	16243 (23.4)	56 (48.7)	3521 (49.6)
20–29 years	22437 (32.3)	33 (28.7)	2089 (29.4)
30–39 years	17471 (25.2)	11 (9.6)	798 (11.2)
≥ 40 years	13309 (19.2)	15 (13)	691 (9.7)
Years from Diagnosis at exit			
Mean (range)	21.2 (5-66.6)	15.5 (5-50.5)	13.6 (5-62.5)
5–9 years	13211 (19)	55 (47.8)	3860 (54.4)
10–19 years	23083 (33.2)	29 (25.2)	1752 (24.7)
20–29 years	17602 (25.3)	15 (13)	816 (11.5)
30–39 years	10290 (14.8)	9 (7.8)	454 (6.4)
≥ 40 years	5274 (7.6)	7 (6.1)	217 (3.1)

Table 2: Characteristics of the 115 childhood cancers survivors who developed a subsequent primary leukaemia (SPL) by first primary neoplasm (FPN).

	Soft Tissue Sarcoma	Leukemia	Hodgkin Lymphoma	Non-Hodgkin Lymphoma	Central Nervous System	Neuroblastoma	Retinoblastoma	Wilms Tumor	Bone Sarcoma	Other and not classifiable†
Overall	**8**	**25**	**19**	**6**	**22**	**6**	**3**	**8**	**3**	**15**
Age at Diagnosis of FPN										
Median	3.2	7.1	12.9	9	9.3	2.4	0.7	1.7	10.1	8.6
(range)	(0.3-9.9)	(1.2-13.5)	(4.3-18.2)	(5.5-13.6)	(1.6-15.9)	(0.7-5.8)	(0.6-10)	(0.6-6.8)	(4.8-13.3)	(1.2-18.6)
0–4 years	5 (62.5)	9 (36)	1 (5.3)	-	7 (31.8)	5 (83.3)	2 (66.7)	6 (75)	1 (33.3)	3 (20)
5–9 years	3 (37.5)	10 (40)	1 (5.3)	3 (50)	5 (22.7)	1 (16.7)	-	2 (25)	-	5 (33.3)
10–14 years	-	6 (24)	13 (68.4)	3 (50)	8 (36.4)	-	1 (33.3)	-	2 (66.7)	1 (6.7)
15–19 years	-	-	4 (21.1)	-	2 (9.1)	-	-	-	-	6 (40)
Decade of Diagnosis of FPN										
Median	1992	1986	1980	1980	1988.5	1980	1968	1974.5	1970	1968
(range)	(1966-2004)	(1971-2000)	(1948-1996)	(1963-1991)	(1957-2006)	(1961-1997)	(1953-1980)	(1954-1989)	(1959-1986)	(1954-2001)
<1970	1 (12.5)	8 (32)	4 (21.1)	1 (16.7)	3 (13.6)	2 (33.3)	2 (66.7)	2 (25)	1 (33.3)	8 (53.3)
1970-1979	1 (12.5)	-	5 (26.3)	2 (33.3)	4 (18.2)	1 (16.7)	-	4 (50)	1 (33.3)	1 (6.7)
1980-1989	2 (25)	10 (40)	8 (42.1)	2 (33.3)	4 (18.2)	1 (16.7)	1 (33.3)	2 (25)	1 (33.3)	3 (20)
1990–1999	1 (12.5)	6 (24)	2 (10.5)	1 (16.7)	8 (36.4)	2 (33.3)	-	-	-	1 (6.7)
≥ 2000	3 (37.5)	1 (4)	-	-	3 (13.6)	-	-	-	-	2 (13.3)
Attained Age at SPL										
Median	16.1	19.3	21.4	16.7	19.6	15.3	41.1	20	20.2	25.5
(range)	(6.4-36.3)	(10.3-30.5)	(13.2-58.7)	(13-56.9)	(8.2-65.3)	(6.5-42.7)	(21.1-47.2)	(10-31.7)	(12.4-40.1)	(11.3-64.6)
5–19 years	7 (87.5)	14 (56)	6 (31.6)	4 (66.7)	11 (50)	4 (66.7)	-	4 (50)	1 (33.3)	5 (33.3)
20–29 years	-	10 (40)	10 (52.6)	-	4 (18.2)	-	1 (33.3)	3 (37.5)	1 (33.3)	4 (26.7)
30–39 years	1 (12.5)	1 (4)	1 (5.3)	-	4 (18.2)	1 (16.7)	-	1 (12.5)	-	2 (13.3)
≥ 40 years	-	-	2 (10.5)	2 (33.3)	3 (13.6)	1 (16.7)	2 (66.7)	-	1 (33.3)	4 (26.7)
Years from Diagnosis at SPL										
Median	8.5	9.2	9.5	10.5	9.7	10.5	37.2	17	10.1	13.1
(range)	(5.3-35.9)	(5-28.7)	(5.4-45.6)	(5.1-43.3)	(5.1-50.5)	(5.1-42.1)	(20.4-40.5)	(9.4-30.6)	(7.6-26.7)	(5.8-46)
5–9 years	5 (62.5)	15 (60)	11 (57.9)	3 (50)	11 (50)	3 (50)	-	1 (12.5)	1 (33.3)	5 (33.3)
10–19 years	2 (25)	6 (24)	6 (31.6)	1 (16.7)	4 (18.2)	1 (16.7)	-	4 (50)	1 (33.3)	4 (26.7)
20–29 years	-	4 (16)	-	1 (16.7)	4 (18.2)	-	1 (33.3)	2 (25)	1 (33.3)	2 (13.3)
30–39 years	1 (12.5)	-	1 (5.3)	-	1 (4.5)	1 (16.7)	1 (33.3)	1 (12.5)	-	3 (20)

≥ 40 years	-	-	1 (5.3)	1 (16.7)	2 (9.1)	1 (16.7)	1 (33.3)	-	-	1 (6.7)

Table 3: SIRs and AERs per 100,000 Person-Years at risk of developing a subsequent primary leukaemia (SPL) among 69,460 5-year survivors of childhood cancer.

Factor	Overall				By years from diagnosis					
					5–19 years			≥ 20 years		
	Person-years	O/E	SIR (95% CI)	AER (95% CI)	O/E	SIR (95% CI)	AER (95% CI)	O/E	SIR (95% CI)	AER (95% CI))
Overall	**1126272.6**	**115/31**	**3.7 (3.1-4.5)**	**7.5 (6-9.2)**	**84/17.6**	**4.8 (3.8-5.9)**	**8.7 (6.9-11.1)**	**31/13.4**	**2.3 (1.6-3.3)**	**4.8 (3-7.7)**
P-values			***<.0001***	***0.0073***		***<.0001***	***0.0084***		***<.0001***	***0.0153***
Country										
Norway	53085.1	2/1.5	**1.4 (0.2-4.9)**	**1 (0.1-14.8)**	2/0.9	**2.3 (0.3-8.4)**	**3 (0.5-18.9)**	0/0.6	**-**	**-**
France	83063.7	9/2.3	**3.9 (1.8-7.4)**	**8 (3.8-17.2)**	5/1	**5 (1.6-11.8)**	**9.3 (3.5-24.7)**	4/1.3	**3 (0.8-7.7)**	**6.7 (2-22.2)**
Hungary	50100.1	11/1.2	**9 (4.5-16.1)**	**19.5 (10.4-36.5)**	10/1	**9.8 (4.7-18)**	**21.5 (11.2-41.3)**	1/0.2	**5 (0.1-28.1)**	**9.7 (1.1-86.5)**
Italy	94233.5	9/2.3	**3.9 (1.8-7.4)**	**7.1 (3.3-15.1)**	8/1.8	**4.5 (1.9-8.8)**	**8.2 (3.7-18)**	1/0.5	**1.9 (0-10.6)**	**2.5 (0.1-43.8)**
Netherlands	103228.6	13/2.6	**5 (2.7-8.6)**	**10.1 (5.5-18.5)**	11/1.8	**6.2 (3.1-11.2)**	**12.4 (6.5-23.7)**	2/0.8	**2.5 (0.3-8.9)**	**4.1 (0.7-24.8)**
Denmark	78940	4/2.7	**1.5 (0.4-3.7)**	**1.6 (0.3-9.1)**	3/1.1	**2.7 (0.6-7.9)**	**3.8 (0.9-15.9)**	1/1.6	**0.6 (0-3.6)**	**-**
Sweden	115357.7	13/3.3	**4 (2.1-6.8)**	**8.4 (4.5-15.8)**	10/1.8	**5.6 (2.7-10.2)**	**10.4 (5.2-20.6)**	3/1.4	**2.1 (0.4-6.2)**	**4.3 (0.9-20.7)**
Finland	104985.9	9/3.4	**2.7 (1.2-5)**	**5.3 (2.3-12.2)**	4/1.5	**2.6 (0.7-6.8)**	**3.7 (1.1-12.9)**	5/1.9	**2.6 (0.9-6.1)**	**8.1 (2.7-24.7)**
Iceland	3462.6	1/0.1	**10.4 (0.3-58)**	**26.1 (3.3-205.1)**	1/0.1	**17.2 (0.4-95.8)**	**36.9 (4.9-278.4)**	0/0	**-**	**-**
Slovenia	24820.8	3/0.7	**4.3 (0.9-12.4)**	**9.2 (2.5-33.7)**	3/0.4	**8.3 (1.7-24.2)**	**16.7 (5-55.9)**	0/0.3	**-**	**-**
Switzerland	46179.1	7/1.2	**6.1 (2.4-12.5)**	**12.7 (5.6-28.5)**	7/1	**7.2 (2.9-14.8)**	**15.1 (6.8-33.5)**	0/0.2	**-**	**-**
UK	368815.6	34/9.9	**3.5 (2.4-4.8)**	**6.5 (4.4-9.8)**	20/5.4	**3.7 (2.3-5.8)**	**6.2 (3.7-10.4)**	14/4.5	**3.1 (1.7-5.2)**	**7.1 (3.8-13.4)**
*P for heterogeneity**			***0.0677***	***0.0775***		***0.2334***	***0.0737***		***0.9891***	***0.9730***
Sex										
Male	601424.4	68/18.9	**3.6 (2.8-4.6)**	**8.2 (6.2-10.8)**	47/10.9	**4.3 (3.2-5.7)**	**8.8 (6.3-12.2)**	21/8	**2.6 (1.6-4)**	**6.8 (3.9-11.7)**
Female	524848.2	47/12.1	**3.9 (2.9-5.2)**	**6.7 (4.8-9.3)**	37/6.6	**5.6 (3.9-7.7)**	**8.6 (6-12.3)**	10/5.4	**1.8 (0.9-3.4)**	**2.7 (1.1-6.6)**
*P for heterogeneity**			***0.6640***	***0.3589***		***0.2381***	***0.9372***		***0.3612***	***0.0836***
Type of Childhood Cancer										
Soft Tissue Sarcoma	82501	8/2.4	**3.3 (1.4-6.5)**	**6.7 (2.9-15.5)**	7/1.2	**5.9 (2.4-12.1)**	**11.2 (5-25.3)**	1/1.2	**0.8 (0-4.5)**	**-**
Leukemia	219899.5	25/5.3	**4.7 (3.1-7)**	**9 (5.8-13.9)**	21/4.1	**5.1 (3.2-7.8)**	**9.8 (6.1-15.8)**	4/1.2	**3.4 (0.9-8.6)**	**5.8 (1.8-18.8)**
Hodgkin Lymphoma	87584.3	19/2.5	**7.8 (4.7-12.1)**	**18.9 (11.7-30.6)**	17/1.4	**12.5 (7.3-20)**	**25.3 (15.4-41.5)**	2/1.1	**1.8 (0.2-6.6)**	**3.5 (0.5-27.7)**
Non-Hodgkin Lymphoma	53751.9	6/1.6	**3.9 (1.4-8.4)**	**8.3 (3.3-21)**	4/0.9	**4.7 (1.3-11.9)**	**8.5 (2.8-25.6)**	2/0.7	**2.9 (0.4-10.4)**	**7.8 (1.4-43.5)**
Central Nervous System	228403.1	22/6.4	**3.5 (2.2-5.2)**	**6.8 (4.2-11.2)**	15/3.4	**4.4 (2.5-7.3)**	**7.6 (4.3-13.6)**	7/3	**2.3 (0.9-4.8)**	**5.3 (2-14)**
Neuroblastoma	55282.1	6/1.4	**4.2 (1.5-9)**	**8.2 (3.3-20.6)**	4/0.9	**4.2 (1.2-10.8)**	**8.5 (2.8-26.1)**	2/0.5	**4 (0.5-14.4)**	**7.7 (1.6-38.4)**
Retinoblastoma	60224.1	3/1.6	**1.8 (0.4-5.4)**	**2.3 (0.4-12.1)**	0/0.8	**-**	**-**	3/0.8	**3.7 (0.8-10.9)**	**8.2 (2.2-30.6)**
Wilms Tumor	95877.7	8/2.4	**3.3 (1.4-6.4)**	**5.8 (2.5-13.3)**	5/1.5	**3.4 (1.1-8)**	**5.9 (2.1-16.8)**	3/1	**3 (0.6-8.8)**	**5.6 (1.4-22.2)**
Bone Sarcoma	51766.7	3/1.6	**1.9 (0.4-5.5)**	**2.7 (0.5-14.2)**	2/0.7	**2.8 (0.3-10)**	**3.8 (0.7-21.4)**	1/0.9	**1.1 (0-6.4)**	**0.7 (0-165.8)**
Other and not classifiable	190982.1	15/5.8	**2.6 (1.5-4.3)**	**4.8 (2.5-9.2)**	9/2.7	**3.3 (1.5-6.2)**	**5.1 (2.3-11.1)**	6/3	**2 (0.7-4.3)**	**4.4 (1.4-13.8)**
*P for heterogeneity**			***0.0577***	***0.0204***		***0.0464***	***0.0126***		***0.9189***	***0.9920***
Age at Diagnosis										

0–4 years	463317.7	39/12	**3.2 (2.3-4.4)**	**5.8 (4-8.5)**	26/7.9	**3.3 (2.1-4.8)**	**5.9 (3.7-9.3)**	13/4.1	**3.2 (1.7-5.4)**	**5.7 (3-11.1)**
5–9 years	255543.1	30/6.5	**4.6 (3.1-6.6)**	**9.2 (6.1-13.8)**	25/3.9	**6.5 (4.2-9.6)**	**12.2 (7.9-18.6)**	5/2.7	**1.9 (0.6-4.4)**	**2.9 (0.8-10.3)**
10–14 years	251894.4	34/7.2	**4.7 (3.3-6.6)**	**10.6 (7.3-15.5)**	26/3.5	**7.5 (4.9-10.9)**	**13.2 (8.8-20)**	8/3.7	**2.2 (0.9-4.2)**	**5.2 (2-13.5)**
15–19 years	155517.3	12/5.3	**2.3 (1.2-4)**	**4.3 (2-9.2)**	7/2.3	**3 (1.2-6.2)**	**4.3 (1.7-10.6)**	5/2.9	**1.7 (0.6-4)**	**4.5 (1.2-17.6)**
*P for heterogeneity**			***0.0776***	***0.0492***		***0.0067***	***0.0119***		***0.5807***	***0.8211***
*P-trend**			***0.8531***	***0.5572***		***0.1998***	***0.4530***		***0.2293***	***0.7611***
Decade of Diagnosis										
<1970	286777.1	24/10.5	**2.3 (1.5-3.4)**	**4.7 (2.8-8)**	8/2.5	**3.2 (1.4-6.4)**	**4.6 (2-10.6)**	16/8	**2 (1.1-3.3)**	**4.8 (2.4-9.6)**
1970-1979	313456.1	27/7.9	**3.4 (2.2-5)**	**6.1 (3.9-9.5)**	15/4.1	**3.7 (2.1-6.1)**	**6 (3.3-10.9)**	12/3.8	**3.1 (1.6-5.5)**	**6.2 (3.1-12.3)**
1980-1989	339267.1	34/8	**4.2 (2.9-5.9)**	**7.6 (5.2-11.2)**	31/6.5	**4.8 (3.2-6.8)**	**8.9 (6-13.2)**	3/1.5	**2 (0.4-5.7)**	**2.3 (0.5-11.6)**
1990–1999	162395.1	21/4	**5.3 (3.3-8.1)**	**10.5 (6.5-16.9)**	21/3.9	**5.4 (3.3-8.2)**	**10.7 (6.6-17.2)**	0/0	**-**	**-**
≥ 2000	24377.1	9/0.6	**14.2 (6.5-27)**	**34.3 (17.4-67.6)**	9/0.6	**14.2 (6.5-27)**	**34.3 (17.4-67.6)**	-	**-**	**-**
*P for heterogeneity**			***<.0001***	***<.0001***		***0.0116***	***0.0007***		***0.6884***	***0.5358***
*P-trend**			***<.0001***	***0.0001***		***0.0067***	***0.0005***		***0.6717***	***0.6270***
Attained Age										
5–19 years	408724.5	56/10.5	**5.4 (4-6.9)**	**11.1 (8.3-14.9)**	56/10.5	**5.4 (4-6.9)**	**11.1 (8.3-14.9)**	-	**-**	**-**
20–29 years	389275.6	33/7.6	**4.4 (3-6.1)**	**6.5 (4.4-9.6)**	26/5.6	**4.7 (3-6.8)**	**7.1 (4.6-10.9)**	7/2	**3.5 (1.4-7.3)**	**5 (2.1-12)**
30–39 years	214076	11/5.6	**2 (1-3.5)**	**2.5 (1.1-5.9)**	2/1.6	**1.3 (0.2-4.7)**	**0.7 (0-13.2)**	9/4	**2.2 (1-4.3)**	**3.3 (1.4-8)**
≥ 40 years	114196.4	15/7.4	**2 (1.1-3.3)**	**6.6 (3.3-13.5)**	0/0	**-**	**-**	15/7.4	**2 (1.1-3.3)**	**6.6 (3.3-13.5)**
*P for heterogeneity**			***0.0006***	***0.0039***		***0.2553***	***0.0505***		***0.4725***	***0.4830***
*P-trend**			***<.0001***	***0.0025***		***0.0576***	***0.0051***		***0.2687***	***0.5531***
Years from Diagnosis										
5–9 years	311750.3	55/7.7	**7.1 (5.4-9.3)**	**15.2 (11.4-20.2)**	55/7.7	**7.1 (5.4-9.3)**	**15.2 (11.4-20.2)**			
10–19 years	449577.9	29/9.9	**2.9 (2-4.2)**	**4.3 (2.7-6.7)**	29/9.9	**2.9 (2-4.2)**	**4.3 (2.7-6.7)**			
20–29 years	236989.1	15/6	**2.5 (1.4-4.1)**	**3.8 (2-7.3)**				15/6	**2.5 (1.4-4.1)**	**3.8 (2-7.3)**
30–39 years	96627.1	9/4.2	**2.1 (1-4)**	**4.9 (2-12.1)**				9/4.2	**2.1 (1-4)**	**4.9 (2-12.1)**
≥ 40 years	31328.2	7/3.2	**2.2 (0.9-4.6)**	**12.2 (4.5-33.3)**				7/3.2	**2.2 (0.9-4.6)**	**12.2 (4.5-33.3)**
*P for heterogeneity**			***<.0001***	***<.0001***		***0.0001***	***<.0001***		***0.9200***	***0.1565***
*P-trend**			***<.0001***	***0.0005***		***0.0001***	***<.0001***		***0.7474***	***0.0857***

*Abbreviations: O – observed number of leukemia, E – expected number of leukemia, SIR- standardized incidence ratio, AER - absolute excess risk per 100,000 person-years, 95%CI- 95% confidence interval (in bold), *P for heterogeneity or P-trend were calculated using two-sided likelihood ratio tests within an univariable Poisson model.*

Table 4: Relative risk (RR) and relative excess risk (RER) of developing a subsequent primary leukaemia (SPL) by demographic and treatment factors (Multivariable analyses).

Factor	Overall		By years from diagnosis			
			5–19 years		≥ 20 years	
	RR (95% CI)	RER (95% CI)	RR (95% CI)	RER (95% CI)	RR (95% CI)	RER (95% CI)
Country						
Norway	Ref	Ref	Ref	Ref	-	-
France	2.8 (0.6-13.5)	8.1 (0.5-136.2)	2 (0.4-10.7)	2.9 (0.4-23.8)	Ref	Ref
Hungary	3.8 (0.8-17.7)	10.5 (0.6-172.6)	2.5 (0.5-11.8)	3.5 (0.5-25.2)	3.2 (0.3-31)	16.5 (0.8-352.2)
Italy	1.8 (0.4-8.7)	4.5 (0.3-74.9)	1.3 (0.3-6.3)	1.6 (0.2-12.2)	1.1 (0.1-10.4)	3.7 (0.1-124)
Netherlands	2.8 (0.6-12.5)	7.5 (0.5-120.8)	1.9 (0.4-8.8)	2.6 (0.4-18.9)	1.6 (0.3-8.9)	5.9 (0.4-92.6)
Denmark	1.3 (0.2-6.9)	1.7 (0.1-41)	1.2 (0.2-7)	1.3 (0.1-13.2)	0.5 (0.1-4.6)	-
Sweden	3 (0.7-13.5)	8.7 (0.5-138.2)	2.3 (0.5-10.7)	3.3 (0.5-23.6)	1.3 (0.3-6.1)	4.8 (0.4-64.2)
Finland	1.9 (0.4-8.9)	4.5 (0.3-75.4)	0.9 (0.2-5.1)	1 (0.1-8.9)	2.1 (0.5-8)	9.2 (0.9-93.8)
Iceland	7.1 (0.6-78.9)	23.8 (0.8-707.6)	6.4 (0.6-71.1)	10.6 (0.7-162)	-	-
Slovenia	2.8 (0.5-17.1)	7.8 (0.4-158.3)	2.7 (0.4-16.3)	3.9 (0.4-35.8)	-	-
Switzerland	2.8 (0.6-14)	7.6 (0.4-130)	2.1 (0.4-10.4)	2.9 (0.4-22)	-	-
UK	2.2 (0.5-9.4)	5.7 (0.4-88.5)	1.3 (0.3-5.7)	1.6 (0.2-10.9)	1.9 (0.6-6.2)	8.4 (1-73)
P for heterogeneity‡	*0.5685*	*0.4174*	*0.5861*	*0.3785*	*0.8275*	*0.5439*
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.8 (0.6-1.2)	0.9 (0.6-1.4)	1 (0.6-1.5)	1.1 (0.7-1.8)	0.5 (0.2-1.1)	0.4 (0.1-1.1)
P for heterogeneity‡	*0.3355*	*0.5932*	*0.9933*	*0.7336*	*0.0667*	*0.0680*
Type of Childhood Cancer						
Soft Tissue Sarcoma	Ref	Ref	Ref	Ref	Ref	-
Leukemia	1.1 (0.5-2.5)	1.2 (0.4-3)	0.8 (0.3-1.9)	1.3 (0.5-3.6)	3.3 (0.4-31.6)	Ref
Hodgkin Lymphoma	2.1 (0.9-4.9)	2.5 (1-6.8)	2 (0.8-5)	3.5 (1.2-10.3)	2 (0.2-22.6)	0.9 (0.1-10.6)
Non-Hodgkin Lymphoma	1 (0.4-3)	1.1 (0.3-3.7)	0.7 (0.2-2.5)	1.1 (0.3-4.6)	3.3 (0.3-37)	2.1 (0.2-18.3)
Central Nervous System	1 (0.4-2.2)	1 (0.4-2.5)	0.7 (0.3-1.7)	1 (0.4-3)	2.8 (0.3-23.2)	1.6 (0.3-8.3)
Neuroblastoma	1.2 (0.4-3.5)	1.3 (0.4-4.5)	0.8 (0.2-2.9)	1.4 (0.3-6)	4.2 (0.4-48.7)	3 (0.4-23.7)
Retinoblastoma	0.6 (0.2-2.5)	0.4 (0.1-3)	-	-	3.7 (0.4-38.3)	2.3 (0.3-15.7)
Wilms Tumor	0.9 (0.3-2.6)	0.9 (0.3-3)	0.6 (0.2-2.1)	1 (0.2-3.9)	3.2 (0.3-32.9)	2 (0.3-13.2)
Bone Sarcoma	0.5 (0.1-2)	0.3 (0.1-2.2)	0.4 (0.1-1.9)	0.5 (0.1-3.4)	1.5 (0.1-24.4)	0.2 (0-58.9)
Other and not classifiable	0.9 (0.4-2)	0.8 (0.3-2.3)	0.6 (0.2-1.6)	0.8 (0.2-2.7)	2.8 (0.3-24.2)	1.7 (0.3-10.4)
P for heterogeneity‡	*0.2976*	*0.0943*	*0.0880*	*0.0246*	*0.9897*	*0.9763*
Age at Diagnosis						

Abbreviations: (RR) and relative (RER) from Poisson adjusted for type of childhood diagnosis, diagnosis, and

Relative risk excess risk multivariable regression model country, sex, cancer, age at decade of attained Age. ‡*P*

for heterogeneity calculated using likelihood ratio multivariable Ref- reference 95%CI- 95% interval.

0–4 years	0.7 (0.3-1.7)	0.7 (0.2-2.4)	0.6 (0.2-1.7)	0.4 (0.1-1.6)	0.8 (0.2-3.6)	1.1 (0.1-9.6)
5–9 years	1 (0.4-2.3)	1.2 (0.4-3.5)	1 (0.4-2.9)	1 (0.3-3.5)	0.6 (0.1-2.7)	0.6 (0.1-5.8)
10–14 years	1.4 (0.6-2.9)	1.8 (0.7-4.5)	1.5 (0.6-3.9)	1.7 (0.6-5.1)	0.9 (0.2-3.2)	1.1 (0.2-7)
15–19 years	Ref	Ref	Ref	Ref	Ref	Ref
P for heterogeneity‡	*0.1425*	*0.0737*	*0.0343*	*0.0047*	*0.9131*	*0.9073*
P-trend‡	*0.3106*	*0.2948*	*0.0214*	*0.0033*	*0.7030*	*0.9952*
Decade of Diagnosis						
<1970	Ref	Ref	Ref	Ref	Ref	Ref
1970-1979	1.1 (0.6-2.1)	1.2 (0.6-2.8)	1 (0.4-2.4)	1 (0.4-3)	1.2 (0.5-2.7)	1.8 (0.6-5.6)
1980-1989	1.2 (0.6-2.4)	1.4 (0.6-3)	1.3 (0.6-2.9)	1.5 (0.6-3.8)	0.6 (0.2-2.6)	0.7 (0.1-5.3)
1990–1999	1.3 (0.6-2.8)	1.4 (0.6-3.6)	1.3 (0.6-3.3)	1.5 (0.5-4.3)	-	-
≥ 2000	2.5 (1-6.7)	3 (1-9.2)	3 (1-8.8)	3.6 (1.1-12.2)	-	-
P for heterogeneity‡	*0.4066*	*0.3434*	*0.2119*	*0.1590*	*0.6430*	*0.3771*
P-trend‡	*0.3167*	*0.2397*	*0.1006*	*0.0701*	*0.5266*	*0.9291*
Attained Age						
5–19 years	2.8 (0.5-14.7)	5.7 (0.6-51.1)	6.8 (1.4-31.9)	26.3 (1.3-543.1)	-	-
20–29 years	1.7 (0.4-6.6)	3.4 (0.5-23)	2.8 (0.6-12)	9.4 (0.5-186.1)	0.5 (0.1-1.6)	0.5 (0.1-2.4)
30–39 years	0.8 (0.3-2.6)	1 (0.2-5)	Ref	Ref	0.4 (0.2-1.1)	0.4 (0.1-1.5)
≥ 40 years	Ref	Ref	-	-	Ref	Ref
P for heterogeneity‡	*0.1992*	*0.1614*	*0.0031*	*0.0023*	*0.2065*	*0.3796*
P-trend‡	*0.3235*	*0.2152*	*0.0001*	*<.0001*	*0.2179*	*0.4471*
Years from Diagnosis						
5–9 years	Ref	Ref				
10–19 years	0.5 (0.3-0.9)	0.4 (0.2-0.8)				
20–29 years	0.9 (0.4-2.4)	0.9 (0.3-2.8)				
30–39 years	1.9 (0.4-8.4)	2.4 (0.3-17.6)				
≥ 40 years	5.1 (0.8-30.6)	8 (0.7-88)				
P for heterogeneity‡	*0.0064*	*0.0053*				
P-trend‡	*0.7823*	*0.6857*				

or P-trend were two-sided tests within a Poisson model.; category, confidence

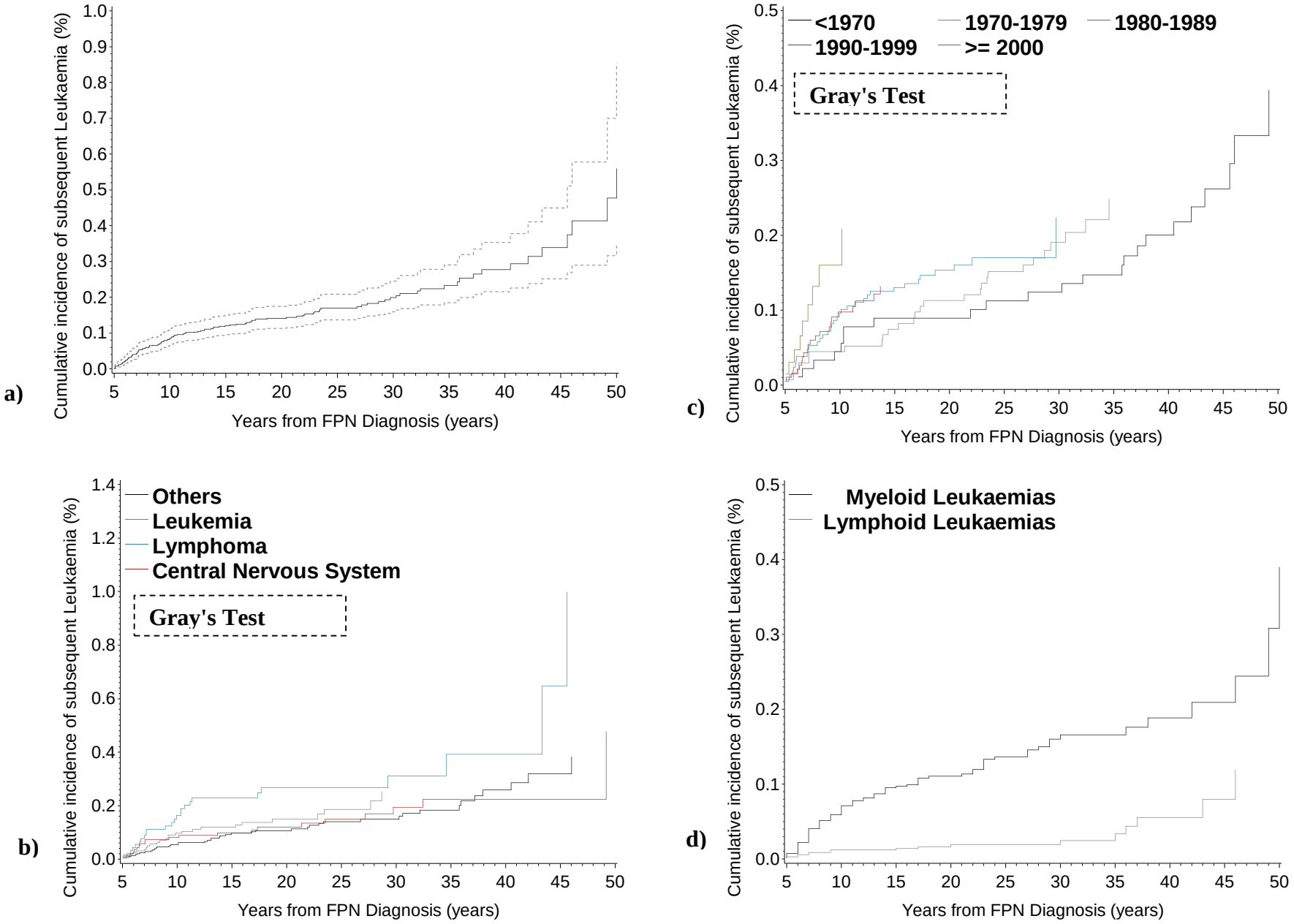

Figure 1. Cumulative incidence of new subsequent leukaemia diagnosed in survivors from the 5-years survivors of childhood cancer of the largest European PCSF study. a) Whole cohort: Solid lines are calculated cumulative incidence values; dashed lines are 95% CIs. Cumulative incidence curves for the main type of childhood cancer (b), and decade of diagnosis (c), and by leukaemia type (d).

Table 5: SIRs and AERs per 100,000 Person-Years at risk of developing a subsequent myeloid primary leukaemia (SPML) among 69,460 5-year survivors of childhood cancer and relative risk (RR) and relative of developing a SPML by demographic and treatment factors (Multivariable analyses).

Factor	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	86/14.9	**5.8 (4.6-7.1)**		**6.3 (5-8)**	
P-values		**<.0001**		**0.0078**	
Country					
Norway	1/0.7	**1.4 (0-7.9)**	Ref	**0.6 (0-20.5)**	Ref
France	8/1.2	**6.6 (2.9-13)**	5.7 (0.7-46.7)	**8.2 (3.9-17.3)**	20 (0.4-984.3)
Hungary	11/0.5	**21.2 (10.6-38)**	7 (0.9-55.8)	**20.9 (11.4-38.3)**	21 (0.4-1013.2)
Italy	9/1.1	**8.2 (3.8-15.6)**	3.2 (0.4-25.5)	**8.4 (4.2-16.8)**	9.1 (0.2-442.6)
Netherlands	8/1.2	**6.5 (2.8-12.9)**	3 (0.4-24.5)	**6.6 (3.1-13.9)**	8.4 (0.2-414)
Denmark	4/1.3	**3.1 (0.8-8)**	2.7 (0.3-24.5)	**3.4 (1-11.3)**	7.9 (0.1-421.5)
Sweden	10/1.5	**6.6 (3.2-12.2)**	4.6 (0.6-36.1)	**7.4 (3.8-14.4)**	15.3 (0.3-733.3)
Finland	6/1.5	**4.1 (1.5-8.9)**	2.6 (0.3-21.4)	**4.3 (1.7-10.8)**	6.8 (0.1-346.8)
Iceland	0/0.1	**-**	-	**-**	-
Slovenia	3/0.4	**8.3 (1.7-24.2)**	5.3 (0.5-51.7)	**10.6 (3.2-35.5)**	18.1 (0.3-982)
Switzerland	3/0.5	**5.9 (1.2-17.2)**	2.2 (0.2-21.6)	**5.4 (1.6-18.7)**	5.3 (0.1-300.7)
UK	23/5.0	**4.6 (2.9-6.9)**	3.1 (0.4-23.3)	**4.9 (3.1-7.8)**	9 (0.2-418.4)
P for heterogeneity		***0.0103****	*0.4094*‡	***0.0274****	*0.2397*‡
Sex					
Male	49/8.5	**5.7 (4.3-7.6)**	Ref	**6.7 (4.9-9.2)**	Ref
Female	37/6.4	**5.8 (4.1-8)**	0.9 (0.6-1.4)	**5.8 (4.1-8.3)**	0.9 (0.6-1.5)
P for heterogeneity		***0.9757****	*0.6867*‡	***0.5498****	*0.8280*‡
Type of Childhood Cancer					
Soft Tissue Sarcoma	6/1.2	**5 (1.9-11)**	Ref	**5.8 (2.3-14.3)**	Ref
Leukemia	22/2.3	**9.6 (6-14.5)**	1.3 (0.5-3.3)	**9 (5.8-13.9)**	1.4 (0.5-4)
Hodgkin Lymphoma	16/1.3	**12.1 (6.9-19.6)**	2.1 (0.8-5.6)	**16.8 (10-27.9)**	2.6 (0.9-7.4)
Non-Hodgkin Lymphoma	4/0.8	**5.1 (1.4-13.1)**	0.9 (0.2-3.2)	**6 (2-17.9)**	0.9 (0.2-3.7)
Central Nervous System	16/3.2	**5.1 (2.9-8.2)**	0.9 (0.3-2.3)	**5.6 (3.3-9.7)**	0.9 (0.3-2.7)
Neuroblastoma	4/0.6	**7 (1.9-17.9)**	1.1 (0.3-4.1)	**6.2 (2.1-17.9)**	1.1 (0.3-4.7)
Retinoblastoma	0/0.7	**-**	-	**-**	-
Wilms Tumor	6/1.1	**5.5 (2-12)**	1 (0.3-3.1)	**5.1 (2.1-12.4)**	1 (0.3-3.6)
Bone Sarcoma	1/0.8	**1.2 (0-6.6)**	0.2 (0-1.8)	**0.3 (0-41.3)**	0 (0-155.3)
Other and not classifiable	11/3.0	**3.7 (1.9-6.7)**	0.8 (0.3-2.1)	**4.1 (2.1-8.4)**	0.8 (0.2-2.4)
P for heterogeneity		***0.0421****	*0.2152*‡	***0.0330****	*0.1872*‡
Age at Diagnosis					
0–4 years	25/4.8	**5.2 (3.3-7.6)**	0.7 (0.2-2)	**4.3 (2.8-6.7)**	0.6 (0.2-2.1)
5–9 years	24/3.2	**7.4 (4.7-11)**	1.2 (0.4-3.2)	**8.1 (5.3-12.4)**	1.2 (0.4-3.8)
10–14 years	28/4	**6.9 (4.6-10)**	1.6 (0.7-3.8)	**9.5 (6.3-14.1)**	2 (0.7-5.4)
15–19 years	9/2.8	**3.2 (1.5-6.1)**	Ref	**3.8 (1.7-8.5)**	Ref
P for heterogeneity		***0.1272****	*0.0660*‡	***0.0275****	*0.0128*‡
P-trend		***0.5240****	*0.1466*‡	***0.2793****	*0.0502*‡
Decade of Diagnosis					
<1970	8/3.7	**2.2 (0.9-4.3)**	Ref	**2.3 (0.9-6.1)**	Ref
1970-1979	15/3.6	**4.2 (2.4-7)**	1.4 (0.6-3.7)	**4.6 (2.6-8.2)**	2 (0.6-6.7)
1980-1989	25/4.4	**5.7 (3.7-8.5)**	1.4 (0.5-3.7)	**5.7 (3.7-8.7)**	1.9 (0.6-6.7)
1990–1999	23/2.6	**8.8 (5.6-13.2)**	1.6 (0.6-4.5)	**7.8 (5-12.1)**	2.4 (0.7-8.3)
≥ 2000	15/0.7	**21.2 (11.9-35)**	2.5 (0.8-7.8)	**17.3 (10.3-29.1)**	3.8 (1-15)
P for heterogeneity		***<.0001****	*0.5499*‡	***0.0006****	*0.3501*‡
P-trend		***<.0001****	*0.3749*‡	***<.0001****	*0.3080*‡
Attained Age					
5–19 years	41/3.1	**13 (9.4-17.7)**	1.3 (0.2-8.5)	**9.3 (6.7-12.7)**	3.5 (0.4-33.4)
20–29 years	29/4.7	**6.2 (4.1-8.9)**	1 (0.2-4.4)	**6.2 (4.2-9.3)**	2 (0.3-13.7)
30–39 years	7/3.6	**2 (0.8-4)**	0.4 (0.1-1.7)	**1.5 (0.5-4.4)**	0.4 (0.1-3.2)
≥ 40 years	9/3.5	**2.5 (1.2-4.8)**	Ref	**4.4 (1.9-10.6)**	Ref
P for heterogeneity		***<.0001****	*0.2743*‡	***0.0092****	*0.0814*‡
P-trend		***<.0001****	*0.2827*‡	***0.0023****	*0.0994*‡

Years from Diagnosis					
5–9 years	42/2.6	**16 (11.5-21.6)**	Ref	**12.6 (9.2-17.3)**	Ref
10–19 years	24/4.9	**4.9 (3.1-7.2)**	0.5 (0.3-1)	**4.2 (2.7-6.6)**	0.6 (0.3-1.1)
20–29 years	13/3.8	**3.4 (1.8-5.9)**	0.9 (0.3-2.8)	**3.8 (2-7.3)**	1.4 (0.4-4.6)
30–39 years	3/2.3	**1.3 (0.3-3.9)**	0.5 (0.1-3.6)	**0.5 (0-8.1)**	0 (0-1591.6)
≥ 40 years	4/1.3	**3.1 (0.8-7.9)**	2.3 (0.3-19.1)	**8 (2.3-27.5)**	6.5 (0.5-81.9)
P for heterogeneity		***<.0001****	*0.0660*‡	***<.0001****	*0.0575*‡
P-trend		***<.0001****	*0.9934*‡	***0.0001****	*0.4852*‡

*Abbreviations: O – observed number of leukemia, E – expected number of leukemia, SIR- standardized incidence ratio, AER - absolute excess risk per 100,000 person-years, 95%CI- 95% confidence interval (in bold), *P for heterogeneity or P-trend were calculated using two-sided likelihood ratio tests within an univariable Poisson model. Relative risk (RR) and relative excess risk (RER) from multivariable Poisson regression model adjusted for country, sex, type of childhood cancer, age at diagnosis, decade of diagnosis, and attained Age. ‡P for heterogeneity or P-trend were calculated using two-sided likelihood ratio tests within a multivariable Poisson model.; Ref- reference category, 95%CI- 95% confidence interval.*

Appendix.

Table S1. International Classification of Diseases for Oncology - Editions1, 2 and 3 codes.

Endpoint	ICD-O 1st edition	ICD-O 2nd edition	ICD-O 3rd edition	N° cases
All leukaemias	9800/3 to 9940/3	9800/3 to 9941/3	9800/3 to 9989/3	**115**
Main leukaemia subtypes				
Myeloid Leukaemias (ML)	9860/3 to 9866/3	9860/3 to 9868/3	9840/3 to 9931/3	**86**
Acute myeloid leukaemia	9861/3	9861/3	9840/3, 9841/3, 9866/3 to 9874/3, 9891/3 to 9920/3, 9931/3	45
Chronic myeloid leukaemia	9863/3	9863/3	9863/3, 9875/3	10
Other and unspecified		9860/3,9867/3	9860/3, 9861/3, 9863/3, 9876/3, 9930/3	31
Lymphoid Leukaemias (LL)	9820/3 to 9825/3	9820/3 to 9827/3	9820/3 to 9837/3	**17**
Acute lymphoid leukaemia	9821/3	9821/3	9835/3	5
Chronic lymphoid leukaemia	9823/3	9823/3	9823/3	4
Other and unspecified			9820/3, 9827/3, 9836/3, 9837/3	8
Others type of Leukaemias	9840/3	9800/3, 9801/3, 9895/3, 9940/3	9800/3, 9801/3, 9805/3, 9940/3	**12**

N° cases= number of subsequent primary leukaemia cases

Table S2: Characteristics of childhood cancers survivors who developed a subsequent primary leukaemia according the main subtypes of leukaemias selected.

Factor	Survivors who developed a subsequent leukaemia, No. (%) or Mean (Range)	Survivors who developed a myeloid leukaemia, No. (%) or Mean (Range)	Survivors who developed a lymphoid leukaemia, No. (%) or Mean (Range)
Overall	**115**	**86**	**17**
Country			
Norway	2 (1.7)	1 (1.2)	-
France	9 (7.8)	8 (9.3)	-
Hungary	11 (9.6)	11 (12.8)	-
Italy*	9 (7.8)	9 (10.5)	-
Netherlands	13 (11.3)	8 (9.3)	4 (23.5)
Denmark	4 (3.5)	4 (4.7)	-
Sweden	13 (11.3)	10 (11.6)	-
Finland	9 (7.8)	6 (7)	2 (11.8)
Iceland	1 (0.9)	-	-
Slovenia	3 (2.6)	3 (3.5)	-
Switzerland	7 (6.1)	3 (3.5)	3 (17.6)
UK	34 (29.6)	23 (26.7)	8 (47.1)
Sex			
Male	68 (59.1)	49 (57)	13 (76.5)
Female	47 (40.9)	37 (43)	4 (23.5)
Type of Childhood Cancer			
Soft Tissue Sarcoma	8 (7)	6 (7)	2 (11.8)
Leukemia	25 (21.7)	22 (25.6)	1 (5.9)
Hodgkin Lymphoma	19 (16.5)	16 (18.6)	1 (5.9)
Non-Hodgkin Lymphoma	6 (5.2)	4 (4.7)	2 (11.8)
Central Nervous System	22 (19.1)	16 (18.6)	5 (29.4)
Neuroblastoma	6 (5.2)	4 (4.7)	2 (11.8)
Retinoblastoma	3 (2.6)	-	2 (11.8)
Wilms Tumor	8 (7)	6 (7)	1 (5.9)
Bone Sarcoma	3 (2.6)	1 (1.2)	-
Other and not classifiable†	15 (13)	11 (12.8)	1 (5.9)
Age at Diagnosis			
Mean (range)	8.1 (0.3-18.6)	8.5 (0.7-18.2)	6.7 (0.3-18.6)
0–4 years	39 (33.9)	25 (29.1)	9 (52.9)
5–9 years	30 (26.1)	24 (27.9)	3 (17.6)
10–14 years	34 (29.6)	28 (32.6)	3 (17.6)
15–19 years	12 (10.4)	9 (10.5)	2 (11.8)
Decade of Diagnosis			
Mean (range)	1980.3 (1948-2006)	1981.8 (1948-2006)	1979.9 (1958-1998)
<1970	24 (20.9)	14 (16.3)	4 (23.5)
1970-1979	27 (23.5)	22 (25.6)	2 (11.8)
1980-1989	34 (29.6)	25 (29.1)	7 (41.2)
1990–1999	21 (18.3)	16 (18.6)	4 (23.5)
≥ 2000	9 (7.8)	9 (10.5)	-
Attained Age			
Mean (range)	23.6 (6.4-65.3)	22.9 (6.4-65.3)	26.3 (6.5-64.6)
5–19 years	56 (48.7)	41 (47.7)	10 (58.8)
20–29 years	33 (28.7)	29 (33.7)	1 (5.9)
30–39 years	11 (9.6)	7 (8.1)	2 (11.8)
≥ 40 years	15 (13)	9 (10.5)	4 (23.5)
Years from Diagnosis			
Mean (range)	15.5 (5-50.5)	14.4 (5.1-50.5)	19.6 (5.1-46)
5–9 years	55 (47.8)	42 (48.8)	8 (47.1)
10–19 years	29 (25.2)	24 (27.9)	2 (11.8)
20–29 years	15 (13)	13 (15.1)	2 (11.8)
30–39 years	9 (7.8)	3 (3.5)	3 (17.6)
≥ 40 years	7 (6.1)	4 (4.7)	2 (11.8)

Table S3: SIRs and AERs per 100,000 Person-Years at risk of developing a subsequent lymphoid primary leukaemia (SPLL) among 69,460 5-year survivors of childhood cancer and relative risk (RR) and relative of developing a SPLL by demographic and treatment factors (Multivariable analyses).

Factor	O/E	SIR (95% CI)	AER (95% CI)
Overall	17/13.6	**1.2 (0.7-2)**	**0.3 (0.1-0.9)**
P-values		**0.4212**	**0.0271**
Country			
Netherlands	4/1.2	**3.3 (0.9-8.5)**	**2.7 (0.8-8.7)**
Finland	2/1.4	**1.4 (0.2-5.2)**	**0.6 (0-7.1)**
Switzerland	3/0.6	**5.2 (1.1-15.1)**	**5.2 (1.5-18.5)**
UK	8/4.2	**1.9 (0.8-3.8)**	**1 (0.4-2.8)**
Others Country [Norway, France, Hungary, Italy, Denmark, Sweden, Iceland and Slovenia]	0/5.9	**-**	**-**
P for heterogeneity		***0.5163****	***0.1600****
Sex			
Male	13/8.6	**1.5 (0.8-2.6)**	**0.7 (0.3-1.9)**
Female	4/4.6	**0.9 (0.2-2.2)**	**-**
P for heterogeneity		***0.3050****	**-**
Type of Childhood Cancer			
Soft Tissue Sarcoma	2/1	**2 (0.2-7.1)**	**1.2 (0.2-8.6)**
Leukemia	1/2.7	**0.4 (0-2.1)**	**-**
Hodgkin Lymphoma	1/0.9	**1.2 (0-6.5)**	**0.2 (0-30.7)**
Non-Hodgkin Lymphoma	2/0.6	**3.2 (0.4-11.6)**	**2.6 (0.5-13.6)**
Central Nervous System	5/2.6	**1.9 (0.6-4.5)**	**1.1 (0.3-3.7)**
Neuroblastoma	2/0.8	**2.6 (0.3-9.3)**	**2.2 (0.4-13)**
Retinoblastoma	2/0.8	**2.6 (0.3-9.3)**	**2 (0.3-11.9)**
Wilms Tumor	1/1.2	**0.8 (0-4.7)**	**-**
Bone Sarcoma	0/0.6	**-**	**-**
Other and not classifiable	1/2.2	**0.5 (0-2.6)**	**-**
P for heterogeneity		***0.7103****	***0.8868****
Age at Diagnosis			
0–4 years	9/6.4	**1.4 (0.6-2.7)**	**0.6 (0.2-1.9)**
5–9 years	3/2.7	**1.1 (0.2-3.2)**	**0.1 (0-4.5)**
10–14 years	3/2.4	**1.2 (0.3-3.6)**	**0.2 (0-3)**
15–19 years	2/1.7	**1.2 (0.1-4.3)**	**0.2 (0-6.5)**
P for heterogeneity		***0.9845****	***0.7809****
P-trend		***0.7933****	***0.4284****
Decade of Diagnosis			
<1970	4/3.8	**1.1 (0.3-2.7)**	**0.1 (0-5.1)**
1970-1979	2/3.1	**0.6 (0.1-2.3)**	**0.1 (0-5.1)**
1980-1989	7/3.7	**1.9 (0.8-3.9)**	**1 (0.3-2.9)**
1990–1999	4/2.2	**1.8 (0.5-4.6)**	**1.1 (0.3-4.8)**
≥ 2000	0/0.4	**-**	**1.1 (0.3-4.8)**
P for heterogeneity		***0.6791****	***0.5026****
P-trend		***0.4558****	***0.1701****
Attained Age			
5–19 years	10/6.8	**1.5 (0.7-2.7)**	**0.8 (0.3-2.3)**
20–29 years	1/2.4	**0.4 (0-2.3)**	**0.8 (0.3-2.3)**
30–39 years	2/1.2	**1.6 (0.2-5.9)**	**0.4 (0-3.4)**
≥ 40 years	4/2.8	**1.5 (0.4-3.7)**	**1.1 (0.2-6.3)**
P for heterogeneity		***0.6738****	***0.7656****
P-trend		***0.9380****	***0.9747****
Years from Diagnosis			
5–9 years	8/4.8	**1.7 (0.7-3.3)**	**1 (0.3-3.1)**
10–19 years	2/4.2	**0.5 (0.1-1.7)**	**1 (0.3-3.1)**
20–29 years	2/1.5	**1.3 (0.2-4.7)**	**0.2 (0-3.5)**
30–39 years	3/1.3	**2.3 (0.5-6.7)**	**1.7 (0.4-7.9)**
≥ 40 years	2/1.4	**1.5 (0.2-5.3)**	**2 (0.2-23.8)**

P for heterogeneity	***0.4969****	***0.5593****
P-trend	***0.7401****	***0.7926****

*Abbreviations: O – observed number of leukemia, E – expected number of leukemia, SIR- standardized incidence ratio, AER - absolute excess risk per 100,000 person-years, 95%CI- 95% confidence interval (in bold), *P for heterogeneity or P-trend were calculated using two-sided likelihood ratio tests within an univariable Poisson model. Ref- reference category, 95%CI- 95% confidence interval.*

Table S4: Sensitivity analysis using different background rates to calculate standardized incidence ratios (SIRs).

	As in manuscript*		Finnish Rates		UK Rates	
Factor	**O/E**	**SIR (95% CI)**	**O/E**	**SIR (95% CI)**	**O/E**	**SIR (95% CI)**
Overall	115/31	**3.7 (3.1-4.5)**	115/31.4	**3.7 (3-4.4)**	115/31	**3.7 (3.1-4.5)**
Country						
Norway	2/1.5	**1.4 (0.2-4.9)**	2/1.5	**1.4 (0.2-4.9)**	2/1.5	**1.4 (0.2-4.9)**
France	9/2.3	**3.9 (1.8-7.4)**	9/2.3	**3.9 (1.8-7.5)**	9/2.3	**3.9 (1.8-7.4)**
Hungary	11/1.2	**9 (4.5-16.1)**	11/1.3	**8.7 (4.3-15.5)**	11/1.2	**9 (4.5-16.1)**
Italy	9/2.3	**3.9 (1.8-7.4)**	9/2.4	**3.8 (1.7-7.2)**	9/2.3	**3.9 (1.8-7.4)**
Netherlands	13/2.6	**5 (2.7-8.6)**	13/2.6	**5 (2.7-8.6)**	13/2.6	**5 (2.7-8.6)**
Denmark	4/2.7	**1.5 (0.4-3.7)**	4/2.7	**1.5 (0.4-3.7)**	4/2.7	**1.5 (0.4-3.8)**
Sweden	13/3.3	**4 (2.1-6.8)**	13/3.3	**4 (2.1-6.8)**	13/3.2	**4 (2.2-6.9)**
Finland	9/3.4	**2.7 (1.2-5)**	9/3.4	**2.7 (1.2-5)**	9/3.4	**2.6 (1.2-5)**
Iceland	1/0.1	**10.4 (0.3-58)**	1/0.1	**10.4 (0.3-58)**	1/0.1	**10.5 (0.3-58.6)**
Slovenia	3/0.7	**4.3 (0.9-12.4)**	3/0.7	**4.4 (0.9-13)**	3/0.7	**4.3 (0.9-12.4)**
Switzerland	7/1.2	**6.1 (2.4-12.5)**	7/1.2	**5.8 (2.3-12)**	7/1.2	**6.1 (2.4-12.5)**
UK	34/9.9	**3.5 (2.4-4.8)**	34/10	**3.4 (2.3-4.7)**	34/9.9	**3.5 (2.4-4.8)**
Sex						
Male	68/18.9	**3.6 (2.8-4.6)**	68/18.5	**3.7 (2.9-4.7)**	68/18.9	**3.6 (2.8-4.6)**
Female	47/12.1	**3.9 (2.9-5.2)**	47/12.9	**3.6 (2.7-4.8)**	47/12.1	**3.9 (2.9-5.2)**
Type of Childhood Cancer						
Soft Tissue Sarcoma	8/2.4	**3.3 (1.4-6.5)**	8/2.5	**3.3 (1.4-6.4)**	8/2.4	**3.3 (1.4-6.5)**
Leukemia	25/5.3	**4.7 (3.1-7)**	25/5.5	**4.5 (2.9-6.7)**	19/2.5	**7.8 (4.7-12.1)**
Hodgkin Lymphoma	19/2.5	**7.8 (4.7-12.1)**	19/2.4	**8 (4.8-12.5)**	25/5.3	**4.7 (3.1-7)**
Non-Hodgkin Lymphoma	6/1.6	**3.9 (1.4-8.4)**	6/1.5	**3.9 (1.4-8.5)**	6/1.6	**3.9 (1.4-8.4)**
Central Nervous System	22/6.4	**3.5 (2.2-5.2)**	22/6.4	**3.4 (2.1-5.2)**	22/6.4	**3.5 (2.2-5.2)**
Neuroblastoma	6/1.4	**4.2 (1.5-9)**	6/1.5	**3.9 (1.4-8.5)**	6/1.4	**4.2 (1.5-9)**
Retinoblastoma	3/1.6	**1.8 (0.4-5.4)**	3/1.7	**1.8 (0.4-5.1)**	3/1.6	**1.8 (0.4-5.4)**
Wilms Tumor	8/2.4	**3.3 (1.4-6.4)**	8/2.5	**3.1 (1.4-6.2)**	8/2.4	**3.3 (1.4-6.4)**
Bone Sarcoma	3/1.6	**1.9 (0.4-5.5)**	3/1.5	**1.9 (0.4-5.7)**	3/1.6	**1.9 (0.4-5.5)**
Other and not classifiable	15/5.8	**2.6 (1.5-4.3)**	15/5.7	**2.6 (1.5-4.3)**	15/5.8	**2.6 (1.5-4.3)**
Age at Diagnosis						
0–4 years	39/12	**3.2 (2.3-4.4)**	39/12.7	**3.1 (2.2-4.2)**	39/12	**3.2 (2.3-4.4)**
5–9 years	30/6.5	**4.6 (3.1-6.6)**	30/6.6	**4.6 (3.1-6.5)**	30/6.5	**4.6 (3.1-6.6)**
10–14 years	34/7.2	**4.7 (3.3-6.6)**	34/7	**4.8 (3.4-6.8)**	34/7.2	**4.7 (3.3-6.6)**
15–19 years	12/5.3	**2.3 (1.2-4)**	12/5.1	**2.4 (1.2-4.1)**	12/5.3	**2.3 (1.2-4)**
Decade of Diagnosis						
<1970	24/10.5	**2.3 (1.5-3.4)**	24/10.4	**2.3 (1.5-3.4)**	24/10.5	**2.3 (1.5-3.4)**
1970-1979	27/7.9	**3.4 (2.2-5)**	27/7.9	**3.4 (2.3-5)**	27/7.9	**3.4 (2.2-5)**
1980-1989	34/8	**4.2 (2.9-5.9)**	34/8.2	**4.2 (2.9-5.8)**	34/8	**4.2 (2.9-5.9)**
1990–1999	21/4	**5.3 (3.3-8.1)**	21/4.2	**5 (3.1-7.7)**	21/4	**5.3 (3.3-8.1)**
≥ 2000	9/0.6	**14.2 (6.5-27)**	9/0.7	**12.1 (5.5-22.9)**	9/0.6	**14.2 (6.5-27)**
Attained Age						
5–19 years	56/10.5	**5.4 (4-6.9)**	56/11.7	**4.8 (3.6-6.2)**	56/10.5	**5.4 (4-6.9)**
20–29 years	33/7.6	**4.4 (3-6.1)**	33/8	**4.1 (2.8-5.8)**	33/7.6	**4.4 (3-6.1)**
30–39 years	11/5.6	**2 (1-3.5)**	11/4.7	**2.3 (1.2-4.2)**	11/5.6	**2 (1-3.5)**
≥ 40 years	15/7.4	**2 (1.1-3.3)**	15/7	**2.1 (1.2-3.5)**	15/7.4	**2 (1.1-3.3)**
Years from Diagnosis						
5–9 years	55/7.7	**7.1 (5.4-9.3)**	55/8.7	**6.3 (4.8-8.3)**	55/7.7	**7.1 (5.4-9.3)**
10–19 years	29/9.9	**2.9 (2-4.2)**	29/10.3	**2.8 (1.9-4)**	29/9.9	**2.9 (2-4.2)**
20–29 years	15/6	**2.5 (1.4-4.1)**	15/5.7	**2.6 (1.5-4.4)**	15/6	**2.5 (1.4-4.1)**
30–39 years	9/4.2	**2.1 (1-4)**	9/3.9	**2.3 (1.1-4.4)**	9/4.2	**2.1 (1-4)**
≥ 40 years	7/3.2	**2.2 (0.9-4.6)**	7/2.8	**2.5 (1-5.1)**	7/3.2	**2.2 (0.9-4.6)**

Abbreviations: O – observed number of leukemia, E – expected number of leukemia, SIR- standardized incidence ratio, 95%CI- 95% confidence interval.

Table S5: Sensitivity analysis using different background rates to calculate absolute excess risk per 100,000 person-years.

	As in manuscript*	Finnish Rates	UK Rates
Factor	**AER (95% CI)**	**AER (95% CI)**	**AER (95% CI)**
Overall	**7.5 (6-9.2)**	**7.4 (6-9.2)**	**7.5 (6-9.2)**
Country			
Norway	**1 (0.1-14.8)**	**1 (0.1-14.8)**	**1 (0.1-14.8)**
France	**8 (3.8-17.2)**	**8.1 (3.8-17.2)**	**8 (3.8-17.2)**
Hungary	**19.5 (10.4-36.5)**	**19.4 (10.4-36.4)**	**19.5 (10.4-36.5)**
Italy	**7.1 (3.3-15.1)**	**7 (3.3-15.1)**	**7.1 (3.3-15.1)**
Netherlands	**10.1 (5.5-18.5)**	**10.1 (5.5-18.5)**	**10.1 (5.5-18.5)**
Denmark	**1.6 (0.3-9.1)**	**1.6 (0.3-9.1)**	**1.7 (0.3-9.2)**
Sweden	**8.4 (4.5-15.8)**	**8.4 (4.5-15.8)**	**8.5 (4.5-15.9)**
Finland	**5.3 (2.3-12.2)**	**5.3 (2.3-12.2)**	**5.3 (2.3-12.2)**
Iceland	**26.1 (3.3-205.1)**	**26.1 (3.3-205.1)**	**26.1 (3.3-205.1)**
Slovenia	**9.2 (2.5-33.7)**	**9.4 (2.6-33.9)**	**9.2 (2.5-33.7)**
Switzerland	**12.7 (5.6-28.5)**	**12.5 (5.6-28.3)**	**12.7 (5.6-28.5)**
UK	**6.5 (4.4-9.8)**	**6.5 (4.4-9.7)**	**6.5 (4.4-9.8)**
Sex			
Male	**8.2 (6.2-10.8)**	**8.2 (6.2-10.9)**	**8.2 (6.2-10.8)**
Female	**6.7 (4.8-9.3)**	**6.5 (4.6-9.1)**	**6.7 (4.8-9.3)**
Type of Childhood Cancer			
Soft Tissue Sarcoma	**6.7 (2.9-15.5)**	**6.7 (2.9-15.4)**	**6.7 (2.9-15.5)**
Leukemia	**9 (5.8-13.9)**	**19 (11.7-30.7)**	**18.9 (11.7-30.6)**
Hodgkin Lymphoma	**18.9 (11.7-30.6)**	**8.8 (5.7-13.8)**	**9 (5.8-13.9)**
Non-Hodgkin Lymphoma	**8.3 (3.3-21)**	**8.3 (3.3-21)**	**8.3 (3.3-21)**
Central Nervous System	**6.8 (4.2-11.2)**	**6.8 (4.2-11.2)**	**6.8 (4.2-11.2)**
Neuroblastoma	**8.2 (3.3-20.6)**	**8.1 (3.2-20.4)**	**8.2 (3.3-20.6)**
Retinoblastoma	**2.3 (0.4-12.1)**	**2.1 (0.4-12)**	**2.3 (0.4-12.1)**
Wilms Tumor	**5.8 (2.5-13.3)**	**5.7 (2.5-13.2)**	**5.8 (2.5-13.3)**
Bone Sarcoma	**2.7 (0.5-14.2)**	**2.8 (0.6-14.3)**	**2.7 (0.5-14.2)**
Other and not classifiable	**4.8 (2.5-9.2)**	**4.9 (2.6-9.3)**	**4.8 (2.5-9.2)**
Age at Diagnosis			
0–4 years	**5.8 (4-8.5)**	**5.7 (3.9-8.3)**	**5.8 (4-8.5)**
5–9 years	**9.2 (6.1-13.8)**	**9.2 (6.1-13.7)**	**9.2 (6.1-13.8)**
10–14 years	**10.6 (7.3-15.5)**	**10.7 (7.3-15.6)**	**10.6 (7.3-15.5)**
15–19 years	**4.3 (2-9.2)**	**4.5 (2.1-9.4)**	**4.3 (2-9.2)**
Decade of Diagnosis			
<1970	**4.7 (2.8-8)**	**4.7 (2.8-8.1)**	**4.7 (2.8-8)**
1970-1979	**6.1 (3.9-9.5)**	**6.1 (3.9-9.6)**	**6.1 (3.9-9.5)**
1980-1989	**7.6 (5.2-11.2)**	**7.6 (5.2-11.2)**	**7.6 (5.2-11.2)**
1990–1999	**10.5 (6.5-16.9)**	**10.4 (6.4-16.7)**	**10.5 (6.5-16.9)**
≥ 2000	**34.3 (17.4-67.6)**	**33.9 (17.1-67)**	**34.3 (17.4-67.6)**
Attained Age			
5–19 years	**11.1 (8.3-14.9)**	**10.8 (8.1-14.5)**	**11.1 (8.3-14.9)**
20–29 years	**6.5 (4.4-9.6)**	**6.4 (4.3-9.5)**	**6.5 (4.4-9.6)**
30–39 years	**2.5 (1.1-5.9)**	**3 (1.4-6.4)**	**2.5 (1.1-5.9)**
≥ 40 years	**6.6 (3.3-13.5)**	**7 (3.5-14)**	**6.6 (3.3-13.5)**
Years from Diagnosis			
5–9 years	**15.2 (11.4-20.2)**	**14.9 (11.1-19.8)**	**15.2 (11.4-20.2)**
10–19 years	**4.3 (2.7-6.7)**	**4.2 (2.6-6.5)**	**4.3 (2.7-6.7)**
20–29 years	**3.8 (2-7.3)**	**3.9 (2.1-7.5)**	**3.8 (2-7.3)**
30–39 years	**4.9 (2-12.1)**	**5.3 (2.2-12.6)**	**4.9 (2-12.1)**

≥ 40 years	**12.2 (4.5-33.3)**	**13.3 (5.1-34.8)**	**12.2 (4.5-33.3)**

Abbreviations: AER - absolute excess risk per 100,000 person-years, 95%CI- 95% confidence interval.

Annexe 2 : *RADLEUK : méta-analyse internationale sur le risque de leucémie secondaire après un cancer durant l'enfance*

Risk of developing Leukemia after Chemotherapy and Radiation Treatment for a Childhood Cancer: An International Pooled Analysis

Rodrigue S. Allodji PhD[1,2,4,‡], Margaret Tucker MD[3], Michael M. Hawkins MD PhD[4], Marie-Cécile Le Deley MD PhD[1,5], Cristina Veres MSc[1,2], Rita Weathers MSc[6], Rebecca Howell PhD[6], Dave Winter MSc[4], Nadia Haddy PhD[1,2], Carole Rubino MD PhD[1,2], Ibrahima Diallo PhD[1,2], Mark P. Little DPhil[3], Lindsay M. Morton PhD[3], Florent de Vathaire PhD[1,2]

[1]CESP-INSERM, Univ. Paris–Sud, UVSQ, Université Paris–Saclay, Villejuif, France

[2]Cancer and Radiation Team, Gustave Roussy, Villejuif, F-94805, France

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

[4]Centre for Childhood Cancer Survivor Studies, School of Health and Population Sciences, University of Birmingham, Public Health Bldg, Edgbaston, Birmingham B15 2TT, United Kingdom

[5]Methodology and Biostatistic Unit, Centre Oscar Lambret, Lille, France.

[6]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas; University of Texas Graduate School of Biomedical Sciences, Houston, Texas.

‡Corresponding author:

Dr Rodrigue S. Allodji, Radiation Epidemiology Group / CESP - Unit 1018 INSERM, Gustave Roussy, B2M, 114, rue Édouard Vaillant, 94805 Villejuif Cedex, Tel 01 42 11 54 98 / Fax 01 42 11 53 15, E-mail: rodrigue.allodji@gustaveroussy.fr

Running title

Pooled analysis of therapy-related leukemia after childhood cancer

Key points

- Childhood cancer survivors treated with topoisomerase II inhibitors (anthracyclines and epipodophyllotoxins) are at a high therapy-related leukemia risk in an international pooled analysis.
- These results are particularly important given increases in topoisomerase II inhibitors use in current treatment approaches.

Abstract

Previous studies of childhood cancer survivors have demonstrated increased risk for therapy-related leukemias. However, individual studies have included limited numbers subjects, limiting understanding of risks associated with specific treatments. We initiated collaborative analyses of studies with detailed treatment data to more thoroughly investigate the respective roles of radiotherapy and chemotherapy in the occurrence of therapy-related leukemia after childhood cancer, in a pooled analysis of 147 therapy-related leukemia cases and 522 individually-matched controls (childhood cancer only) from France, Great Britain, and an American-led consortium. Radiation dose to the red bone marrow (RBM) and cumulative doses of chemotherapy were calculated based on data abstracted from medical records; pooled multivariable odds ratios (ORs) were calculated using conditional logistic regression.

For all combined data, in a multivariable model including radiation dose to the RBM and cumulative exposure to topoisomerase II inhibitors (anthracyclines and epipodophyllotoxins), alkylating agents, platinum compounds, and vinca-alkaloids, only topoisomerase II inhibitors were independently associated with an increased therapy-related leukemia risk (OR = 4.1, 95% CI: 2.2–7.7) and the risk increased with increasing cumulative dose of topoisomerase II inhibitors (P-trend =0.0002). Risk was even higher (OR = 14.5, 95% CI: 5.2–40.3) when patients received both topoisomerase II inhibitors and alkylating agents, compared to childhood cancer survivors who did not received chemotherapy. These results are particularly important given increases in topoisomerase II inhibitors use in current treatment approaches and have implications for the follow-up of childhood cancer survivors regarding risks of therapy-related leukemia.

Keywords: Therapy-related leukemia, childhood cancers, radiotherapy, chemotherapy, alkylating agents, topoisomerase II inhibitors, radition to red bone marrow.

Abbreviations: RBM = Red Bone Marrow; OR = odds ratios.
Word Count: 2139 of 3000; Abstract: 242 of 250

INTRODUCTION

The survival of children with cancer has improved substantially over recent decades,[39] and consequently, adverse effects of treatment have become increasingly important. One of the most serious late effects is the occurrence of second malignant neoplasms (SMN) (39-45). Therapy-related leukemia is of specific interest because there is substantial information, both epidemiological and biological, on the increased risk of this disease after exposure to ionizing radiation, various chemotherapeutic agents, or both.[46,47] Ionizing radiation is a known carcinogen to which children are particularly vulnerable and sensitivity to radiation is highest early in life (48). Potential associations between leukemia risk and various chemotherapy (CT) drugs have been evaluated in a number of cohorts of paediatric or young adult cancer survivors (43-49). Those studies have demonstrated strongly increased risk of acute myeloid leukemia (AML) after certain types of chemotherapy drugs, in particular, alkylating agents (e.g., cyclophosphamide, melphalan, ifosfamide, procarbazine, or nitrogen mustard) and topoisomerase II inhibitors (e.g., epipodophyllotoxins, anthracyclines) (49). However, because drugs are often given in combination, individual studies have had limited ability to disentangle risks associated with specific agents. Another key unresolved question is the potential role for radiotherapy (RT) in leukemia risk, either with or without CT (44,50). However, previous studies among childhood cancer survivors have yielded inconsistent but mostly null findings on the association between therapeutic radiation and therapy-related leukemia (43,44,47,49).

To address these gaps in knowledge, we pooled data from prior studies of leukemia after childhood cancer with high quality information on specific CT agents and radiation dose to the red bone marrow (RBM). These comprise: (a) the British Childhood Cancer

Survivor Study (BCCSS) (45); (b) two parallel French datasets, the Société Française d'Oncologie Pédiatrique (SFOP) dataset (49,50), and the Euro2K dataset, which recently became the French Childhood Cancer Survivor Study (FCCSS) (43,44); and (c) the international Late Effects Study Group (LESG) study (47). This current pooled analysis, with information on 147 cases and 522 matched controls, offers a unique opportunity to more thoroughly investigate the respective roles of CT and RT in the occurrence of therapy-related leukemia after childhood cancer.

DATA AND METHODS

Selection criteria and data inclusion

We invited all principal investigators of studies on therapy-related leukemia after childhood cancer published during 1987-2015 and including information on CT and radiation dose to RBM to participate in the present collaborative international study. Four case–control studies including patients from six countries (France, United Kingdom, United States, Canada, Italy, the Netherlands) contributed data (Table 1) (6-9,12). Briefly, each study was a nested case–control study of leukemia occurring among childhood cancer survivors. Controls were matched by basic demographic characteristics (meaning age at first treatment, sex) and survival time at least as long as the index matched case's interval from childhood cancer to leukemia diagnosis.

CT and RT Data

In each study, RT and CT exposures were ascertained from the start of childhood cancer treatment until the development of leukemia for each case or the corresponding interval

for each matched control. Individual-level data on RT were utilized to reconstruct the mean radiation dose to the whole RBM (44-47,50,51).

Each study also abstracted detailed data from medical records regarding CT exposures for both initial and subsequent therapy. Data collected included drug name, dates of administration, and total dose per unit of body surface area measured as grams per square metre (mg/m^2). Because of multiple-agent therapies, we classified drugs into classes as follows: (a) alkylating agents, (b) Anthracyclines / Topo II inhibitors include both anthracyclines and epipodophyllotoxins (c) platinum compounds, (d) vinca-alkaloids and (e) antimetabolites (Supplementary eTable 1). We were unable to group CT drugs together into regimens administered in cycles since these data were not collected in some studies. However, we have also look at broad combinations of agents across different classes. Except for the alkylating agents, the sum of cumulative dose of different CT agents within specific groups was done, based on the simple assumption that all agents within a particular class share an equal leukemogenic potency. To sum the alkylating agents doses, we used the cyclophosphamide dose equivalent score for toxicity proposed by Green et al (52). The quartiles and median of the distribution of controls exposed were used to define the dose intervals for the classes of CT drugs and for whole RBM dose respectively (Supplementary Figure 1).

Statistical analysis

Conditional logistic regression analysis was conducted to derive estimated odds ratios (ORs) of leukemia associated with specific treatments (53,54). We firsly ran univariate models including each CT drug (supplementary eTable 1, available online) or each class of CT drugs and radiotherapy as indicator variables (no vs yes). Similar models were

employed in which the chemotherapeutic doses per class and RBM radiation doses were divided into categories (using the quartiles of the distribution of the whole RBM dose and the median of the distribution of each cumulative dose of CT in the control group). Then, adjusted ORs for treatment-related variables (indicator variables and categorical variables) were estimated.

Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA) (55). A type I error of P=0.05 was assumed, i.e., P-values of 0.05 or less were deemed statistically significant.

RESULTS

Selected characteristics of studies contributing to the international pooled analysis are reported in Table 1 and Table 2 summarises the patient and treatment characteristics of the cases and controls in the individual studies and the overall pooled study population, (147 cases and 522 controls aged 0–17 years at diagnosis). Most (N=101, 68.7%) of the cases were AML, with the remaining cases acute lymphoblastic leukemia (N=18), chronic myeloid leukemia (N=6), myelodysplastic syndromes (N=17) or other leukemia (N=5) (Table 2). The two French studies, which contributed the majority of cases (65.3%), had a younger median age at diagnosis than the other studies. For cases, the median interval from the first primary neoplasm to leukemia was around 5 years. The proportion of lymphoma was 27.9% and 20.7% among the cases and controls, respectively. Cases received RT more frequently than controls. Chemotherapy was involved in the treatment of about 90% of cases, whereas the proportion of controls treated with CT was 71.1%. While 57% of cases had received CT plus RT they were only about 41% among controls.

Cases received alkylating agents, anthracyclines / topo II inhibitors, platinum compounds, vinca-alkaloids or antimetabolites more frequently than controls (Table 3) and Figure 1 shows separately the doses of these chemotherapy drugs administered to cases and controls. These comparisons do not take into consideration that doses of drugs vary when they are given in combination with other drugs. Statistically significant differences were found for the doses of alkylating agents (P<.0001), anthracyclines / topo II inhibitors (P<.0001) and vinca-alkaloids (P=0.0002) between cases and controls (Figure 1).

For all combined data, the nonadjusted OR associated with any CT was significantly elevated, it was also for RT. When CT and RT were included simultaneously in a multivariate analysis, the OR for CT was similar than that found previously (OR = 6.1, 95% CI: 2.8–13.2), but a P value borderline significant (OR = 1.5, 95% CI: 0.98–2.3; P=0.0630) was found for RT (supplementary eTable 2). The nonadjusted OR were also elevated for individual therapies, specifically topoisomerase II inhibitors (P<0.0001), alkylating agents (P=0.0333), platinum compounds (P=0.008) and vinca-alkaloids (P=0.0009). However, after controlling for RT and other CT classes, only topoisomerase II inhibitors were independently associated with an increased therapy-related leukemia risk (OR = 4.1, 95% CI: 2.2–7.7; P<0.0001) (Table 4).

Crude ORs were elevated for cumulative dose of individual therapies, low-dose (OR of 3.2 95% CI 1.7-5.9) and high-dose (OR of 5.6 95% CI 3.1-10.0) of topoisomerase II inhibitors, high-dose of alkylating agents (OR of 3.0 95% CI 1.8-5.0), high-dose of platinum compounds (OR of 2.1 95% CI 1.1-4.1), high-dose of vinca-alkaloids (OR of 2.4 95% CI 1.4-3.9) and high-dose average radiation dose to the whole RBM (OR of 2.1 95% CI 1.1-3.9). Multivariate analysis including the above cumulative dose of CT groups and average

RBM radiation dose showed significant association only for topoisomerase II inhibitors (P-trend = 0.0002). The adjusted OR for the dose categories of topoisomerase II inhibitors >0-427.37 g/m^2 versus No and >427.37 g/m^2 versus No were 3.10 (95% CI 1.5-6.2) and 4.4 (95% CI 2.1-9.3), respectively.

The multivariate model including irradiation and some CT combinations (topoisomerase II inhibitors with alkylating agents or vinca-alkaloids, or with both) revealed significantly elevated ORs of 14.5 (95% CI 5.2-40.3) for of topoisomerase II inhibitors and alkylating agents; 11.8 (95% CI 3.2-17.5) for topoisomerase II inhibitors and vinca-alkaloids and 7.5 (95% CI 3.2-17.5) for topoisomerase II inhibitors with both alkylating agents and vinca-alkaloids, compared to childhood cancer survivors who did not received CT (Tables 5).

DISCUSSION

This pooled analysis of all studies that had individual RBM dose estimates and information on chemotherapy (44,45,47,50), is the largest to our knowledge to assess the risk of therapy-related leukemia among childhood cancer survivors, with 147 therapy-related leukemia cases. As in most previous studies, we found a very high chemotherapy risk of therapy-related leukemia (44,45,47,50,58-61). Important new findings of this study is the association between topoisomerase II inhibitors (anthracyclines and epipodophyllotoxins) with the risk of therapy-related leukemia and the risk increased with increasing cumulative dose of topoisomerase II inhibitors. These results are particularly important given increases in topoisomerase II inhibitors use in current treatment approaches and are in line with previous studies that had found an increasing risk of therapy-related leukemia from anthracyclines and epipodophyllotoxins (44,45,49). Le

Deley et al. observed a 3-fold greater risk of therapy-related leukemia in SFOP children who were treated for solid tumours who received more than 170 mg/m^2 anthracyclines as compared to those who received lower doses of these drugs (49). However, the risk of therapy-related leukemia is influenced by treatment factors, including the schedule of administration and concomitant medications (62). Unfortunately, as the current pooled analysis combined the available data from the four selected studies only (without the corresponding schedule of administration), we could not examine the relationship between the varying schedules of topoisomerase II inhibitors administration and an increased risk of therapy-related leukemia. As some previous studies, our findings have aslo confirmed that treatment with topoisomerase II inhibitors in combination with alkylating agents increases the probability of therapy-related leukemia (62,63).

Leukemia induced by therapeutic radiation alone among childhood cancer survivors studies is rare (43,44,47,49,61). Our current study, the largest study on this topic thus far, to our knowledge, showed that a slightly elevated but nonsignificant therapy-related leukemia for radiotherapy after adjustment for the chemotherapy agents (Table 4 and supplementary eTable 2). This finding might reflect the swamping effects of chemotherapy (44).

One of the limitations to our study was that a voxel-based approach or dose-volume histogram (DVH) was not used to investigate the relationship between radiation dose to RBM and therapy-related leukemia risk. The voxel-wise analysis would permit the identification of subregions within the organs at risk, which may be responsible for secondary effects, hence highlighting heterogeneous intra-organ radio-sensitivity (64). Further and more extensive research into the novel innovative dosimetric (voxel) method

may open new avenues of research in radiation epidemiology, clinical oncology, and cancer survivorship.

Among the strengths of our study is the inclusion of all studies on therapy-related Leukemia after childhood cancer with information on chemotherapy and radiation dose to RBM published in the interval 1987 - 2015. Previous studies have been generally limited by inadequate sample sizes in attempts to detect modest associations; many did not have either the power or data necessary to examine therapy-related leukemia risk (44,45,47,50). In our pooled dataset, we were able to evaluate the risk of leukemia associated with radiotherapy and/or chemotherapy treatments, even for subgroup analyses.

Cancer survival rates are expected to increase further with improved diagnosis, treatment, and survival (65). For these and other reasons, additional attention must be paid to reduce the incidence of treatment-related morbidity, such as therapy-related leukemia. Our results provide therapy-related leukemia stratified risks that may have implications both for the planning of new treatments and for the follow-up of childhood cancer survivors.

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Conflict of interest

The authors declare no conflict of interest.

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FIGURE LEGENDS

Figure. 1: Cumulative dose per chemotherapy drug group (mg/m^2) and radiation doses to the red bone marrow for therapy-related leukaemia cases and controls.

Table 1: Selected characteristics of the contributing studies

Characteristics	LESG[†]	SFOP[¥]	FCCSS[£]	BCCSS[§]
Source population	13 medical centers throughout US, Canada, and Western Europe	Société Française d'Oncologie Pédiatrique (Case-Control Study)	National Cohort	National Register of Childhood Tumours maintained by the Childhood Cancer Research Group
Cohort (n)	9170	-	~15,000	18,422
Calendar period	1936-1979	1980-1997	1946-2000	1940-1983
Eligible age at first primary childhood cancer	<18 years	<18 years	<20 years	<15 years
Minimal survival time	2 years	1 year	2 years	3 years
Eligible first primary childhood cancers	Any	Solid tumor, non-Hodgkin lymphoma, or Langerhans cell histiocytosis	Malignant tumor (except leukemias)	Any
Study population				
Cases (n)	25	61	35	26
Controls (n)	90	196	140	96
Control matching criteria				
Sex	X	X	X	X
Childhood cancer type	X	-	-	X
Age at childhood cancer	X (±2 years)	X (±2 years)	X	X
Year of childhood cancer	-	X (±2 years)	X	-
Duration of follow-up	X	X	X	X
Hospital	-	X	X	-
Race	X	-	-	-
Case pathology review	Pathology report review	Medical records / Paediatric histopathologist	Medical records / general practitioner	Paediatric histopathologist

[†]LESG = Late Effects Study Group (Tucker et al [8]); [¥]SFOP = Société Française d'Oncologie Pédiatrique (Le Deley et al [9]); [£]FCCSS = French Childhood Cancer Survivor Study (Allodji et al [6]); [§]BrCCSS = British Childhood Cancer Survivor Study (Hawkins et al [7]); X = matching variable.

Table 2: Patient and treatment characteristics of therapy-related leukemia cases and controls, by study and in the pooled analysis

Characteristics	LESG		SFOP		FCCSS		BCCSS		Pooled	
	Cases (n = 25)	Controls (n =90)	Cases (n = 61)	Controls (n = 196)	Cases (n = 35)	Controls (n = 140)	Cases (n = 26)	Controls (n = 96)	Cases (n = 147)	Controls (n = 522)
Gender										
Female (%)	15 (60.0)	52 (57.8)	32 (52.5)	103 (52.6)	14 (40.0)	56 (40.0)	14 (53.8)	50 (52.1)	75 (51.0)	261 (50.0)
Male (%)	10 (40.0)	38 (42.2)	29 (47.5)	93 (47.4)	21 (60.0)	84 (60.0)	12 (46.2)	46 (47.9)	72 (49.0)	261 (50.0)
Age at childhood cancer diagnosis										
Median (range), years	9.1 (0–16.0)	7.0 (0–16.0)	8.0 (0–17.0)	8.0 (0–17.0)	5.1 (0–15.9)	5.5 (0–17.0)	8.5 (2–15.0)	8.0 (0–15.0)	8.0 (0–17.0)	7.0 (0–17.0)
Year of childhood cancer diagnosis										
Median (range), years	1971 (1950–1977)	1966 (1930–1977)	1991 (1980–1996)	1991 (1980–1997)	1986 (1966–1999)	1986 (1964–2000)	1978 (1945–1983)	1975 (1951–1983)	1985 (1945–1999)	1985 (1930–2000)
First primary childhood cancer type										
Lymphoma (%)	12 (48.0)	32 (35.6)	10 (16.4)	14 (7.1)	10 (28.6)	27 (19.3)	9 (34.6)	35 (36.5)	41 (27.9)	108 (20.7)
Neuroblastoma (%)	1 (4.0)	6 (6.7)	9 (14.8)	21 (10.7)	3 (8.6)	15 (10.7)	2 (7.7)	8 (8.3)	6 (4.1)	29 (5.6)
Osteosarcoma (%)	3 (12.0)	6 (6.7)	8 (13.1)	10 (5.1)	2 (5.7)	11 (7.9)	2 (7.7)	7 (7.3)	15 (10.2)	34 (6.5)
Other cancers (%)	9 (36.0)	46 (51.1)	34 (55.7)	150 (76.5)	20 (57.1)	87 (62.1)	13 (50)	46 (47.9)	85 (57.8)	351 (67.2)
Radiotherapy										
No	5 (20.0)	12 (13.3)	27 (44.3)	111 (56.6)	14 (40.0)	71 (50.7)	4 (15.4)	30 (31.3)	50 (34.0)	224 (42.9)
Yes	20 (80.0)	78 (86.7)	34 (55.7)	85 (43.4)	21 (60.0)	69 (49.3)	22 (84.6)	66 (68.7)	97 (66.0)	298 (57.1)
Chemotherapy										
No	5 (20.0)	34 (37.8)	1 (1.6)	37 (18.9)	1 (2.9)	37 (26.4)	8 (30.8)	43 (44.8)	15 (10.2)	151 (28.9)
Yes	20 (80.0)	56 (62.2)	60 (98.4)	159 (81.1)	34 (97.1)	103 (73.6)	18 (69.2)	53 (55.2)	132 (89.8)	371 (71.1)
Treatment combination										
Neither radiotherapy nor chemotherapy	-	6 (6.7)	-	24 (12.2)	1 (2.9)	19 (13.6)	1 (3.8)	16 (16.7)	2 (1.4)	65 (12.5)
Radiotherapy only	5 (20)	6 (6.7)	27 (44.3)	87 (44.4)	13 (37.1)	52 (37.1)	3 (11.5)	14 (14.6)	48 (32.7)	159 (30.5)
Chemotherapy only	5 (20)	28 (31.1)	1 (1.6)	13 (6.6)	-	18 (12.9)	7 (26.9)	27 (28.1)	13 (8.8)	86 (16.5)
Both radiotherapy and chemotherapy	15 (60)	50 (55.6)	33 (54.1)	72 (36.7)	21 (60)	51 (36.4)	15 (57.7)	39 (40.6)	84 (57.1)	212 (40.6)
Interval from childhood cancer to leukemia[§]										
Median (range), years	6.0 (2.0–18.0)		4.0 (2.0–14.0)		6.2 (2–35.7)		4.0 (1.0–27.0)		4.4 (1.0-35.7)	
Leukemia subtypes										
Acute myeloblastic leukemia (%)	20 (80.0)		34 (55.7)		28 (80.0)		19 (73.1)		101 (68.7)	
Acute lymphoblastic leukemia (%)	3 (12.0)		8 (13.1)		3 (8.6)		4 (15.4)		18 (12.2)	
Chronic myeloid leukemia (%)	2 (8.0)		1 (1.6)		3 (8.6)		-		6 (4.1)	

Myelodysplastic syndromes (%)	-	17 (28.0)	-	-	17 (11.6)
Other (%)	-	1 (1.6)	1 (2.8)	3 (11.5)	5 (3.4)

Data presented as n (%), unless otherwise noted. [§]Matched time period for control

Table 3: Distribution of chemotherapy for therapy-related leukemia cases and controls, by study and in the pooled analysis

Chemotherapy groups	LESG		SFOP		FCCSS		BCCSS		Pooled	
	Cases (n = 25)	Controls (n =90)	Cases (n = 61)	Controls (n = 196)	Cases (n = 35)	Controls (n = 140)	Cases (n = 26)	Controls (n = 96)	Cases (n = 147)	Controls (n = 522)
Alkylating agents										
No	9 (36)	58 (64.4)	10 (16.4)	60 (30.6)	18 (51.4)	70 (50)	11 (42.3)	56 (58.3)	48 (32.7)	244 (46.7)
Yes	16 (64)	32 (35.6)	51 (83.6)	136 (69.4)	17 (48.6)	70 (50)	15 (57.7)	40 (41.7)	99 (67.3)	278 (53.3)
Topoisomerase II inhibitors[§]										
No	18 (72)	84 (93.3)	3 (4.9)	68 (34.7)	14 (40)	71 (50.7)	15 (57.7)	71 (74)	50 (34)	294 (56.3)
Yes	7 (28)	6 (6.7)	58 (95.1)	128 (65.3)	21 (60)	69 (49.3)	11 (42.3)	25 (26)	97 (66)	228 (43.7)
Platinum compounds										
No	25 (100)	90 (100)	35 (57.4)	135 (68.9)	24 (68.6)	106 (75.7)	24 (92.3)	95 (99)	108 (73.5)	426 (81.6)
Yes	0(0)	0(0)	26 (42.6)	61 (31.1)	11 (31.4)	34 (24.3)	2 (7.7)	1 (1)	39 (26.5)	96 (18.4)
Vinca-alkaloids										
No	8 (32)	61 (67.8)	20 (32.8)	64 (32.7)	14 (40)	56 (40)	8 (30.8)	45 (46.9)	50 (34)	226 (43.3)
Yes	17 (68)	29 (32.2)	41 (67.2)	132 (67.3)	21 (60)	84 (60)	18 (69.2)	51 (53.1)	97 (66)	296 (56.7)
Antimetabolites										
No	25 (100)	82 (91.1)	45 (73.8)	142 (72.4)	25 (71.4)	112 (80)	16 (61.5)	68 (70.8)	111 (75.5)	404 (77.4)
Yes	0(0)	8 (8.9)	16 (26.2)	54 (27.6)	10 (28.6)	28 (20)	10 (38.5)	28 (29.2)	36 (24.5)	118 (22.6)

Data presented as n (%); [§]Topoisomerase II inhibitors include both anthracyclines and epipodophyllotoxins.

Table 4: Risk of therapy-related leukemia in relation to radiotherapy (RT) and selected chemotherapy groups in international pooled data.

Treatment	Univariable analyses	Multivariable analysis
	Odds ratio (95% CI)	**Odds ratio (95% CI)**
Radiotherapy		
No	**1.0 (Reference)**	**1.0 (Reference)**
Yes	1.6 (1.0-2.4)	1.5 (0.94-2.2)
P-value for heterogeneity	0.0333	0.0879
Alkylating agents		
No	**1.0 (Reference)**	**1.0 (Reference)**
Yes	1.9 (1.2-3.0)	1.0 (0.57-1.8)
P-value for heterogeneity	0.0041	0.9785
Topoisomerase II inhibitors[§]		
No	**1.0 (Reference)**	**1.0 (Reference)**
Yes	4.3 (2.5-7.4)	4.1 (2.2-7.7)
P-value for heterogeneity	<0.0001	<0.0001
Platinum compounds		
No	**1.0 (Reference)**	**1.0 (Reference)**
Yes	1.7 (1.1-2.8)	1.1 (0.63-1.9)
P-value for heterogeneity	0.0296	0.7706
Vinca-alkaloids		
No	**1.0 (Reference)**	**1.0 (Reference)**
Yes	1.6 (1.0-2.5)	1.0 (0.57-1.7)
P-value for heterogeneity	0.0477	0.9965
Antimetabolites		
No	**1.0 (Reference)**	
Yes	1.2 (0.72-1.9)	
P-value for heterogeneity	0.5154	

[§]Topoisomerase II inhibitors include both anthracyclines and epipodophyllotoxins. Abbreviations: 95% CI = 95% confidence interval. Antimetabolites aren't included in the multivariable model, because they were not statistically significant in univariate analysis.

Table 5: Risk of therapy-related leukemia in relation to cumulative dose of radiation dose to red bone marrow (RBM) and selected chemotherapy groups in international pooled data.

Treatment	Dose category¥	Cases / Controls	Univariable analyses	Multivariable analysis
			Odds ratio (95% CI)	Odds ratio (95% CI)
Radiotherapy (whole red bone marrow dose)	**0 Gy**	51/230	**1.0 (Reference)**	**1.0 (Reference)**
	> 0-2.21	22/69	1.5 (0.86-2.7)	1.3 (0.69-2.3)
	> 2.21-4.38	22/74	1.5 (0.81-2.8)	1.5 (0.80-2.9)
	> 4.38-9.80	21/75	1.4 (0.77-2.5)	1.1 (0.55-2)
	> 9.80	31/74	2.1 (1.1-3.9)	1.4 (0.73-2.8)
P-value for trend			0.0263	0.2664
Alkylating agents	**0 mg/m²**	48/246	**1.0 (Reference)**	**1.0 (Reference)**
	> 0-8952.12	27/137	1.1 (0.61-1.9)	0.8 (0.40-1.7)
	> 8952.12	72/139	3 (1.8-5)	1.5 (0.77-2.9)
P-value for trend			<.0001	0.3098
Topoisomerase II inhibitors§	**0 mg/m²**	50/295	**1.0 (Reference)**	**1.0 (Reference)**
	> 0-427.37	36/113	3.2 (1.7-5.9)	3 (1.5-6.2)
	> 427.37	61/114	5.6 (3.1-10)	4.4 (2.1-9.3)
P-value for trend			<.0001	0.0002
Platinum compounds	**0 mg/m²**	108/426	**1.0 (Reference)**	**1.0 (Reference)**
	> 0-1160.50	17/48	1.4 (0.77-2.7)	0.9 (0.43-1.7)
	> 1160.50	22/48	2.1 (1.1-4.1)	1 (0.46-2.2)
P-value for trend			0.0176	0.8052
Vinca-alkaloids	**0 mg/m²**	50/227	**1.0 (Reference)**	**1.0 (Reference)**
	> 0-17.57	28/147	0.9 (0.51-1.6)	0.6 (0.31-1.3)
	> 17.57	69/148	2.4 (1.4-3.9)	1.4 (0.76-2.6)
P-value for trend			0.0004	0.1114
Antimetabolites	**0 mg/m²**	109/404	**1.0 (Reference)**	
	> 0-2958.59	20/59	1.3 (0.72-2.5)	
	> 2958.59	18/59	1.3 (0.68-2.3)	
P-value for trend			0.3723	

§Topoisomerase II inhibitors include both anthracyclines and epipodophyllotoxins. ¥The categories of whole RBM dose were defined by the quartiles of the distribution in the control group. The categories of doses for chemotherapy groups were defined by the median of the distribution in the control group. Abbreviations: 95% CI = 95% confidence interval. Antimetabolites aren't included in the multivariable model, because they were not statistically significant in univariate analysis.

Table 6: Risk of therapy-related leukemia for selected chemotherapy combinations and the average radiation dose to red bone marrow (RBM) in international pooled data

Treatment characteristics[ǁ]	Cases / Controls	Univariable analyses	Multivariable analysis
		Odds ratio (95% CI)	Odds ratio (95% CI)
No chemotherapy	15/151	**1.0 (Reference)**	**1.0 (Reference)**
Alkylating agents and vinca-alkaloids	16/74	2.9 (1.1-7.5)	2.8 (1.1-7.3)
Topoisomerase II inhibitors and vinca-alkaloids	10/18	13.2 (4.4-39.9)	11.8 (3.9-36)
Topoisomerase II inhibitors and alkylating agents	22/36	15.3 (5.6-41.8)	14.5 (5.2-40.3)
Topoisomerase II inhibitors, alkylating agents and vinca-alkaloids	62/171	7.7 (3.3-17.9)	7.5 (3.2-17.5)
Other chemotherapy combined	22/72	5.5 (2.3-13.4)	5.5 (2.3-13.6)
P-value for heterogeneity		<.0001	<.0001
Whole red bone marrow dose (Gy)[¥]			
0 Gy	51/230	**1.0 (Reference)**	**1.0 (Reference)**
> 0-2.21	22/69	1.5 (0.86-2.7)	1.4 (0.79-2.7)
> 2.21-4.38	22/74	1.5 (0.81-2.8)	1.4 (0.75-2.7)
> 4.38-9.80	21/75	1.4 (0.77-2.5)	1.3 (0.68-2.4)
> 9.80	31/74	2.1 (1.1-3.9)	1.5 (0.80-2.9)
P-value for trend		0.0263	0.1913

[¥]The classes of whole red bone marrow dose were defined by the quartiles of the distribution in the control group. [§]Topoisomerase II inhibitors include both anthracyclines and epipodophyllotoxins. [ǁ]Because of interaction between chemotherapy groups, they were combined. Abbreviations: 95% CI = 95% confidence interval. Odds ratio (OR) of therapy-related leukemia for the average radiation dose to the whole red bone marrow and for selected chemotherapy combinations.

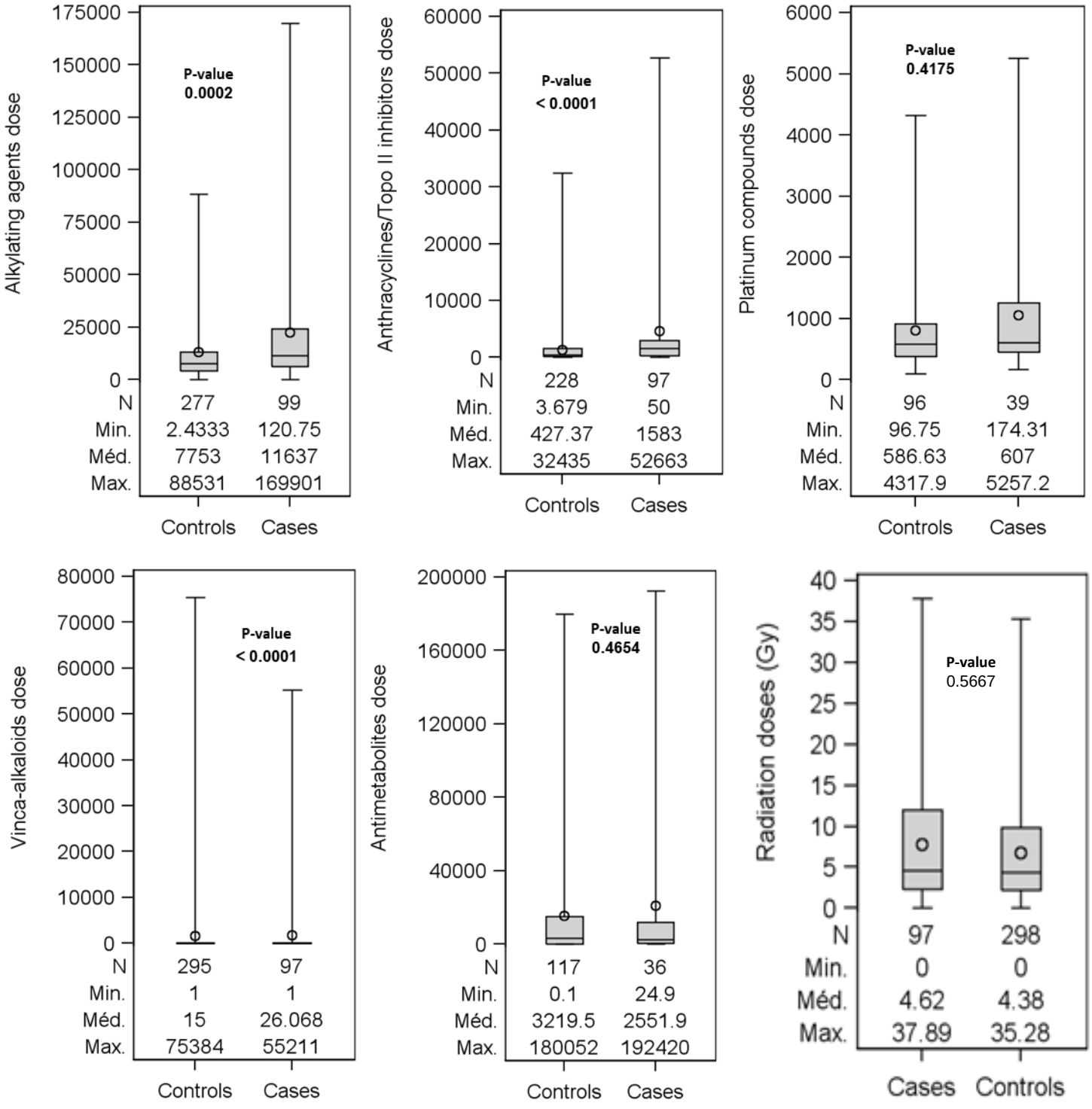
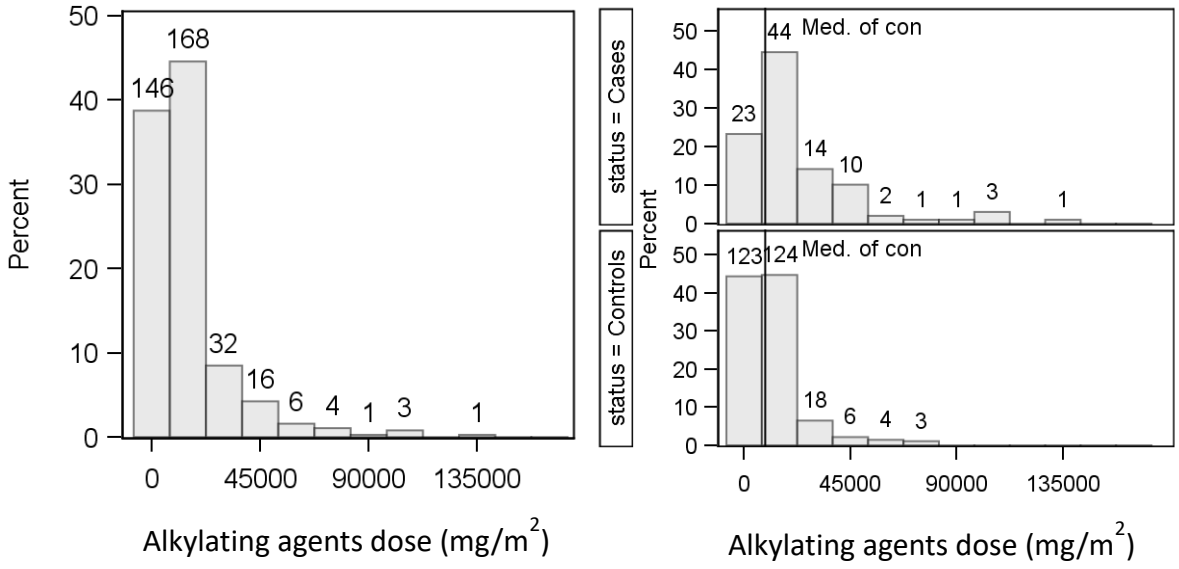


Figure 1: Cumulative dose per chemotherapy drug group (mg/m^2) and radiation doses to the red bone marrow for therapy-related leukemia cases and controls.

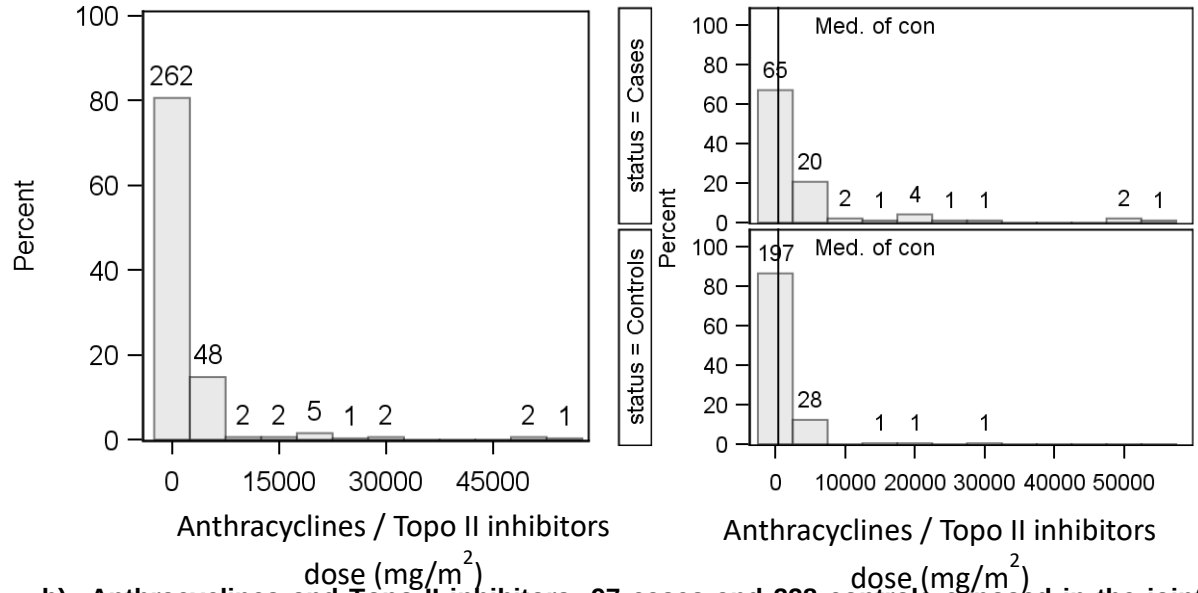
eTable 1: Chemotherapy drugs and group

Drug Groups	Drug Name
Alkylating agents group	CYCLOPHOSPHAMIDE IFOSFAMIDE PROCARBAZINE BCNU CCNU MELPHALAN THIOTEPA NITROGEN MUSTARD BUSULFAN DACARBAZINE
Anthracyclines / Topo II inhibitors group	ADRIAMYCIN EPIADRIAMYCINE DAUNORUBICIN VP-16 VM-26
Platinum compounds group	CISPLATIN CARBOPLATIN
Vinca-alkaloids group	VINCRISTINE VINDESINE VINBLASTINE VINORELBINE
Antimetabolites	CYTARABINE HYDREA 6-THIOGUANINE METHOTREXATE 6-MERCAPTOPURINE 5-FLUORO-URACIL METHYL-GAG
Antibiotics and other	ACTINOMYCIN BLEOMYCIN ASPARAGINASE

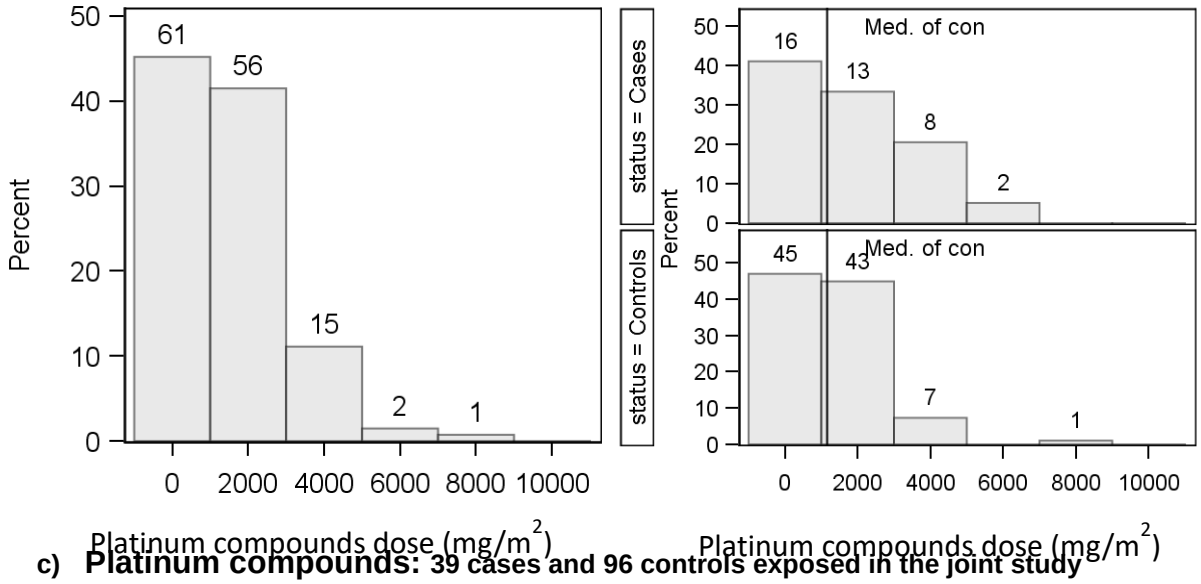
eFigure 1: Distribution of chemotherapy cumulative dose of therapy-related leukemia cases and controls among exposed in the joint study (Med. of contr. = median of controls among exposed)



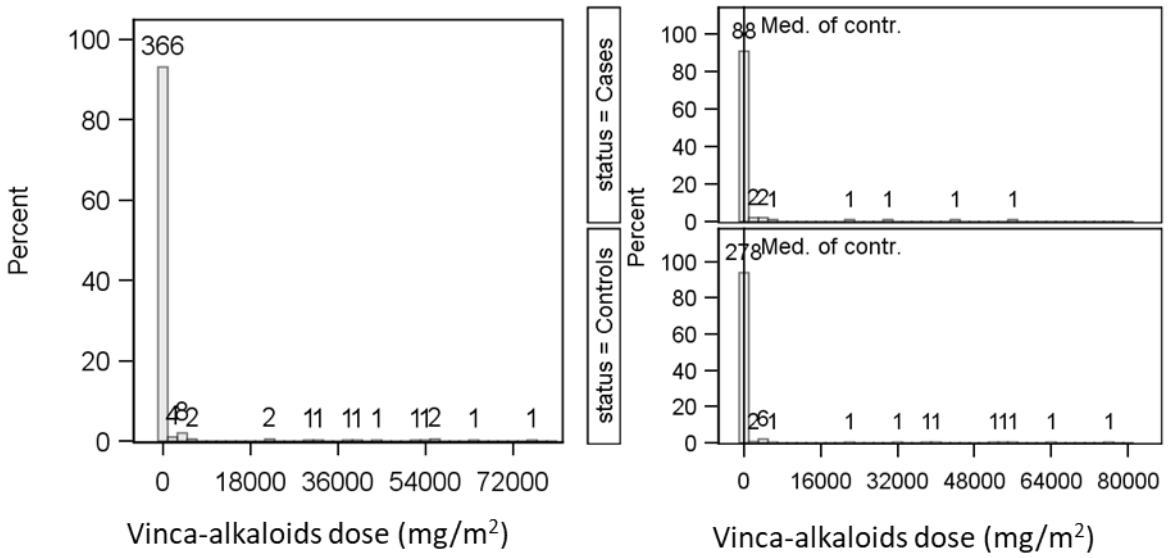
a) Alkylating agents: 99 cases and 278 controls exposed in the joint study



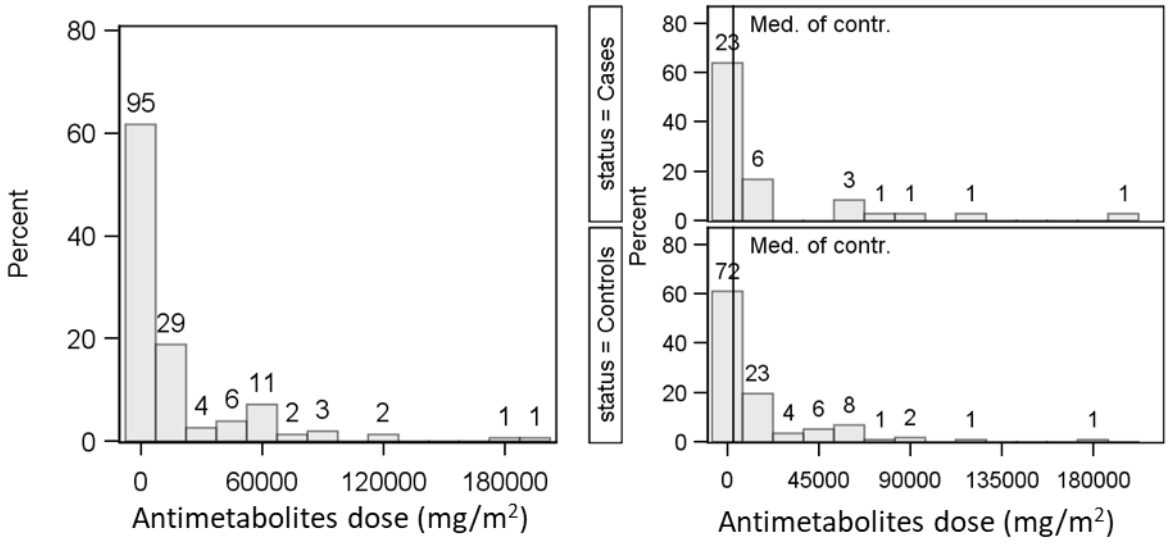
b) Anthracyclines and Topo II inhibitors: 97 cases and 228 controls exposed in the joint study



c) Platinum compounds: 39 cases and 96 controls exposed in the joint study



d) Vinca-alkaloids: 97 cases and 296 controls exposed in the joint study



e) Antimetabolites: 36 cases and 118 controls exposed in the joint study

eTable 2: Risk of therapy-related leukemia in relation to radiotherapy or/and chemotherapy in international pooled data.

Treatment characteristics	Cases / Controls	Univariable analyses	Multivariable analysis
		Odds ratio (95% CI)	Odds ratio (95% CI)
Radiotherapy			
No	50/224	**Ref (OR=1)**	**Ref (OR=1)**
Yes	97/298	1.6 (1.0-2.4)	1.5 (0.98-2.3)
P-value for heterogeneity		0.0333	0.0630
Chemotherapy			
No	15/151	**Ref (OR=1)**	**Ref (OR=1)**
Yes	132/371	6.2 (2.9-13.3)	6.1 (2.8-13.2)
P-value for heterogeneity		<0.0001	<0.0001

Abbreviations: 95% CI = 95% confidence interval.

Annexe 3 : RADLEUK : comparaison des approches dosimétriques

Inter-comparisons with other dose estimation software as stated in PCSF project were done. Through a validation study comparing dose-estimation between our group (INSERM/IGR) and the medical physicist group of M.D. Anderson Hospital group (Stovall group) that we called MDACC, we have compared the dose estimation of ionizing radiation received by active bone marrow in various parts of skeletal bones.

For this comparison, 41 patients have been selected randomly from data of a pooled analysis on long-term risk of subsequent leukaemia after treatment for childhood Cancer (Tucker et al. 1987; Hawkins et al. 1992; Le Deley et al 2003, Allodji et al 2015). Patient characteristics are shown in Table 1.

Table 1 : Patient characteristics and selected studies

	Population	Calendar period	N	Age		Gender	
				Mean	Min-Max	Female (n)	Male (n)
All patients			41	6.2	0-15	18	23
FCCSS	FCCSS = French Childhood Cancer Survivor Study (Allodji et al 2015)	1946-2000	10	5.8	0.3-14	6	4
SFOP	SFOP= Société Française d'Oncologie Pédiatrique [Case-Control Study (Le Deley et al 2003)];	1980-1997	10	5.9	1.4-14	4	6
BCCSS	BCCSS = British Childhood Cancer Survivor Study (Hawkins et al 1992).	1940-1983	10	8.7	0.8-15	4	6
LESG	LESG = Late Effects Study Group: 13 medical centers throughout US, Canada, and Western Europe (Tucker et al 1987)	1936-1979	11	4.4	0-13	4	7

Min=Minimal; Max=maximal.

Then, the dose estimation of ionizing radiation received by active bone marrow in each of major skeletal bones was done by each dosimetric group. Doses were estimated in each case using Cristy (Cristy 1981) bone marrow compartments.

Inter-comparisons results are shown in the following figures (1-5) and tables (2-6).

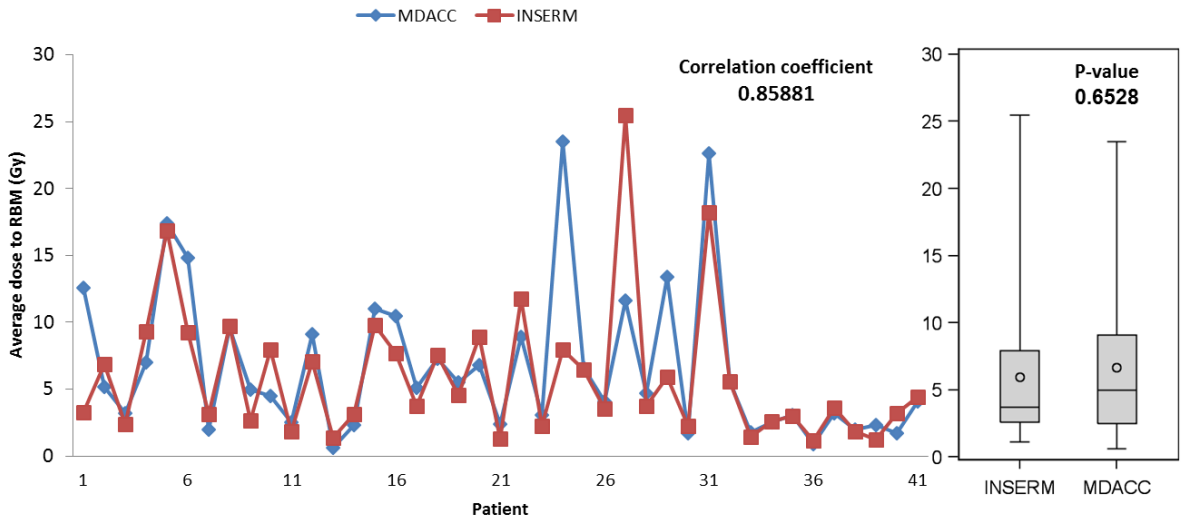


Fig. 1 Plots of individual patient average radiation dose to the whole Red Bone Marrow (RBM) for estimated by INSERM team and MDACC team for all patients.

Table 2: Average doses to the whole ABM and to the 12 sub-regions estimated by INSERM team and MDACC team for all patients.

Site	**INSERM**		**MDACC**	
	Mean	Min- Max	Mean	Min -Max
Whole reb bone marrow	6	1,1-25,5	6,6	0,6-23,5
Cranium	5	0-49,5	5,6	0-34,2
Mandible	3,9	0-25,2	3,9	0-22,5
Scapulae	4,9	0-27,9	5,7	0,1-20,7
Clavicles	5,6	0-23,2	6,8	0-36,9
Sternum	9,6	0,1-31,6	9,3	0-36,8
Sacrum	11,4	0-56,2	11	0-68,3
Femora UH¥	5	0-40,3	5	0-35,4
Femora LHξ	1,3	0-26,3	1,6	0-30
T.F.P¦	3	0-9,2	1,4	0-25,6
Humeri UH¥	1	0-8,3	1,1	0-9,4
Humeri LHξ	0,8	0-3,8	0,7	0-9,5
Wrist-hand	1,5	0-7,1	0,5	0-9,5

¥upper half; ξlower half; ¦Tibiae fibulae patellae; ¦¦Ankle and foot bones; Min=Minimal; Max=maximal.

There was no significant difference (P-value=0.6528) in average radiation dose to the whole Red Bone Marrow (RBM) for estimated by INSERM team and MDACC team for all patients. Interestingly, the correlation coefficient was 0.9 between the radiation dose to the whole Red Bone Marrow (RBM) for estimated by the two dosimetry groups (Fig.1).

Additionally, overall the doses estimated by both teams are relatively close (Table 2). These metrics (P-values and coefficient correlation) are presented for each population in below.

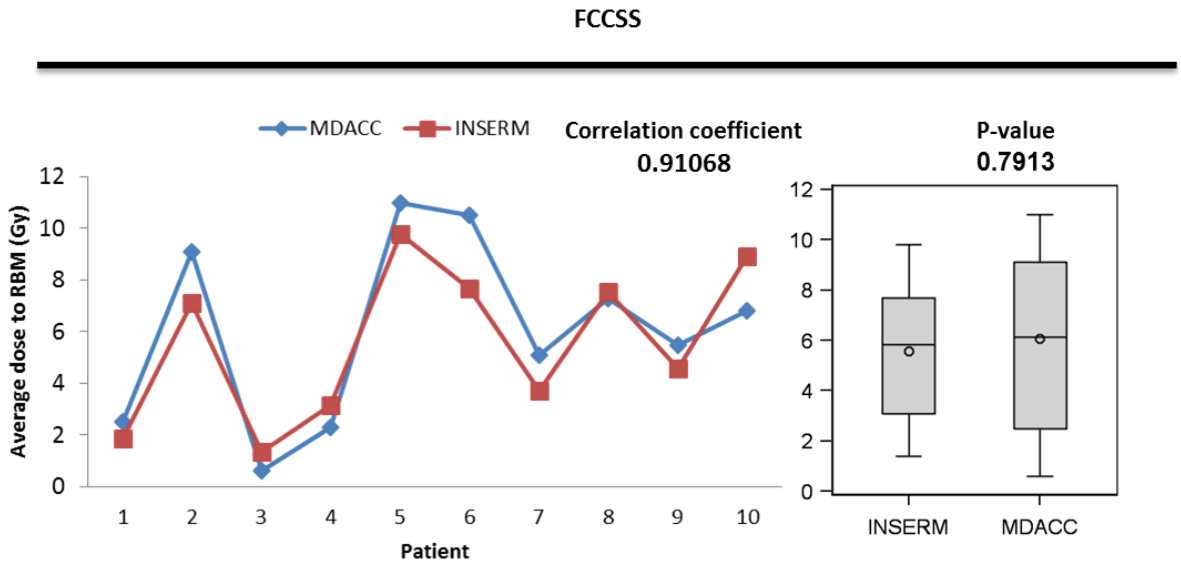


Fig. 2 Plots of individual patient average radiation dose to the whole Red Bone Marrow (RBM) for estimated by INSERM team and MDACC team for FCCSS patients.

Table 3: Average doses to the whole ABM and to the 12 sub-regions estimated by INSERM team and MDACC team for FCCSS patients.

Site	**INSERM**		**MDACC**	
	Mean	Min- Max	Mean	Min -Max
Whole reb bone marrow	5,6	1,4-9,8	6,1	0,6-11
Cranium	3,4	0-25,7	5,9	0-34,2
Mandible	1,9	0-14,4	2	0-14,4
Scapulae	3,3	0-11,6	5	0,1-16,9
Clavicles	3,1	0-11,8	3,3	0-12,3
Sternum	7,9	0,1-20,6	7,5	0-20,4
Sacrum	13,9	0-29,7	10,6	0-30,7
Femora UH[¥]	6,1	0-21,9	5	0-16,8
Femora LH[ξ]	0,4	0-1,2	0,2	0-0,5
T.F.P[ˈ]	2,3	0-9,2	0	0-0,1
Humeri UH[¥]	0,5	0-1,6	0,4	0-1,6
Humeri LH[ξ]	0,8	0-2,7	0,2	0-0,7
Wrist-hand	1,4	0-5,2	0,1	0-0,8

[¥]upper half; [ξ]lower half; [ˈ]Tibiae fibulae patellae; [ˈˈ]Ankle and foot bones; Min=Minimal; Max=maximal.

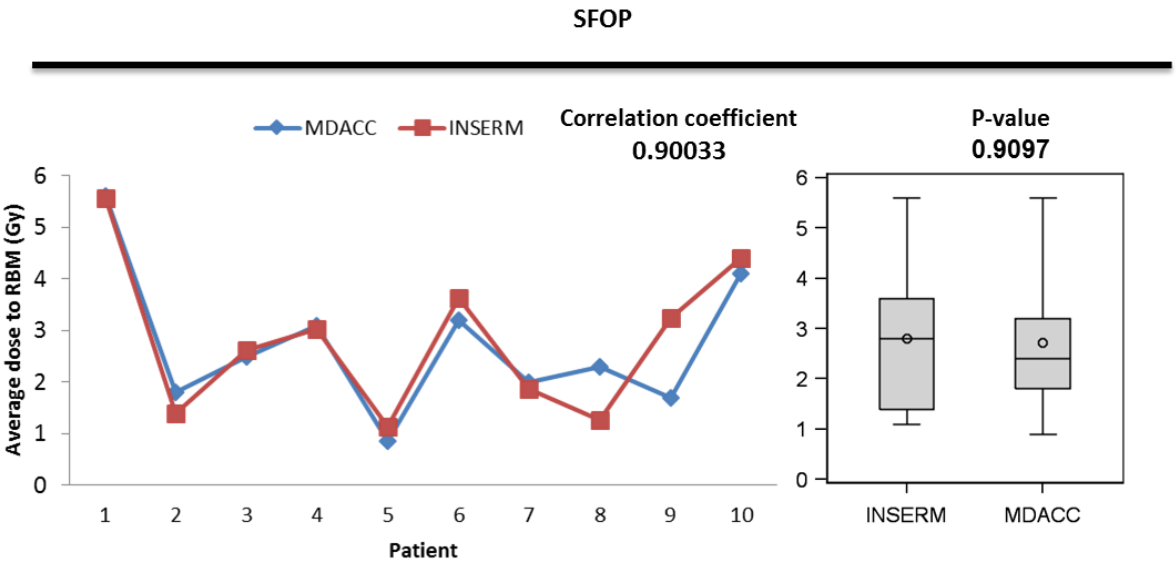


Fig. 3 Plots of individual patient average radiation dose to the whole Red Bone Marrow (RBM) for estimated by INSERM team and MDACC team for SFOP patients.

Table 4: Average doses to the whole ABM and to the 12 sub-regions estimated by INSERM team and MDACC team for SFOP patients.

Site	**INSERM**		**MDACC**	
	Mean	Min- Max	Mean	Min -Max
Whole reb bone marrow	2,8	1,1-5,6	2,7	0,9-5,6
Cranium	2,3	0-6,9	1,6	0-10,3
Mandible	2,6	0,1-10,5	2,3	0,1-8,2
Scapulae	2,4	0-9,8	4,4	0,2-20,4
Clavicles	3,7	0-12,2	5,9	0,2-20,1
Sternum	7	0,2-25,1	6,7	0,1-29,6
Sacrum	4,4	0-30,2	0,4	0-1,2
Femora UH[¥]	0,3	0-1,4	0,2	0-0,6
Femora LH[ξ]	0,1	0-0,2	0,1	0-0,2
T.F.P[ˈ]	4,4	0,1-8,7	0,1	0-0,3
Humeri UH[¥]	1,5	0-8,3	0,4	0,2-0,8
Humeri LH[ξ]	0,8	0,1-3,7	0,2	0,1-0,4
Wrist-hand	1,8	0,1-6,4	0,1	0-0,2

[¥]upper half; [ξ]lower half; [ˈ]Tibiae fibulae patellae; [ˈˈ]Ankle and foot bones; Min=Minimal; Max=maximal.

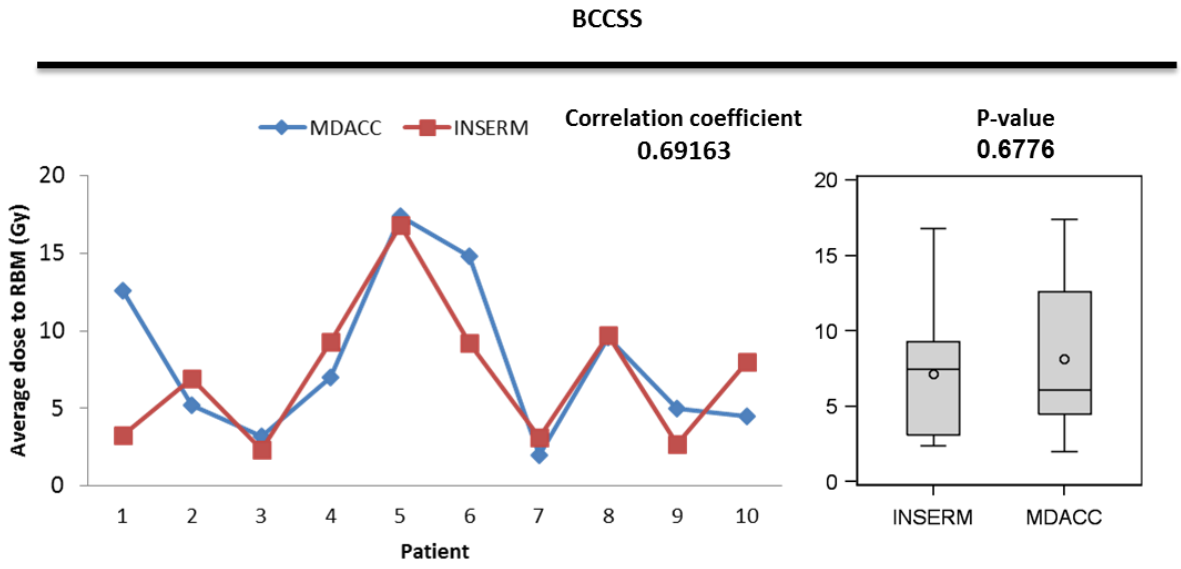


Fig. 4 Plots of individual patient average radiation dose to the whole Red Bone Marrow (RBM) for estimated by INSERM team and MDACC team for LESG patients.

Table 5: Average doses to the whole ABM and to the 12 sub-regions estimated by INSERM team and MDACC team for LESG patients.

Site	**INSERM**		**MDACC**	
	Mean	Min- Max	Mean	Min -Max
Whole reb bone marrow	7,1	2,4-16,8	8,1	2-17,4
Cranium	6	0-21,1	8,2	0-30,6
Mandible	5,6	0-25,1	7,5	0,1-21,9
Scapulae	8,4	0-27,9	7	0,1-20,5
Clavicles	8,4	0-23,2	9,8	0,1-31,4
Sternum	12,5	0,4-29,4	11,1	0,2-32
Sacrum	9,7	0,1-33,1	13,5	0-31,2
Femora UH[¥]	5,5	0,1-25,4	6,2	0-15,9
Femora LH[ξ]	2,8	0-26,3	4,1	0-30
T.F.P[ˈ]	2	0,1-5,4	1	0-9
Humeri UH[¥]	1	0-2,7	1,8	0,1-9,4
Humeri LH[ξ]	0,6	0-1,3	1,2	0,1-9,5
Wrist-hand	0,6	0,3-1	1	0-9,5

[¥]upper half; [ξ]lower half; [ˈ]Tibiae fibulae patellae; [¨]Ankle and foot bones; Min=Minimal; Max=maximal.

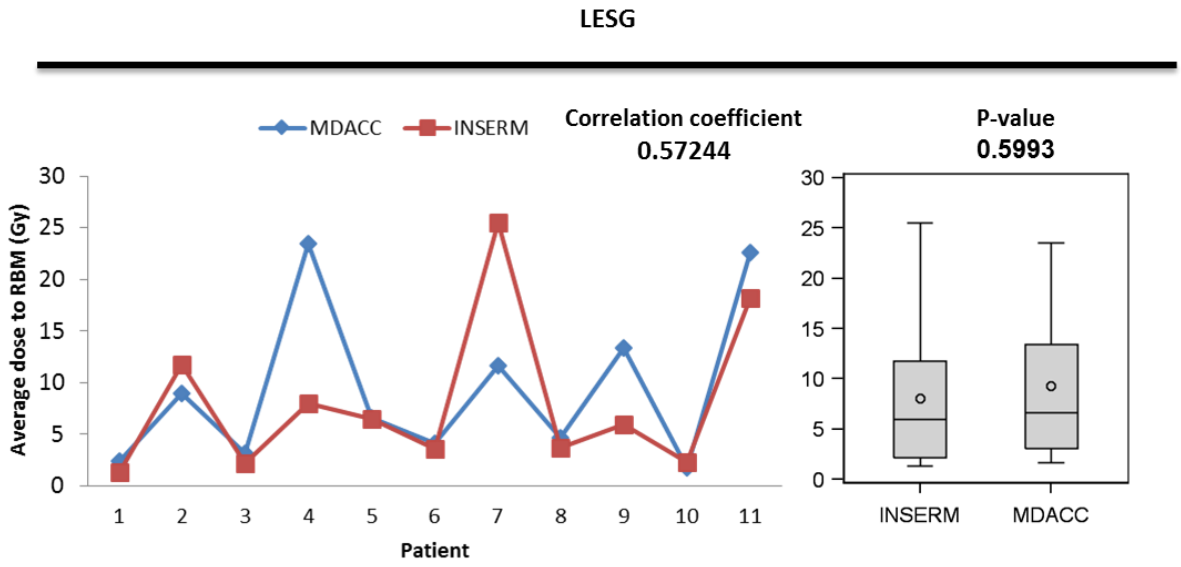


Fig. 5 Plots of individual patient average radiation dose to the whole Red Bone Marrow (RBM) for estimated by INSERM team and MDACC team for BCCSS patients.

Table 6: Average doses to the whole ABM and to the 12 sub-regions estimated by INSERM team and MDACC team for BCCSS patients.

Site	**INSERM**		**MDACC**	
	Mean	Min- Max	Mean	Min -Max
Whole reb bone marrow	8,1	1,3-25,5	9,3	1,7-23,5
Cranium	8,2	0,2-49,5	6,7	0,2-24,7
Mandible	5,5	0,2-25,2	3,7	0,4-22,5
Scapulae	5,6	0,2-19,1	6,2	0,4-20,7
Clavicles	7	0,3-20,3	8,2	0,5-36,9
Sternum	10,8	0,2-31,6	11,8	0,3-36,8
Sacrum	16,9	0-56,2	18,8	0,1-68,3
Femora UH[¥]	7,9	0-40,3	8,3	0,1-35,4
Femora LH[ξ]	1,8	0-12,4	2,1	0-15,5
T.F.P[ˈ]	2,9	0,1-7,8	4,1	0-25,6
Humeri UH[¥]	1,1	0,2-3,9	1,8	0,3-4
Humeri LH[ξ]	1	0-3,8	1,1	0,1-3,5
Wrist-hand	1,7	0,3-7,1	0,7	0-3,2

[¥]upper half; [ξ]lower half; [ˈ]Tibiae fibulae patellae; [ˈˈ]Ankle and foot bones; Min=Minimal; Max=maximal.

Overall, the doses estimated by the INSERM team and MDACC are very similar (Tables 3-6). The highest correlation coefficients have been found for FCCSS and SFOP patients, which may be explain by the fact that within these cohorts have a large majority of patients treated more recently (up to 2000). Unlike LESG patients treated until 1979. In fact, for patients treated

a long time ago, the quality and completeness of data on patient and treatment is sometimes not assured.

In conclusion, the inter-comparison results showed overall excellent coherence between the estimates, with a statistical correlation greater than 0.9. The results of this comparison will be drafted and submitted for publication in the near future..