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Economic burden of the long-term effects of treatments for childhood cancer

*Poids économique des effets à long terme des
traitements des cancers de l'enfant*

Thèse de doctorat de l'université Paris-Saclay

École doctorale n°570: Santé publique (EDSP)
Spécialité de doctorat : Économie de la santé
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Thèse préparée dans l'unité de recherche **CESP (Université Paris-Saclay, UVSQ, Inserm)**
sous la direction de **Florent DE VATHAIRE**, directeur de recherche et
la co-direction de **Nathalie PELLETIER-FLEURY**, directrice de recherche.

Thèse soutenue à Villejuif, le 12 juin 2023, par

Daniel BEJARANO QUISOBONI

Composition du Jury

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Title : Economic burden of the long-term effects of treatments for childhood cancer.

Keywords : Health care expenditures, hospitalisations, childhood cancer, survivorship, late effects, France.

Abstract : Childhood cancer survivors (CCS) may require lifelong medical care due to the late effects of cancer treatments. However, little is known about their healthcare utilization and expenditures at long-term, especially in publicly funded health care system. This thesis aimed to estimate and analyse the long-term health care expenditures and hospitalisation rates among CCS in France and to study their associated factors.

The research presented in this thesis was based on data from the French Childhood Cancer Survivors Study (FCCSS), which is a retrospective cohort of 7,670 5-year CCS diagnosed before the age of 21 years between 1946 and 2000 in France. The FCCSS is linked to the National Health Data System (SNDS), which contains comprehensive data on billing and reimbursement of the beneficiaries' health care expenditures since 2006.

We found that the annual mean healthcare expenditures among CCS was € 4,255 (SD: 18,790). Expenditures on hospitalization and pharmacy represented ~60% of total expenditures. Our results also showed that female gender and being survivor of a central nervous system (CNS) tumour were associated with increased health care expenditures.

We then estimated hospitalisation rates among CCS and detailed the hospitalisation-related clinical diagnoses compared with those of the French general population with the same gender, age and region of residence. We found that survivors were hospitalised more than twice as often as the matched reference population and they had more than three times as many in-patient bed-days. Our results showed that the highest risk for hospitalisation in CCS was related to neoplasm, followed by endocrine diseases, blood diseases, and diseases of the circulatory system. Finally, we compared the health care expenditures of the FCCSS with that of the general French population mentioned above and found that the annual mean excess healthcare expenditures for CCS compared with the median of the reference population was € 3,920 (95% CI: 3539 - 4301). A higher excess was significantly associated with having been treated before the 1990s and having survived a CNS tumour, whereas a lower excess was associated with not receiving treatment with radiotherapy.

In conclusion, this thesis showed that CCS are at higher risk of health care use and expenditure, leading to considerable excess compared with the median health care expenditure of the general population of the same sex and age. This high expenditure was related to high hospitalisation rates among CCS. Older survivors, CNS tumours survivors, and those treated with radiotherapy had a higher risk of health service use and expenditure. These results led us to recommend that special attention be paid to this population, especially in terms of follow-up and prevention of complications, and to support the development of effective innovative treatments.

Titre : Poids économique des effets à long terme des traitements des cancers de l'enfant.

Mots clés : Dépenses de santé, hospitalisations, cancer de l'enfant, survie, effets tardifs, France.

Résumé : Les survivants du cancer de l'enfant (CCS) peuvent avoir besoin de soins médicaux à vie en raison des effets tardifs des traitements anticancéreux. Cependant, on sait peu de choses sur leur utilisation des soins de santé et leurs dépenses à long terme, en particulier dans les systèmes de soins de santé financés par l'État. Ce projet de thèse avait pour objectif d'estimer et d'analyser les dépenses de santé et les taux d'hospitalisation à long terme des personnes atteintes d'un cancer dans l'enfance en France et d'étudier les facteurs associés.

La recherche présentée dans cette thèse est basée sur les données de la French Childhood Cancer Survivors Study (FCCSS) qui est une cohorte rétrospective de 7,670 CCS à cinq ans diagnostiqués avant l'âge de 21 ans entre 1946 et 2000 en France. L'étude FCCSS est liée aux données du Système National des Données de Santé (SNDS), qui contient des données complètes sur la facturation et le remboursement des dépenses de santé des bénéficiaires depuis 2006.

Nous avons constaté que le montant moyen annuel des dépenses de santé parmi les CCS était de 4 255 € (ét: 18 790). Les dépenses liées aux hospitalisations et à la pharmacie représentaient environ 60 % des dépenses totales. Nos résultats ont également montré que le sexe féminin et être survivant de tumeur du système nerveux central (SNC) étaient associés à des dépenses de santé plus élevées.

Lorsque nous avons estimé les taux d'hospitalisation parmi les CCS et détaillé les diagnostics cliniques liés à l'hospitalisation par rapport à ceux de la population générale française avec le même sexe, âge et région de résidence, nous avons constaté que les survivants étaient hospitalisés plus de deux fois plus souvent que la population de référence appariée et qu'ils avaient plus de trois fois plus de jours d'hospitalisation. Nos résultats ont montré que le risque plus élevé d'hospitalisation des CCS concernait les hospitalisations liées à des néoplasmes, suivies par les maladies endocriniennes, les maladies du sang et les maladies de l'appareil circulatoire. Enfin, nous avons comparé les dépenses de santé de la FCCSS à celles de la population française générale mentionnée ci-dessus et nous avons constaté que l'excédent annuel moyen des dépenses de santé pour les CCS par rapport à la médiane de la population de référence était de 3 920 € (IC à 95 % : 3 539 - 430). Un excès plus élevé était significativement associé au fait d'avoir été traité avant les années 1990 et d'avoir survécu à une tumeur du SNC, alors qu'un excès plus faible était associé au fait de n'avoir pas reçu de traitement par radiothérapie.

En conclusion, cette thèse a démontré que les CCS présentent un risque plus élevé d'utilisation de soins et de dépenses de santé, conduisant à un excès considérable par rapport à la médiane des dépenses de santé de la population générale du même sexe et du même âge. Ces dépenses élevées étaient liées à des taux d'hospitalisation élevés parmi les CCS. Les survivants plus âgés, ceux ayant eu une tumeur du SNC et les patients traités par radiothérapie présentaient un risque plus élevé d'utilisation des services de santé et de dépenses. Ces résultats nous amènent à recommander qu'une attention particulière soit accordée à cette population, notamment en termes de suivi et de prévention des complications, et de soutenir le développement de traitements innovants et efficaces.

*A mis padres,
Jair y María Eugenia,
por vuestro amor y por vuestras enseñanzas para enfrentar la vida.*

RESUME SUBSTANTIEL

Titre : Poids économique des effets à long terme des traitements des cancers de l'enfant.

Mots clés : Dépenses de santé, hospitalisations, cancer de l'enfant, survie, effets tardifs, France.

La survie des enfants atteints de cancer s'est nettement améliorée ces dernières décennies grâce aux progrès réalisés dans le traitement. Plus de 80% des patients atteints de cancer pédiatrique atteignent une survie de 5 ans dans la plupart des pays à revenu élevé. Cette amélioration de la survie signifie qu'une personne sur 1000 dans la population générale est un survivant du cancer de l'enfant (CCS). En Europe, on estime qu'il y a entre 300 000 et 500 000 CCS, et il est prévu que cette population continue de croître, étant donné que l'incidence du cancer pédiatrique a légèrement augmenté ces dernières décennies.

Cependant, les CCS présentent un risque important de souffrir de séquelles tardives induites par la maladie et le traitement du cancer, qui peuvent affecter, dans des degrés variables, presque n'importe quel organe ou système corporel. Les séquelles tardives somatiques et mentales comprennent les seconds néoplasmes, les maladies cardiovasculaires, l'infertilité, les problèmes de croissance, la dépression, les déficits d'apprentissage, et bien d'autres. De plus, les conséquences économiques et sociales à l'âge adulte peuvent être potentiellement importantes et varient d'un pays à l'autre. Les CCS peuvent être exposés à un risque de niveau d'éducation inférieur et sont plus susceptibles d'être incapables de travailler ou de manquer des jours de travail en raison de problèmes de santé. Toutes ces conséquences augmentent l'utilisation des prestations de sécurité sociale, telles que le chômage, congé de maladie ou pension d'invalidité.

Le fardeau plus élevé de morbidité et les résultats socio-économiques défavorables pour les CCS à long terme sont probablement associés à des coûts plus élevés pour le système de santé. Cependant, il existe un manque d'études sur les effets économiques à long terme des CCS dans le système de santé financé par des fonds publics. L'objectif principal de cette thèse est de quantifier la charge économique globale des séquelles à long terme des traitements du cancer pédiatrique en France et de l'analyser en fonction du type de cancer, des traitements reçus et d'autres facteurs cliniques et socio-économiques.

Pour atteindre nos objectifs, nous avons utilisé des données de l'étude French Childhood Cancer Survivor Study (FCCSS) en conjonction avec le Système national des données de santé (SNDS). Le FCCSS est une cohorte rétrospective de 7 670 CCS diagnostiqués pour un cancer solide ou un lymphome, avant l'âge de 21 ans entre 1946 et 2000, dans cinq centres de lutte contre le cancer en France. Cette cohorte a été suivie prospectivement jusqu'à ce jour en utilisant plusieurs sources, notamment les dossiers médicaux, les questionnaires auto-déclarés, les consultations de suivi à long terme et les données du SNDS.

Le SNDS rassemble les principales bases de données relatives aux soins de santé en France, contenant tous les remboursements effectués par le régime d'assurance maladie, qui couvre plus de 95 % de la population. Les données sont disponibles à partir du 1er janvier 2006, mais tous les systèmes d'information ne sont pas disponibles à cette date et ont été ajoutés au fil du temps. La liaison et l'accès entre les données du SNDS de la cohorte FCCSS ont été assurés par la Caisse nationale de l'Assurance Maladie (CNAM).

Dans notre première étude, nous quantifions et décrivons les dépenses de soins de santé chez les CCS à très long terme en France. Ensuite, nous comparons le niveau des dépenses entre les survivants de la cohorte FCCSS et ceux d'autres contextes inclus dans les registres français existants sur le cancer pendant la période de recrutement de la cohorte FCCSS.

Nous avons utilisé des données provenant de deux sources, la FCCSS et le Réseau français des registres des cancers (FRANCIM). Le FRANCIM comprend tous les registres de cancer basés sur la population en France. La population couverte par la base de données FRANCIM représente 22 % de l'ensemble de la population française.

À partir des deux bases de données, nous avons sélectionné tous les CCS solides diagnostiqués sur une période de 5 ans avant janvier 2001, qui étaient en vie en janvier 2011 et qui étaient liés au SNDS. Nous avons réalisé cette étude du point de vue de la CNAM (payeur). Nous avons estimé les dépenses en tenant compte de tous les remboursements effectués par la CNAM dans le cadre du régime obligatoire de remboursement entre janvier 2011 et décembre 2016 ou la date du décès. Notre principal critère de jugement était le total des dépenses directes de soins de santé pour chaque année civile et pour chaque patient dans les deux cohortes. Des modèles linéaires généralisés ont été utilisés pour déterminer les associations entre les dépenses de soins de santé et les caractéristiques des survivants.

Un total de 5 319 CCS ont été inclus dans l'étude, dont 67,5 % appartenaient à la FCCSS. Près de la moitié des patients étaient des femmes et ont été diagnostiqués après 1990, et plus de 50 % des patients avaient plus de 30 ans au début du suivi. Le cancer primaire le plus courant était le lymphome (20,1 %), suivi des tumeurs du système nerveux central (SNC) (14,2 %). La moyenne annuelle et la médiane des dépenses de soins de santé pour les survivants étaient de 4 255 € (SD : 18 790) et de 494 € (IQR : 105-2151). Le principal poste de dépenses était les hospitalisations, représentant 45 % des dépenses totales et vécu par 65 % des survivants pendant la période de l'étude. La pharmacie était également un poste de dépenses important, représentant 16 % des dépenses totales de soins de santé avec une moyenne annuelle de 676 € par patient. Dans notre analyse multivariée, nous avons constaté que les dépenses totales de soins de santé augmentaient avec l'âge ($\beta = 0,04$, $p < 0,0001$), étaient plus élevées chez les femmes ($\beta = 0,30$, $p < 0,0001$), chez les patients atteints de tumeurs du SNC ($\beta = 0,70$, comparé au neuroblastome, $p < 0,0001$), et chez les survivants décédés entre 2011 et 2016 ($\beta = 1,85$, $p < 0,0001$). Les dépenses annuelles de soins de santé des survivants de la FCCSS n'étaient pas significativement plus élevées que celles des survivants de la FRANCIM ($\beta = 0,12$, $p = 0,23$). Ces résultats n'ont pas varié lorsque la variable "décès" a été exclue du modèle ou lorsque les survivants décédés ont été exclus de la population étudiée.

Étant donné que la majeure partie des dépenses totales de santé est due aux hospitalisations, nous jugeons nécessaire d'approfondir cette question. Ainsi, notre deuxième étude a pour objectif d'estimer les taux d'hospitalisation chez les enfants et adolescents traités pour un cancer en France, par rapport à ceux de la population générale française. Nous avons également décrit les diagnostics cliniques liés aux hospitalisations et étudié les facteurs liés au cancer associés à une augmentation du taux d'hospitalisation.

Pour étudier les dossiers d'hospitalisation de la FCCSS, nous avons sélectionné les survivants en vie en janvier 2006, résidant en France métropolitaine et ayant été reliés au SNDS. Nous avons obtenu un échantillon de référence pour les survivants de la FCCSS à partir de l'Échantillon généraliste des bénéficiaires (EGB), un échantillon aléatoire de la population incluse dans le SNDS, représentatif de la population générale française. Nous avons sélectionné l'échantillon de référence en appariant le sexe, l'année de naissance et la région (zone administrative française) de résidence, puis nous les avons assignés aléatoirement à chaque survivant de la FCCSS présentant les mêmes caractéristiques.

En utilisant le PMSI, nous avons obtenu les dossiers d'hospitalisation dans les unités hospitalières conventionnelles de janvier 2006 à décembre 2018 ou jusqu'au décès, pour chaque

enfant ou adolescent traité pour un cancer et pour chaque individu de la population de référence. Nos critères d'intérêt étaient (1) le nombre total d'hospitalisations et (2) le nombre total de jours passés à l'hôpital. Nous avons calculé les taux d'hospitalisation et de jours d'hospitalisation pour la FCCSS et la population de référence, exprimés en taux pour 1 000 personnes-années (PY). Pour comparer les taux d'hospitalisation des survivants du cancer chez les FCCSS à la population de référence, nous avons calculé : (1) le risque absolu excédentaire (AER) et (2) les taux d'hospitalisation relatifs (RHR) ainsi que les ratios relatifs des jours-lits (RBDR) avec leurs intervalles de confiance à 95 % correspondants. Enfin, nous avons utilisé un modèle linéaire généralisé pour étudier l'association entre le nombre d'hospitalisations et de jours-lits et les caractéristiques des survivants.

Nous avons inclus un total de 5 439 survivants du cancer chez les FCCSS et 386 073 personnes de référence dans l'étude. Chaque survivant du cancer a été associé à une moyenne de 71 (73,9) « témoins » uniques. Entre le 1er janvier 2006 et le 31 décembre 2018, 3 756 survivants du cancer (69 %) et 208 217 personnes de référence (54 %) ont été hospitalisés au moins une fois. Nous avons identifié 27 598 hospitalisations chez les survivants du cancer, ce qui représente 74 814 jours-lits en hospitalisation complète. Pour les survivants du cancer, l'AER était de 239,9 pour 1 000 PY pour les hospitalisations et de 773,2 pour 1 000 PY pour les jours-lits en hospitalisation complète. Le RHR était de 2,49 (intervalle de confiance à 95 % de 2,46 à 2,52, $p < 0,001$), ce qui signifie que les survivants du cancer étaient hospitalisés plus de deux fois plus souvent que la population de référence appariée. De plus, ils avaient plus de trois fois plus de jours-lits en hospitalisation complète que la population de référence (RBDR 3,49, intervalle de confiance à 95 % de 3,46 à 3,51, $p < 0,001$). Les AER les plus élevés ont été observés dans les hospitalisations liées aux néoplasmes (105,8), suivies des maladies du système génito-urinaire (34,4), des facteurs influençant l'état de santé et du contact avec les services de santé (autres facteurs ; 26,6) et des maladies du système circulatoire (19,2). Dans les analyses ajustées, les résultats montrent que les femmes présentaient un risque d'hospitalisation inférieur à celui des hommes. Cependant, les femmes présentaient un risque plus élevé d'admissions hospitalières sur une base quotidienne. En revanche, le risque d'hospitalisation augmentait chez les survivants d'une tumeur du SNC et chez les survivants d'une tumeur du rein par rapport au neuroblastome.

Après avoir observé cette surconsommation en termes d'admissions hospitalières par rapport à la population générale, les objectifs de notre dernière étude sont d'estimer les dépenses de soins de santé excessives pour les survivants du cancer chez les FCCSS en France par rapport à la

population générale, avec le même sexe, le même âge et la même région de résidence, et d'étudier les facteurs associés à cet excès.

Selon les informations de remboursement, nous avons ajouté les dépenses directes de soins de santé pour chaque année civile et pour chaque survivant et contrôle entre janvier 2011 et décembre 2018, ou la date du décès, selon la première échéance. Nous avons ensuite estimé l'excès de dépenses annuelles de soins de santé en tant que différence entre les dépenses pour les survivants de CCS et la dépense médiane pour leurs contrôles. Notre principale variable de résultat était l'excès total des dépenses directes de soins de santé pour chaque année civile pour chaque survivant de CCS. Nous avons utilisé des modèles linéaires mixtes pour évaluer l'association entre l'excès de dépenses de soins de santé et les caractéristiques des survivants. Étant donné que nous avons calculé l'excès de dépenses pour chaque survivant avec un nombre différent de contrôles, nous avons pondéré les modèles en fonction du nombre de contrôles utilisés pour chaque survivant chaque année.

Nous avons inclus un total de 5 353 survivants de FCCSS et 382 757 contrôles dans l'étude. La dépense annuelle moyenne en excès de soins de santé était de 3 920 € (IC à 95 % : 3 539 € - 4 301 €). Sur l'ensemble de la cohorte, la dépense la plus élevée était liée à l'hospitalisation (1 552 €), représentant 39,6 % de l'excès total, suivie de la pharmacie (668 €) avec 17 %. La pharmacie était le poste le plus important parmi les survivants de tumeurs thyroïdiennes (1 346 €), représentant 35,7 % de leur excès annuel total. La pharmacie était également un poste important pour les survivants de tumeurs rénales (1 408 €) et de tumeurs gonadiques (1 037 €), représentant respectivement 29,6 % et 26,4 % de l'excès annuel total.

Dans l'analyse ajustée, la dépense annuelle moyenne en excès de soins de santé était plus élevée chez les survivants traités dans les années 1980 (2 306 € ; $p \leq 0,01$), les années 1970 (3 848 € ; $p \leq 0,01$) et avant les années 1970 (4 389 € ; $p \leq 0,05$) par rapport aux survivants traités après les années 1990. Les survivants de tumeurs du SNC avaient également une dépense annuelle plus élevée par rapport aux survivants d'autres types de cancers primaires. L'excès annuel total n'était pas significativement plus élevé chez les femmes par rapport aux hommes survivants (231 € ; $p = 0,48$). En ce qui concerne le traitement, les survivants n'ayant pas été traités par radiothérapie ou chimiothérapie (1 910 € ; $p < 0,01$) et les survivants traités uniquement par chimiothérapie (1 464 € ; $p < 0,05$) présentaient un excès de dépense moyenne annuelle en soins de santé significativement inférieure à celle des personnes traitées uniquement par radiothérapie.

Les conclusions de cette thèse fournissent des preuves d'un risque accru d'utilisation des soins de santé et de dépenses chez les survivants de cancer chez les enfants et les adolescents, entraînant des dépenses considérables par rapport aux dépenses médianes de soins de santé de la population générale du même sexe et du même âge. Ces dépenses élevées sont liées à la multimorbidité, qui est plus fréquente chez les survivants que dans la population générale. Par conséquent, nos résultats nous amènent à recommander une attention particulière à cette population, notamment en termes de suivi et de prévention des complications. Réduire les effets tardifs du traitement du cancer chez les survivants est essentiel pour réduire les dépenses de santé. Cela nécessite un plan de suivi coordonné fournissant les soins complets et spécialisés dont ils ont besoin, ainsi que des stratégies d'intervention précoce aux âges clés de transition pour surmonter les éventuels effets tardifs et améliorer la santé et la qualité de vie des survivants à l'âge adulte.

De plus, il est nécessaire d'identifier les survivants présentant un risque élevé de dépenses de santé élevées afin de mettre en place des interventions. Nos résultats suggèrent qu'une attention particulière soit portée aux survivants traités : 1) avant les années 1980, 2) pour une tumeur du SNC et 3) par radiothérapie. Les survivants plus âgés, ou ceux ayant un intervalle plus long depuis la fin du traitement, ont été identifiés comme des prédicteurs de non-fréquentation des soins de suivi. Des efforts sont nécessaires pour aider ces survivants à accéder à ces soins spécialisés. En ce qui concerne les tumeurs du SNC, les médecins, les survivants et leurs familles doivent être conscients des effets tardifs physiques et socio-économiques afin de faciliter la détection précoce des problèmes de santé et d'obtenir le soutien social nécessaire. Enfin, nos résultats suggèrent qu'un levier d'action est le type de traitement administré, en particulier la radiothérapie, bien que les survivants examinés dans cette thèse aient été traités il y a des décennies et que les traitements aient évolué au fil du temps. Les radiothérapeutes doivent prendre en compte le coût des effets à long terme de la radiothérapie dans leurs paramètres et plans de traitement afin de réduire les doses cumulatives et la toxicité.

L'utilisation à long terme des soins de santé et les coûts liés au cancer chez l'enfant restent peu étudiés, en particulier dans les systèmes de santé financés par des fonds publics. Comprendre cela apparaît essentiel pour développer des stratégies qui servent mieux les survivants de cancer chez les enfants et les adolescents et potentiellement réduire les coûts de traitement de cette population. Par conséquent, une analyse prospective minutieuse et des rapports de tous les coûts et modèles d'utilisation depuis le diagnostic du cancer chez l'enfant jusqu'à la fin de vie dans différentes cohortes aux niveaux national et international sont nécessaires.

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TABLE OF CONTENTS

Chapter I Introduction	1
I.1 Epidemiology of childhood cancer	1
I.1.1 Incidence.....	1
I.1.2 Survivorship.....	2
I.2 Treatment of childhood cancer.....	4
I.2.1 Radiotherapy.....	5
I.2.2 Chemotherapy.....	6
I.2.3 Surgery.....	7
I.3 Late effects of childhood cancer treatments.....	7
I.4 Socioeconomic difficulties in childhood cancer survivors	11
I.5 Financial hardship among childhood cancer survivors	12
I.6 Research hypotheses and objectives	14
Chapter II Data sources	15
II.1 The French Childhood Cancer Survivor Study (FCCSS).....	15
II.1.1 Overview	15
II.1.2 Data collection and follow-up	17
II.2 The National Health Data System (SNDS).....	17
II.2.1 National Inter-Scheme Health Insurance Information System (SNIIRAM).....	19
II.2.2 National Hospital Discharge Database (PMSI).....	21
II.2.3 Register of causes of death (CepiDC).....	22
II.2.4 The General Sample of Beneficiaries (EGB).....	22
II.3 FCCSS linkage to the SNDS.....	23
II.3.1 Linkage until 2016	24
II.3.2 Linkage until 2018	25
Chapter III Health care expenditures among long-term survivors of paediatric solid tumours	28
III.1 Introduction	28
III.2 Materials and methods.....	28
III.2.1 Study population	28
III.2.2 Primary measures.....	29

III.2.3 Covariates	30
III.2.4 Statistical analysis	30
III.3 Results	31
III.3.1 Survivor characteristics and total health care expenditures	31
III.3.2 Health care expenditures	33
III.3.3 Health care expenditures by the type of primary cancer.....	33
III.3.4 Multivariate analysis of survivor characteristics associated with health care expenditures	36
III.4 Discussion.....	39
Chapter IV Long-term hospitalisations in survivors of paediatric solid tumours	42
IV.1 Introduction	42
IV.2 Materials and methods.....	42
IV.2.1 Study population.....	42
IV.2.2 Reference sample.....	42
IV.2.3 Hospitalisation measures	43
IV.2.4 Statistical analysis.....	43
IV.3 Results	44
IV.3.1 Total numbers of hospitalisations and bed-days.....	44
IV.3.2 Hospitalisations and bed-days by the main diagnostic groups	45
IV.3.3 Association between survivor characteristics and hospitalisations and bed days .	51
IV.3.4 Association between initial treatments and hospitalisations and bed days.....	53
IV.4 Discussion	55
Chapter V Excess health care expenditures in survivors of paediatric solid tumours	59
V.1 Introduction.....	59
V.2 Materials and methods	59
V.2.1 Study population	59
V.2.2 Estimating excess healthcare expenditure.....	60
V.2.3 Statistical analysis	60
V.3 Results.....	60
V.3.1 Survivor characteristics.....	60
V.3.2 Excess healthcare expenditures.....	61
V.3.3 Excess healthcare expenditures by type of primary cancer	64

V.3.4 Factors associated with excess healthcare expenditures	64
V.4 Discussion.....	67
Chapter VI General conclusion	70
VI.1 Main findings	70
VI.2 Clinical implications.....	73
VI.3 Perspectives for future research	74
Appendices	76
Appendix 1 Late effects.....	76
A.1.1 Selected examples of treatment-specific adverse outcomes.	76
Appendix 2 Supplementary results for Chapter III	79
A.2.1 Population characteristics	79
A.2.2 Health care expenditures.....	81
A.2.3 Multivariate analysis	84
Appendix 3 Supplementary results for Chapter IV	89
A.3.1 Flowchart	89
A.3.2 Hospital admission diagnosis.....	90
A.3.3 Relative hospitalisation and bed-days ratios	95
A.3.4 Multivariate analysis	99
A.3.5 Discussion	107
Appendix 4 Supplementary results for Chapter V.....	109
A.4.1 Excess healthcare expenditure	109
A.4.2 Multivariate analysis	111
References	114
PUBLICATIONS DURING THE THESIS	126

LIST OF TABLES

Table 1. Overview of selected late effects observed in young adult survivors of childhood cancer.	10
Table 2. Characteristics of the survivors included in the FCCSS cohort.	16
Table 3. Information available or not available in the SNIIRAM database in as of 2016.	20
Table 4. Characteristics of the FCCSS survivors by linkage to the SNDS data until 2016.	25
Table 5. Characteristics of the FCCSS survivors by linkage to the SNDS data until 2018.	26
Table 6. Survivor characteristics and health care expenditures.	32
Table 7. Health care expenditures by item.	34
Table 8. Annual mean health care expenditure (%) by item and the type of primary cancer. .	35
Table 9. Multivariate analysis*.	36
Table 10. Survivor characteristics and hospitalisation and bed-day rates.	46
Table 11. Hospitalisations and bed days in the FCCSS survivors and the reference sample by the main ICD-10 groups.	50
Table 12. Multivariate analysis of the total number of hospitalisations and bed days.	54
Table 13. Survivor characteristics and excess health care expenditures.	62
Table 14. Excess health care expenditures by item.	63
Table 15. Multivariate analysis: predictors of annual excess health care expenditures.	66

LIST OF FIGURES

Figure 1. Proportional distribution of cancer type by age group, 2001–2010.	1
Figure 2. Five-year actuarial cumulative survival, by European region and period of diagnosis.	3
Figure 3. Age-adjusted 5-year observed survival for all childhood cancers combined for the follow-up periods of 2004–2006, 2007–2009, and 2010–2014, in Europe.....	4
Figure 4. Range of health-related and quality-of-life outcomes among long-term survivors of childhood and adolescent cancers.	8
Figure 5. Factors contributing to the costs of childhood cancer care.....	13
Figure 6. The SNIIRAM and its construction stages before the SNDS (in French).	18
Figure 7. Data feed of the entire SNDS (in French).....	23
Figure 8. Adjusted* annual mean health care expenditures by the type of primary cancer.....	38
Figure 9. The absolute excess risk of hospitalisation and bed day according to the International Classification of Diseases (ICD-10).....	48
Figure 10. The relative hospitalisation and bed day ratios according to the International Classification of Diseases (ICD-10).....	49
Figure 11. The relative hospitalisation and bed-day ratios by type of primary cancer.	52
Figure 12. Distribution of excess health care expenditure by item and the type of primary cancer*.	65

LIST OF ABBREVIATIONS

AER: Absolute excess risk

ALD: Long-term conditions

AML: Acute myeloid leukaemia

ASR: Age-standardised rates

ATIH: Technical agency for information on hospitalisations

CCS: Childhood cancer survivors

CepiDC: Centre for Epidemiology on Medical Causes of Death

CI: Confidence interval

CLCC: Centres for the Fight Against Cancer

CNAM: National Health Insurance Fund

CNAMTS: National Health Insurance Fund for Salaried Workers

CNAVTS: National Insurance Contributions Office

CNIL: National Data Protection Authority

CNS: Central nervous system

DCIR: Outpatient Health Care Consumption Database

EGB: General Sample of Beneficiaries

FCCSS: French Childhood Cancer Survivor Study

FRANCIM: French Network of Cancer Registries

GLM: generalised linear model

HAD: Homecare units

ICCC: International Classification of Childhood Cancer

ICD-10: International Classification of Diseases, 10th revision

INSEE: National Institute for Statistics and Economic Studies

INSERM: French National Institute of Health and Medical Research

IMRT: Intensity-modulated radiotherapy

IQR: Interquartile range

LTFU: Long-term follow-up

MCO: Conventional hospital units

MSA: Agricultural Social Mutual Organisation

NIR: Social security number

NCI: National Cancer Institute

OR: Odds ratio

PMSI: National Hospital Discharge Database

PSY: Psychiatric institutions

PY: Person-years

RBDR: Relative bed-day ratio

RHR: Relative hospitalisation rate

RNCE: National Registry of Childhood Cancers

RR: Risk ratio

RSI: Regime for the self-employed

SD: Standard deviation

SNDS: National Health Data System

SNIRAM: National Inter-Scheme Health Insurance Information System

SSR: Rehabilitation units

Chapter I Introduction

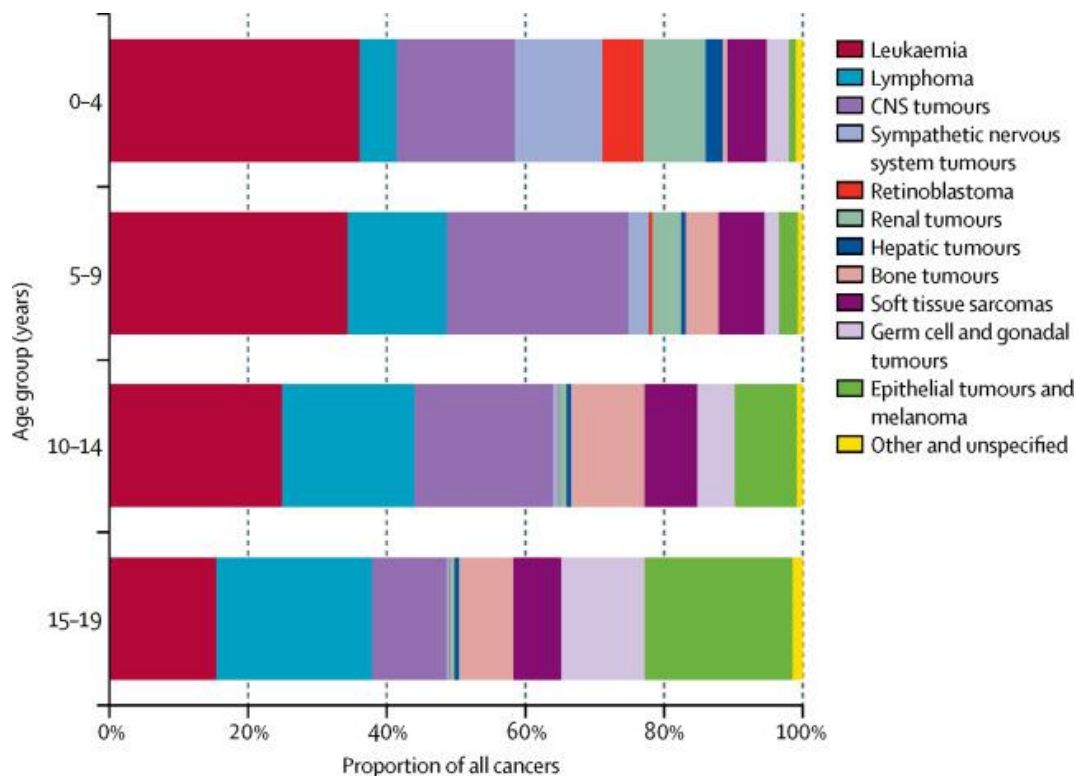
In this introduction chapter, we first describe the epidemiology and survival of childhood cancers, globally and in France. Second, we show the evolution of childhood cancer treatments in the last decades. We then detail the current state of knowledge on the long-term effects of treatment and, finally, we present the hypothesis and objectives of the thesis.

I.1 Epidemiology of childhood cancer

I.1.1 Incidence

Childhood cancer is rare, but it is a major cause of death in children worldwide. It is estimated that 360,114 total childhood cancer cases occurred worldwide in 2015 (1). The overall age-standardised rates (ASR), a measure that account for the differences in the age distribution of the populations being compared, were 140.6 per million person-years (PY) in children aged 0–14 years and 155.8 per million PY in those aged 0–19 years (2). The most common cancers were leukaemia (ASR 46.4), followed by central nervous system (CNS) tumours (ASR 28.2) and lymphomas (ASR 15.2) (Figure 1).

Figure 1. Proportional distribution of cancer type by age group, 2001–2010.



Reprinted from Steliarova-Foucher E et al. 2017 (2).

In France, cancer is the second most important cause of death for children aged less than 15 years (3). According to the general and specialised cancer registries (*Registres des cancers généraux et Registres des cancers spécialisés*), the ASRs per million children were 137.5 for all cancers combined, 42.3 for leukaemia, 29.1 for CNS tumours and 15.6 for lymphomas over the period of 1990–1999 (3). Since 2000, the National Registry of Childhood Cancers (*Registre National des Cancers de l'Enfant*, French acronym: RNCE) reported an ASR of 156.6 cases per million children per year, with the same distribution of the primary cancer types (<https://rnce.inserm.fr>) (4).

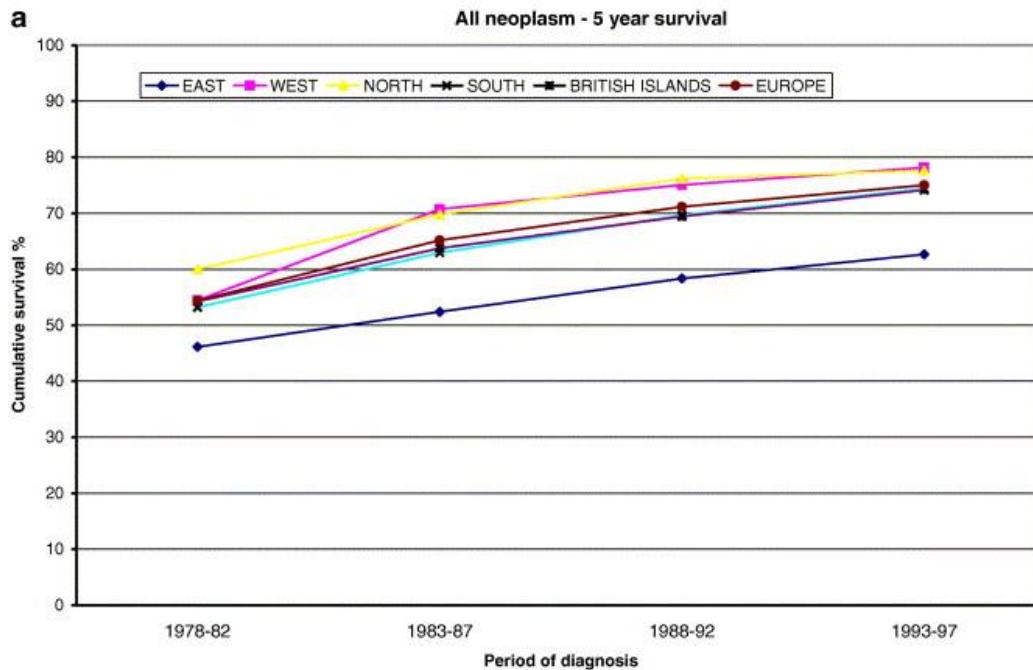
For the years 1991–2010, an significant increase in cancer incidence in children and adolescents of 0.54% (95% confidence interval (CI) 0.44–0.65) per year on average, has been observed in Europe (5). One study from Switzerland showed that incidence of childhood cancer increased by 0.7% (95% CI 0.4%–1.0%) per year for all cancers for the years 1985–2014 (6). For leukaemia's over the same period the incidence increase was 0.8% (95% CI 0.2%–1.4%), and 3.0% (95% CI 0.2%–1.4%) for CNS tumours during 1985–2002 (6). Although improvements in diagnosis and increased registration of cancers over time may partly explain the observed increase in incidence (6), childhood cancer incidence trends require continued monitoring at national and international levels (5).

I.1.2 Survivorship

Childhood cancer survivorship has improved considerably in the last few decades. Before 1950, some childhood cancers, especially leukaemia, were considered deadly because they were incurable (7). The 5-year survival rates from all malignant neoplasms increased from 23% in 1943–1952 to 33% in 1963–1972 (8). During the subsequent years, overall 5-year survival increased substantially in Europe, from 54% in 1978–1982 to 75% in 1993–1997 (9) (Figure 2).

After 2000, 5-year survival rose from 76.1% for 1999–2001 to almost 80% for 2005–2007 (10), which is similar to the current rate. However, inequalities persist among European countries, with 5-year survival ranging from 71% to 87% in 2010–2014 (11). In France, survival has remained high after 2000 with an increase from 79.5% in 2000–2002 to 83.2% in 2006–2008 (12), and up to 87.7% in childhood head and neck cancers in 2008–2015 (13).

Figure 2. Five-year actuarial cumulative survival, by European region and period of diagnosis.

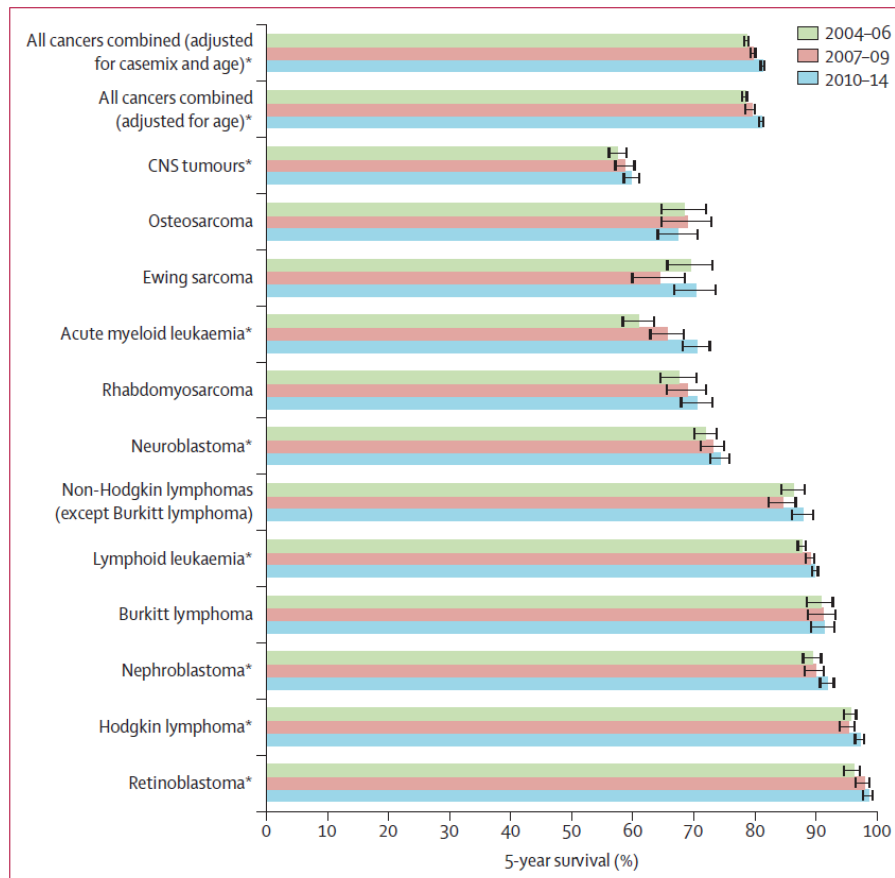


Reprinted from Magnani C et al. 2006 (9).

Despite overall progress, survival varies widely in Europe by the type of childhood cancer, regardless of the country's wealth and the health care system. The cure rate ranges from 60% for CNS tumours to 99% for retinoblastoma (Figure 3) (11). Between 2000 and 2008 in France, the cancers with a 5-year survival of < 65% were acute myeloid leukaemia (AML), CNS tumours and liver carcinoma, while retinoblastoma, Hodgkin's disease, nephroblastoma, thyroid carcinoma and gonadal germ cell tumours had a 5-year survival of > 90% (12).

Other factors for childhood cancer survivorship can include gender and age at diagnosis as well as disease subtype, site, histology, grade, stage, and other clinical or socioeconomic factors (14). Infants (< 1 year) and older children (>10 years) tend to have a lower survival (10–12,15). Additionally, there is increasing evidence that a low socioeconomic status like a lower parental education, single parents or children with siblings are associated with worse survival in high-income European countries (16–19) where access to health care is available to all inhabitants. The underlying mechanisms involved are not clear and more studies are needed (20).

Figure 3. Age-adjusted 5-year observed survival for all childhood cancers combined for the follow-up periods of 2004–2006, 2007–2009, and 2010–2014, in Europe.



Reprinted from Botta L et al. 2022 (11).

I.2 Treatment of childhood cancer

The overall improvement in childhood cancer survival is without a doubt due to advances in cancer treatment. Although surgery, chemotherapy and radiotherapy are currently the most common types of cancer treatments, their history has been characterised by ups and downs, due to the effectiveness of treatments as well as the side effects (21).

Before the 1960s, surgery and radiotherapy dominated the field of cancer therapy; however, cure rates had stagnated at around 33%, despite increasingly radical treatments, due to the presence of previously unappreciated micro-metastases (22), loco-regional involvement and resistance to radiotherapy. Then, a significant change in treatment occurred when the first children with leukaemia were cured with chemotherapy (23). After that, many different anticancer drugs were tested as single agents, but all patients died (7). In 1958, the National Cancer Institute (NCI) conducted the first anticancer drug combination trials for the treatment of childhood leukaemia

after promising results (7,24). That effort continued, with the study on the use of poly-chemotherapy and adjuvant chemotherapy after radiotherapy or surgery in patients with advanced cancer (21,25). Today, combined modality treatment has become standard clinical practice, tailoring each of the three modalities to maximise their antineoplastic effects with minimal toxicity to normal tissues (22).

I.2.1 Radiotherapy

Radiotherapy originated from the discovery of X-rays by the German physicist Wilhelm C. Röntgen in 1895 and its first clinical use the following year (26). That first era for radiation oncology was one of curiosity, experimentation and empiricism (27). In the following years, X-ray radiation was introduced for the treatment of some inoperable cancers and physicians reported cases of control or regression of cancers due to radiation exposure (27–29). In 1902, the first causal relationship between X-rays and cancer was observed when a radiation-induced carcinoma was reported in the hand of an X-ray technician (29), leading to the discovery that radiation could cause cancer as well as cure it.

Initial radiotherapy relied on low energy with significantly low penetration power, where there was neither an exact concept of the radiation dose nor the location of the tumour (28). A major breakthrough came when it was discovered in France that if radiation was administered in small daily fractions over a few weeks, then radioactive materials could be delivered without damaging normal tissue (30). After the 1920s, radiologists strived to advance radiation treatment by selecting the best therapeutic modality with attention to the size, location, histological type and grade of the cancer (31). All the advances made resulted in longer recurrence-free survival for the majority of patients with cancer by the end of the 1930s (31).

The development of radiotherapy after the use of low-voltage radiation continued as advances in radiation technology, radiation physics and radiobiology were made (32). Over the mid-20th century, following the work of several pioneers, radiotherapy became an integral part of the management of many paediatric tumours (33). The modern era of radiotherapy began after the introduction of megavoltage therapy, cobalt teletherapy, the use of proton beam and the electron linear accelerator (32). These developments, together with advances in computer technology, have enabled the development of intensity-modulated radiotherapy (IMRT) and high-energy proton therapy, the most high-precision radiotherapy that delivers precise radiation doses to a malignant tumour or specific areas within the tumour (33).

Radiotherapy is currently one of the main treatment modalities and is used in more than 50% of all patients with cancer, commonly in combination with surgery and chemotherapy (26). A number of factors including the radiation source, the cumulative dose, volume, fractionation and demographic factors such as sex and age at the time of radiation exposure can influence the clinical outcome following radiotherapy. However, it is known that organ-specific radiation exposure affects the risk of organ-specific adverse outcomes. Details of the established radiation-associated late effects are reported in Supplementary Table 1.

I.2.2 Chemotherapy

The history of chemotherapy began in the early 20th century, when the German chemist Paul Ehrlich, interested in alkylating agents, defined the term ‘chemotherapy’ as the use of chemicals to treat disease (21). In 1943, nitrogen mustard was used as the first chemotherapeutic agent to treat lymphomas, after data showed that men exposed to mustard gas during World War II presented atrophy of their bone marrow and lymph nodes (22,25). With the idea that mustard gas affects cell division – and this ability could potentially be used to suppress cancer cell division in acute leukaemia and lymphomas – several related alkylating compounds were tested in the subsequent years, including oral derivatives such as chlorambucil and ultimately cyclophosphamide (25). Farber et al. (22) tested folic acid and folate antagonists including aminopterin and amethopterin, now better known as methotrexate, in children with leukaemia and, in 1948, showed real remissions. Later, 6-thioquanine and 6-mercaptopurine were developed to treat leukaemia and 5-fluorouracil was used to treat solid tumours (21).

Into the 1950s, monotherapy drugs only achieved temporary responses in some cancers and scepticism surrounded the clinical usefulness of cancer chemotherapy (21). It was not until 1958 that the first cancer to be cured with chemotherapy – choriocarcinoma with an intensive, intermittent therapy including amethopterin and 6-mercaptopurine – triggered the first investigations into combination chemotherapy (34). In the following years, the combination of drugs that have different mechanisms of action, intermittent administration (which allows the regeneration of normal tissues but not tumour tissues), and chemotherapy used as a complementary modality (‘adjuvant chemotherapy’) with surgery and radiotherapy (to eradicate possible micro-metastases that might be present and undetectable at the time of initial curative treatment) became the main pillars of chemotherapy (25).

Currently, specific classes of chemotherapeutic drugs such as alkylating agents, anthracycline

antibiotics, antimetabolites, corticosteroids, epipodophyllotoxins and vinca alkaloids are used successfully to treat children and adolescents with cancer (35). However, they are well known to be associated with a wide range of potential long-term late effects (Supplementary Table 2), generally dependent on the cumulative dose, the scheduling and route of administration and the sex and age of the patient (35).

I.2.3 Surgery

Surgery was the only definitive treatment for cancer from antiquity until the 20th century (32). Although radiotherapy and chemotherapy became available, surgery continued to maintain its primacy in the treatment of most patients with cancer, and super-radical surgical procedures became increasingly popular in the 1940s and 1950s (32). The use of radical surgical techniques was eventually restricted to certain circumstances in the late 1960s, after several super-radical surgical treatments were abandoned. Moreover, surgery has started to be combined with adjuvant chemotherapy and radiotherapy (32).

Children and adolescents who undergo surgery as part of cancer treatment may experience long-term effects on their health status and quality of life. Examples include amputation and limb-sparing procedures, which can adversely affect physical function and mobility; ocular enucleation, which affects craniofacial development; oophorectomy or orchiectomy, which affects reproduction; cystectomy, which affects bladder function; nephrectomy, which subsequently affects kidney function; and neurosurgical procedures, which can cause neuropathic pain (35). In addition to the functional effects of surgery, scarring and disfigurement can have effects on the quality of life of survivors (35).

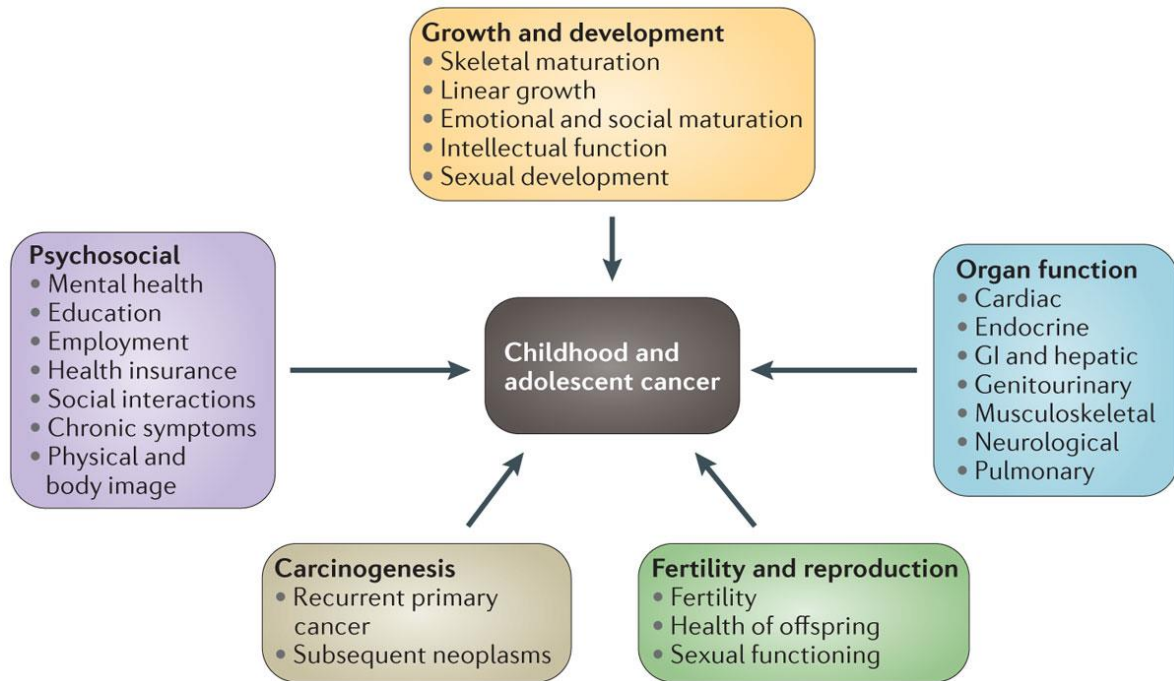
Although factors such as demographics, premorbid conditions, underlying genetic predisposition and health-related behaviours can modify the risks that are associated with treatment, treatment-specific factors usually determine the risk of adverse late effects with the exception of specific conditions (such as mutations in relevant genes) (35).

I.3 Late effects of childhood cancer treatments

In recent decades, it has become increasingly obvious that childhood cancer survivors (CCS) may experience a wide range of adverse health outcomes, which can affect almost any organ or body system to varying degrees, as a consequence of previous therapeutic exposures (35). Europe and North America have established comprehensive CCS cohorts to assess the risk of a wide range of

somatic and mental late effects and have provided evidence of a substantial disease burden among CCS (14) of both physical and psychosocial nature (Figure 4 and Table 1).

Figure 4. Range of health-related and quality-of-life outcomes among long-term survivors of childhood and adolescent cancers.



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In a quite recent study from USA, it was found that at key transition ages, 18 and 26, survivors experienced (per 100 individuals) an average of 22.3 and 40.3 disabling conditions, respectively versus 3.5 and 5.7 in community controls (36). Another study reported that by age 50 years, a survivor had experienced, on average, 17.1 chronic health conditions of any grade, of which 4.7 were severe or disabling (grade 3), life-threatening (grade 4), or death (grade 5) (37). However, the 20-year cumulative incidence of at least one grade 3–5 chronic condition decreased significantly from 33.2% for those diagnosed in the 1970-79 period to 29.3% for those in 1980-89, and 27.5% for those in 1990-99 (38).

European studies have demonstrated that CCS face an elevated risk of developing a second malignancy (39), with a 4-fold increased risk of subsequent primary leukaemia (40), a 3-fold increased risk of subsequent neoplasms of the digestive system (41) and a 15.7-fold risk of developing a soft-tissue sarcoma (42) compared with the general population. They are also 22 times more likely to experience a bone sarcoma and 60% more likely to develop a lymphoma (43)

compared the general population. Other studies have shown that CCS are at increased risk of cardiovascular diseases (44,45), endocrine disorders (46), pulmonary diseases (47), infectious complications (48), auditory complications (49) and pregnancy and labour complications (50), among others.

CCS are also at risk of experiencing late mental effects. Post-traumatic stress disorder (51); symptoms of depression, anxiety (52) and somatic distress (53); post-traumatic growth (54); fatigue; and sleep disturbances (55) are significantly more likely to occur than in sibling controls or the general population. Table 1 provides an overview of some major late effects of childhood cancer treatment, their major causes and monitoring approaches reported by Freyer (56).

It is now widely recognised that being a CCS has long-term implications that require continued medical follow-up and other specific forms of support throughout the lifespan (56,57) (Table 1). Several studies have found that CCS have at least twice as high a risk of being hospitalised and experience longer stays in hospitals than population-based comparisons (14,58–60). CCS also have a higher number of general practitioner and specialist visits than the general population (61–63).

Table 1. Overview of selected late effects observed in young adult survivors of childhood cancer.

Organ System	Late Effect	Major Treatment-Related Factor(s)	Periodic Evaluation/Screening
Eyes	Cataracts	Corticosteroids, RT	Regular eye examination
Ears	Hearing loss, tinnitus	Cisplatin, RT	Audiologic evaluation
Oral	Dental caries, dysgenesis	RT, alkylators (at young age)	Regular dental examination
	Dry mouth	RT	
Cardiovascular	Cardiomyopathy	Anthracyclines, RT	Serial echocardiography
	Coronary artery disease	RT	Clinical history
	Carotid artery narrowing	RT	Carotid artery ultrasound
Lungs	Pulmonary fibrosis, restrictive or obstructive lung disease	Bleomycin, busulfan, lomustine, carmustine, RT	Chest x-ray, pulmonary function testing
Urinary tract	Reduced GFR	Cisplatin, RT	Serum creatinine
	Tubular dysfunction	Cisplatin, ifosfamide	Serum electrolytes, Mg, Phos
	Hemorrhagic cystitis, bladder fibrosis	Cyclophosphamide, ifosfamide, RT	Urinalysis
Musculoskeletal	Osteopenia/osteoporosis	Corticosteroids, methotrexate	Bone density measurement
	Osteonecrosis (AVN)	Corticosteroids	Clinical examination, MRI
	Altered bone growth	RT	Clinical examination
Neurologic	Neurocognitive delay	Methotrexate, cytarabine, RT	Neuropsychological testing
	Leukoencephalopathy	Methotrexate, cytarabine, RT	Neurologic examination, MRI
	Peripheral neuropathy	Vincristine, vinblastine	Neurologic examination
Endocrine	Hypothyroidism	RT	TSH, free T4
	Growth hormone deficiency	RT	Serial height
	Gonadal failure	RT, alkylators	Testosterone, estradiol, FSH, LH
Reproductive	Infertility	Alkylators, RT	Clinical history, specialty assessment
Secondary neoplasm	Melanoma, breast carcinoma, thyroid carcinoma, sarcoma, bowel cancer, brain tumor	RT	Site-specific surveillance (eg, clinical examination, mammography or MRI, or colonoscopy)
	Acute myeloid leukemia/myelodysplastic syndrome	Etoposide, anthracyclines, RT	CBC
Psychosocial	Post-traumatic stress syndrome, interpersonal difficulties, special educational needs, career and vocational challenges, insurance deficits	The cancer experience; functional disabilities arising from specific late effects	Clinical history, psychological evaluation, social work assessment

Abbreviation: RT, radiation therapy; GFR, glomerular filtration rate; Mg, magnesium; Phos, phosphorous; AVN, avascular necrosis; MRI magnetic resonance imaging; TSH, thyroid stimulating hormone; FSH, follicle-stimulating hormone; LH, leuteinizing hormone.

Reprinted from Freyer, DR. 2010 (56)

I.4 Socioeconomic difficulties in childhood cancer survivors

In addition to the somatic and mental late effects of cancer therapy, long-term CCS are at risk of adverse socioeconomic and social conditions that may decrease overall quality of life (14,35).

Some studies have found that long-term CCS have lower educational attainment than the general population (64–66). Others suggest that educational attainment is the same (67,68) or even better (69). It has been reported that CCS have a significantly higher use of special education (70,71). However, in a recent meta-analysis of 26 studies from high-income countries, the authors found CCS are less likely to complete secondary and tertiary level education (72), and the literature agrees that CNS tumour survival is associated with poorer educational attainment overall (72).

On the other hand, it has been reported that CCS have higher odds of health-related unemployment than comparison populations or siblings (73–75). However, like educational attainment, this result varies by country/region, and in other studies there was not a significant increase in unemployment compared with controls (64,69,76). Similarly, there are discrepancies in occupational attainment, with CCS found to be more (69) and less (73) likely often in higher-skilled managerial/professional positions. Finally, an updated meta-analysis of 56 studies found that CCS are 1.5 times more likely to be unemployed than control subjects (77). However, it is important to mention that the authors found lower unemployment rates in Europe compared with the United States and Canada, and with Asia (77). These discrepancies may be due to differences in the social security systems of the regions. While in the United States there may be discrimination against patients who had cancer in the past, because many companies pay for their employees' health insurance, in France, for example, health insurance provides universal public coverage, and disability benefits are granted to people with disabilities (69).

The effect of a higher risk of lower schooling or longer unemployment experience on CCS income has also been studied. Several studies have reported significantly lower income in CCS than controls (64,78,79) and an increased risk of being economically dependent (80), with a higher risk of social security benefit uptake than the cancer-free population (81,82). This phenomenon, together with the findings that CCS are more than twice as likely to live dependently (83) – with a lower probability of living in a couple (75,84) and being a parent (84) – continues to lead to challenges among long-term survivors.

I.5 Financial hardship among childhood cancer survivors

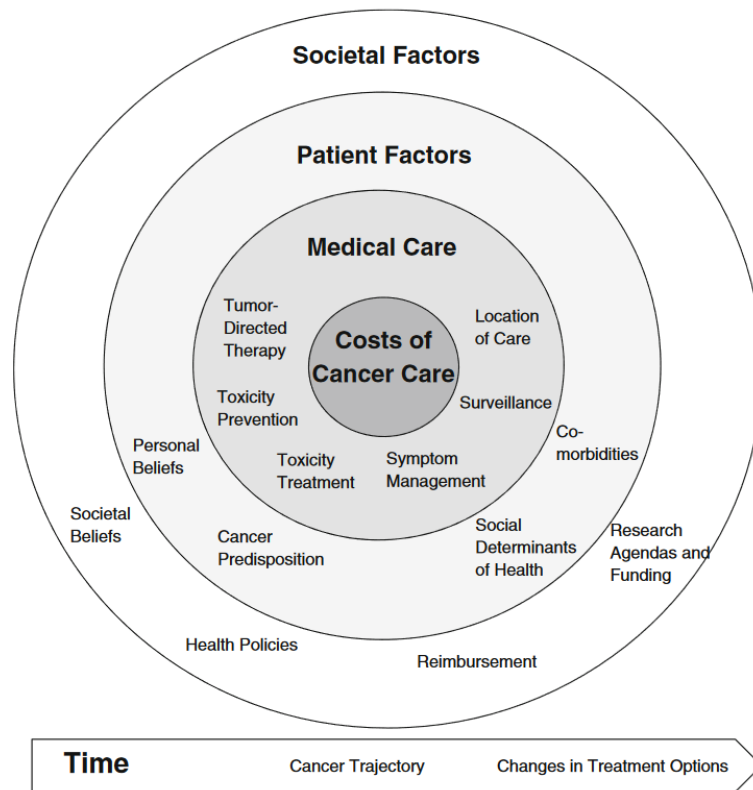
Although the somatic and mental late effects and adverse socioeconomic outcomes of CCS have been well described, the impact of late effects on their financial outcomes, especially in the long term, have been under-investigated (85). The direct and indirect health care costs of physical, neurocognitive and psychological late effects may lead to financial burden in adults CCS (57). This may subsequently translate into diminished quality of life; limited access to care; and other aspects of hardship, such as depleted savings, accumulated medical debt, the inability to meet daily living expenses and bankruptcy (86,87).

A few studies from the United States have reported that long-term CCS have higher out-of-pocket expenses, defined as spending more than 10% of their household income on out-of-pocket medical expenses during the past year, than siblings (88,89). Moreover, CCS with higher medical expenses are more likely to borrow money and to report deferring care and skipping a test, treatment, or follow-up (89). These results remain despite safeguards introduced by health care reform in the United States (90). Again, these consequences may result in poorer health outcomes in CCS.

Although financial hardship may be particularly reported in the United States, it is now recognised as a global issue affecting countries across health care systems and income levels (86,91,92). Patients and survivors with cancer may not be fully protected against financial hardships, even in settings with universal health coverage, where non-medical costs have been identified as important drivers of financial hardship (91).

According to Russell and Bernhardt (93), the total health care costs attributed to childhood cancer are the result of the number of people receiving treatment or follow-up, the types of health care services that they are receiving, and their related costs. Hence, several factors can contribute to the cost of cancer care, many of which are not dependent on patients, their families or their health professionals (Figure 5). Nevertheless, there is an awareness that late effects and their management-related costs might contribute as much or more to the overall costs of childhood cancer as the tumour-directed therapies (93).

Figure 5. Factors contributing to the costs of childhood cancer care.



Reprinted from Russell H et al. 2016 (93).

To date, most of the studies on financial hardship have been conducted in the United States and its health care system, which lacks fully implemented universal health coverage and a social security system, factors that can also foster financial hardship (92). These features are in contrast to the French system. More studies on the financial hardship and the long-term economic effect of CCS in publicly funded health care systems are needed.

Studies describing the cost of health care are analogous to descriptive epidemiological studies. They define the economic burden of a disease on patients, families and health care systems (94). This information is useful for policymakers to budget and reallocate resources, especially in investing in the development of new radiotherapy therapies such as proton therapy. Cost reduction efforts targeting relatively small patient populations that use a disproportionate amount of care, such as CCS, may have an impact on health care spending (93). This is the subject of this thesis.

I.6 Research hypotheses and objectives

Based on the existing and previously analysed literature, we formulated several hypotheses:

- 1) Given that CCS are at risk of late effects, they require significantly more health care resources across their lifespan to prevent or treat these health conditions and diseases. Therefore, their increased burden of morbidity and health care utilisation is likely to be associated with higher health care expenditures in the health system.
- 2) Given the potentially life-threatening or disabling late effects, we hypothesise that hospitalisations are an important component of these health care expenditures.
- 3) We also hypothesise that there are some clinical and socioeconomic variables of survivors that influence health care expenditures – notably, gender, the type of cancer, the era of treatment and the type of treatment, especially for those treated intensively (combined therapy).

The main objective of this thesis is to quantify the overall economic burden of the long-term sequelae of childhood cancer treatments in France and to analyse it according to the type of cancer, the treatments received and other clinical and socioeconomic factors.

This thesis aims to address the following specific objectives:

- 1) To estimate the health care expenditures of CCS in France and to study their associated factors based on survivor data from the French Childhood Cancer Survivor Study cohort and the cancer registries.
- 2) To detail the hospitalisation rate of CCS compared with the general population and to study the associated factors; and
- 3) To estimate excess health care expenditures among CCS in France compared with the general population and to study the associated factors.

Chapter II describes the data used in this thesis. Chapter III quantifies and details health care expenditures among long-term CCS in France based on two population sources. Chapter IV presents analyses of hospitalisation rates among CCS compared with those of the general French population of the same sex, age and region of residence. Chapter V presents our estimates of the excess health expenditures of CCS compared with the French general population, and its associated factors. Finally, Chapter VI summarises the main results of the thesis and their possible clinical and public health implications, and proposes perspectives for future research.

Chapter II Data sources

To achieve our objectives, we have used data from the French Childhood Cancer Survivors Study (FCCSS) (<https://fccss.fr>) in conjunction with National Health Data System (*Système national des données de santé*, French acronym: SNDS) (<https://www.snds.gouv.fr>). The SNDS includes the General Sample of Beneficiaries (*Échantillon généraliste des bénéficiaires*, French acronym: EGB), a representative sample of the French population. In this chapter we provide general information about our study population, data sources and data availability for each cohort.

II.1 The French Childhood Cancer Survivor Study (FCCSS)

II.1.1 Overview

The FCCSS is a retrospective cohort of 7,670 five-year CCS diagnosed for any type of malignant neoplasm except leukaemia, before the age of 21 years between 1946 and 2000 in five cancer centres in France. The centres participating in the study are: Gustave Roussy Institute (Paris area), Institute Curie (Paris area), Jean Godinot Institute (Reims), Claudius Regaud cancer centre (Toulouse) and Antoine Lacassagne cancer centre (Nice) (Table 2).

The cohort was established between 1985 and 1995 by exploring the medical archives of several cancer centres; it was called ‘Euro2K’ because it included survivors treated in France ($\approx 3,300$ people) and the United Kingdom ($\approx 1,200$ people). It only included CCS diagnosed before 1986 (95). Since 2012, the Euro2K cohort has expanded to become the FCCSS cohort, which now only includes French survivors and has added survivors treated up to the year 2000 at the Gustave Roussy Institute and Institute Curie.

The aim of the FCCSS is to analyse the long-term effects related to childhood cancer and their treatments in all its aspects – medical, social, economic and psychological – in an attempt to improve their management and prevention. The FCCSS protocol has been approved by the ethics committee of the French National Institute of Health and Medical Research (*Institut National de la Santé et de la Recherche Médicale*, French acronym: INSERM) and the French National Data Protection Agency (*Commission Nationale de l’Informatique et des Libertés*, French acronym: CNIL).

Table 2. Characteristics of the survivors included in the FCCSS cohort.

Total	n = 7670	%
Gender		
Male	4201	54.8
Female	3469	45.2
Centres		
Gustave Roussy Institute	5504	71.8
Institute Curie	1917	25
Antoine Lacassagne cancer centre	15	0.2
Jean Godinot Institute	75	0.98
Claudius Regaud cancer centre	159	2.07
Year of primary cancer diagnosis		
<1970	658	8.58
1970–1979	1549	20.2
1980–1989	2484	32.4
≥1990	2979	38.8
Year of primary cancer diagnosis		
Mean (range)	1985 (1946-2000)	
Age at primary cancer diagnosis		
0–1	1727	22.5
2–4	1783	23.2
5–9	1736	22.6
10–14	1609	21
≥15	815	10.6
Age at primary cancer diagnosis		
Mean (IQR)	6.6 (2-11)	
First primary cancer type		
Kidney tumours	1128	14.7
Neuroblastoma	1035	13.5
Lymphoma	1279	16.7
Soft tissue sarcomas	819	10.7
Bone sarcomas	701	9.14
Central nervous system tumour	1138	14.8
Gonadal/Germ cell tumours	439	5.72
Thyroid tumour	71	0.93
Retinoblastoma	619	8.07
Other solid cancer	441	5.75
Treatment		
No radiotherapy nor chemotherapy	905	11.8
Radiotherapy	1089	14.2
Chemotherapy	2569	33.5
Radiotherapy and chemotherapy	3107	40.5
Status at December 2022		
Alive	6167	80.4
Dead	1503	19.6
Follow-up in years at December 2022		
Mean (IQR)	37 (28-44)	

FCCSS: French Childhood Cancer Survivors Study

IQR: interquartile range.

II.1.2 Data collection and follow-up

Based on hospital medical records, the FCCSS has detailed information on the clinical and histopathological characteristics of the first cancers and their classification according to the International Classification of Childhood Cancer (ICCC), third edition (96). Information on treatments administered initially or for recurrences of the first cancer was collected from medical charts and radiotherapy files in the participating centres. Radiotherapy data were validated by physicians or hospital physicists.

FCCSS patients are followed up prospectively to the present day based on access to the medical records and other research instruments. Between 2005 and 2010, a self-report questionnaire that addressed various adverse health, social and psychological outcomes was sent to the French CCS in the ‘Euro2K’ cohort whose addresses were known or had been found by the National Health Insurance Fund (*Caisse Nationale d’Assurance Maladie*, French acronym: CNAM). The contact letter included a participation agreement to be signed and an authorisation to contact the physician and medical facilities and was approved by a ministerial decree. Among 2,471 CCS who could be contacted to ask for their participation, 1,920 (78%) responded to the questionnaire. Health outcomes and diagnoses were self-reported initially and then confirmed by relevant hospital doctors following written confirmation or by telephone contact. Since 2012, a long-term follow-up (LTFU) programme has been in place at the Gustave Roussy Institute and the Institut Curie.

Data on patient outcomes, including cause of death for deceased patients, are obtained by linkage with the national register of causes of death coordinated by the Centre for Epidemiology on Medical Causes of Death (*Centre d’épidémiologie sur les causes médicales de Décès*, French acronym: CepenDC) which is part of INSERM (97), and by linkage with the national health insurance information system, currently known as the SNDS.

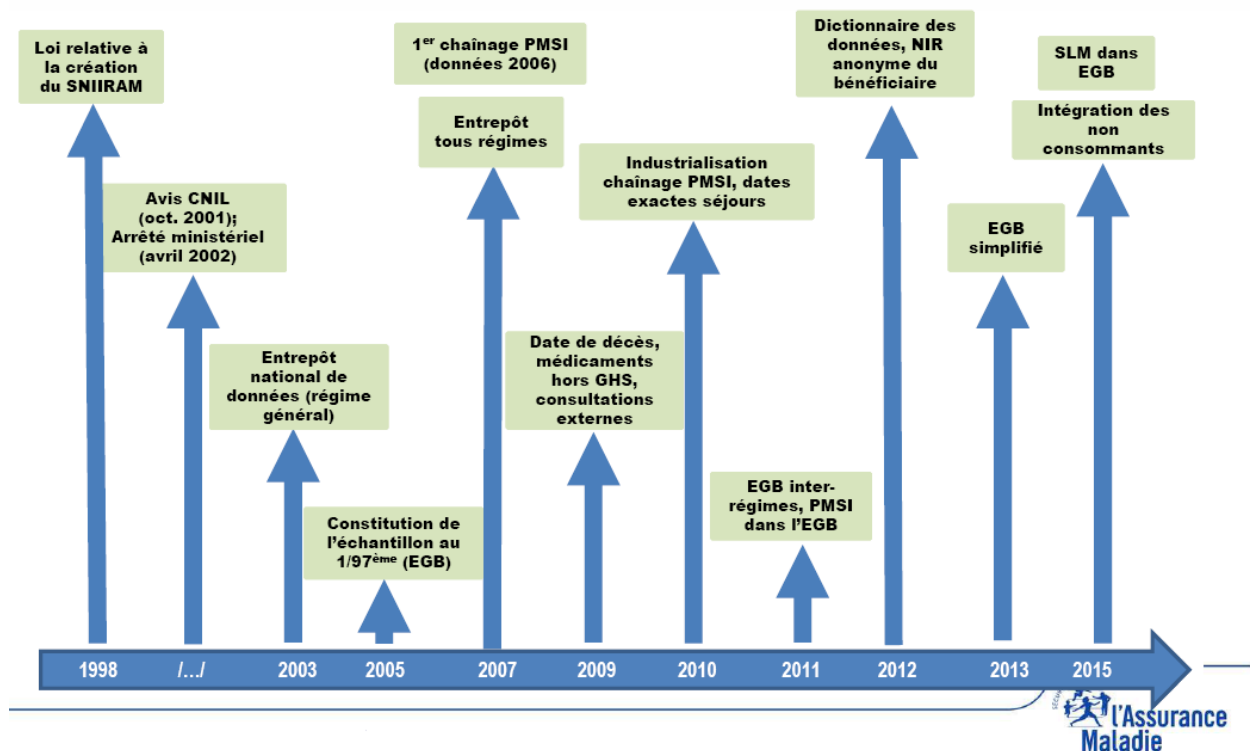
II.2 The National Health Data System (SNDS)

The SNDS is the health care claims dataset in France containing all the reimbursements made by the CNAM, which covers around 99% of the population (98). However, it has progressively evolved from his creation in 1999 as the National Inter-Scheme Health Insurance Information System (*Système National d’Information Inter Régimes de l’Assurance Maladie*, French acronym: SNIIRAM) to the SNDS. The French Social Security funding bill created the SNIIRAM data warehouse to monitor the individual activity of health care providers, care pathways and health care consumption and expenditures in order to contribute to the elaboration and implementation

of budgets and health policies (99). The constitution of the SNIIRAM data warehouse was based on reliable identification of individuals by the social security number (*Numéro d'inscription au Répertoire*, French acronym: NIR).

Since 2001, the SNIIRAM has gradually improved in terms of the exhaustiveness of beneficiaries, the information available and the use of these data for research purposes with the approval by the CNIL (Figure 6). In 2006, the SNIIRAM was transformed into a functional tool with the availability of individual data and comprises the characteristics and medical information of the beneficiaries of the various national health insurance schemes, as well as the inpatient hospital or office medicine health care reimbursed to this population (99).

Figure 6. The SNIIRAM and its construction stages before the SNDS (in French).



Reprinted from Training course “Architecture and data of the SNDS” version September 2019.

In 2016, article 193 of the law on the modernisation of French health system used the SNIIRAM as the cornerstone to create the SNDS. The article describes: the components of the SNDS, the authorised purposes for processing data from the SNDS and the security conditions for processing these data. The objectives of the SNDS are similar to those of the SNIIRAM and consist of producing information on health, health care and medical and social welfare management. The CNAM is responsible for the development of the SNDS (99).

Currently, the SNDS regroups several databases from the SNIIRAM, the National Hospital Discharge Database (*Programme de Médicalisation des Systèmes d'Information*, French acronym: PMSI) and the statistical data on causes of death provided by CepiDC.

II.2.1 National Inter-Scheme Health Insurance Information System (SNIIRAM)

The SNIIRAM essentially contains individual data used for billing and reimbursement of by the outpatient health care consumption database (*Datamart de Consommation Inter-Régime*, French acronym: DCIR). It includes information from the three main claims systems the general regime (*Caisse Nationale d'Assurance Maladie des Travailleurs Salariés*, French acronym: CNAMTS), the regime for the self-employed (*Régime social des indépendants*, French acronym: RSI) and the Agricultural Social Mutual Organisation (*Mutualité sociale agricole*, French acronym: MSA) for agricultural workers, and almost all the smaller systems (100). Data are collected locally from *carte vitale* records, claim forms and invoices from public and private institutions. The data are linked to the patient's name to ensure reimbursement; however, the NIR is pseudonymised and then centralised by the CNAM (99).

Information in the DCIR includes demographic data such as sex, age, date of birth, date of death, department and commune of residence (Table 3). There is also information on membership of the French government's complementary programmes as the *Couverture médicale universelle complémentaire* (CMU-C), *l'Aide à la complémentaire santé* (ACS), and *l'Aide médicale de l'État* (AME), which indicates low-income status.

Moreover, the DCIR records the diagnosis of long-term conditions (*Affections de Longue Durée*, French acronym: ALD) defined as a disease in which the severity and/or the chronicity requires a long-term costly treatment. There is a list of 30 ALD with a total of 3,448 International Classification of Diseases, 10th revision (ICD-10) codes included in these ALD (100). The registration of an ALD is obtained at the request of the patient's physician and validated by the doctor of the health insurance system. Patients with ALD benefit from full coverage of all medical expenses related to the disease.

Table 3. Information available or not available in the SNIIRAM database in as of 2016.

Available information	Limited or no information
Patients	Other socioeconomic characteristics: employment, type of job, income, marital status. . .
Date of birth	Risk factors: smoking, alcohol, sedentary lifestyle, nutrition, family history. . .
Sex	Results of clinical examinations: blood pressure, body mass index. . .
Date of death	Reasons for or diagnosis of medical or paramedical consultations
CMUC, ACS, AME	Laboratory test results, histology, pathology, radiology. . .
Adult disability allowance (AAH)	Drugs not reimbursed or procedures not billed
Town of residence	Drugs delivered in hospital or long-stay wards, other than those on the excess list (SSR, PSY, Ehpad with internal pharmacy. . .), or in the context of lump sum payments (health clinics, health care networks, medical examination centres, etc.)
Geographical social disadvantage index	Whether or not the drugs are taken (information limited to reimbursement, with no data on adherence)
ALD (ICD-10)	Prescribed dosage of drugs (information limited to the quantity dispensed, requiring estimation of the daily dose)
Daily allowances (ICD-10 code if > 6 months)	Matching of treatment with test results (HT, lipids. . .)
Occupational diseases (ICD-10)	Causes of death (will be included in SNDS)
Disability (ICD-10)	
Reimbursements (number of procedures and dates of care)	
Drugs, Clinical pathology (NABM)	
Procedures, products and benefits (CCAM, LPP)	
Health care professionals (type, place. . .)	
Hospitalisations (public and private) in PMSI-MCO, HAD, SSR, PSY	
Dates of care	
Primary, related and associated diagnoses	
Procedures, products, benefits (CCAM, LPP)	
Excess expensive drugs and devices	
Stays billed directly to national health insurance (private clinics or associations, medical and social welfare centres. . .)	
Outpatient consultations	
Hospital dispensing	
Reimbursable and reimbursed expenditure, including cash benefits	

SNIIRAM: Système National d'Information Inter Régimes de l'Assurance Maladie; AAH: allocation aux adultes handicapés; AME: aide médicale de l'État.

Reprinted from Tuppin P et al. 2017 (99).

The DCIR has also information on the nature and date of procedures performed by general practitioners and specialists, dentists, midwives, physiotherapists, nurses, speech therapists and orthoptists, among others allied health professionals, in their offices, at the patient's home, in private clinics or in certain health or medical and social welfare centres (99). Health care consumption information corresponding to reimbursable drugs, clinical pathology tests and medical devices; services related to the functioning of these devices; and transport expenses are also recorded. Basic information on the location and activity of the prescribing health professional is also recorded. However, diagnoses and reasons for medical consultations, as well as the results of laboratory tests or other examinations are not available in the DCIR (99,100).

Finally, the DCIR has data concerning the payment of daily allowances for sick leave related to illness, maternity, paternity, work accidents and occupational diseases, as well as payment of disability pensions, work accident or occupational disease compensation or death benefits by the CNAM (99).

II.2.2 National Hospital Discharge Database (PMSI)

The PMSI is the data warehouse for private and public hospital information and is managed by the Technical Agency for Information on Hospitalisations (*Agence Technique de l'Information sur l'Hospitalisation*, French acronym: ATIH). The PMSI is divided into four categories corresponding to hospitalisations in conventional hospital units (short stays) (*Médecine, Chirurgie, Obstétrique*, French acronym: MCO), homecare units (*Hospitalisation à Domicile*, French acronym: HAD), rehabilitation units (*Soins de Suite ou de Réadaptation*, French acronym: SSR) and psychiatric institutions (*Psychiatrie*, French acronym: PSY).

The available information includes the admission date and duration of stay; the main, related and associated diagnoses, based on the ICD-10 codes; as well as procedures performed (medical acts and biology) (100). The PMSI also includes information on the source of the admission and the destination of discharge, which may be another department of the same hospital or another hospital, in addition to death or discharge to home. Outpatient visits and laboratory and medical procedures performed in the hospital are also available, as well as the specialty of the health care professional consulted.

II.2.3 Register of causes of death (CepiDC)

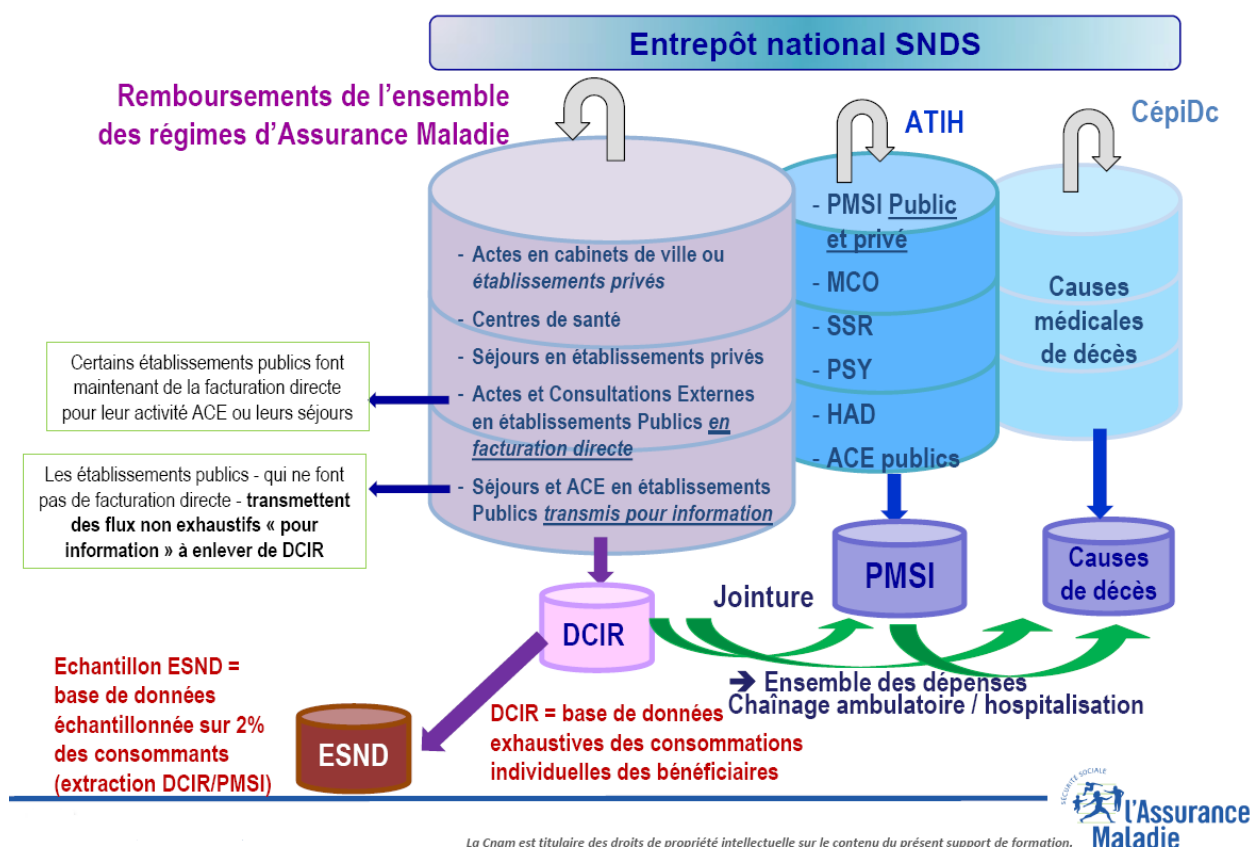
The CepiDC has recorded and logged all death certificates issued in France since 1979 together with the national death registry maintained by the National Institute for Statistics and Economic Studies (*Institut national de la statistique et des études économiques*, French acronym: INSEE). These certificates contain information such as the subject's age and sex and the chain of events leading to his or her death (101). Causes of death are categorised according to the ICD-10 (102). The CepiDC provides free and anonymous datasets for mortality research in France.

II.2.4 The General Sample of Beneficiaries (EGB)

The EGB is a 1/97th anonymised random permanent sample of the population included in the SNDS ($n \approx 660,000$), which has been shown to be representative of the French general population (100). It was started in 2004 and has been progressively enriched over time, including the RSI and the MSA since 2011 (100). The EGB includes new eligible individuals (neonates, foreign nationals arriving to work in France and their dependents) and removes deceased people, foreign nationals returning to their country of origin or people leaving the scheme(s), who are no longer covered by these schemes (99). The EGB also includes a population not consuming any health care. All the health care claims and reimbursement data included in the SNDS are available in the EGB, except for PMSI SSR and PSY, which were not supplied. The data are stored for a period of 20 years starting in 1 January 2006.

In summary, the SNDS has an extensive medical and administrative information system, which covers almost the entire population living in the country and all of their health care expenditures reimbursed by the CNAM. As the SNDS is continually evolving towards enrichment by medicalised information, the use of the SNDS requires very good knowledge of the data supply chain (Figure 7), the various coding systems and their changes over time. However, the use of the SNDS data has contributed to public health information and decision support, and has resulted in a large number of international publications that rank it as one largest continuous and homogeneous claims databases in the world (99,100).

Figure 7. Data feed of the entire SNDS (in French).



Reprinted from Training course “SNDS Exhaustive and sampled Individual Beneficiary Data (DIB)” version October 2022.

II.3 FCCSS linkage to the SNDS

Linkage and access between the SNDS data of the FCCSS cohort was provided by the CNAM. Because the FCCSS study did not collect NIR, patients were identified within the SNDS by probabilistic matching with the full involvement of different French health care-related organisations: the National Insurance Contributions Office (Caisse nationale de l'assurance vieillesse des travailleurs salariés, French acronym: CNAVTS) is the third party for NIR reconstruction and the CNAMTS is the trusted third party for the SNDS health data gathering based on a non-identifiable number derived from the retrieved NIR. The very specific identification data that INSERM provided to the CNAMTS are the following: family and first name, sex, date and place of birth, and unique arbitrary number of survivors. The CNAMTS was in charge of both communication with the CNAVTS and SNDS data extraction.

The study was approved by the CNIL (Authorisation n° 902287) and by the ethics committee of INSERM. Informed consent was obtained for patients who could be contacted (n = 3,312). Finally, a specific act in law from the French Conseil d'Etat, the highest court in France (Order 2014-96 of 2014 February 3), approved the cession of the SNDS data for all patients included in the FCCSS with or without informed consent.

II.3.1 Linkage until 2016

Of the 7,670 five-year CCS from the FCCSS, 6,818 (88.9%) were still alive on 1 January 2006 (the SNDS start date) and therefore eligible for linkage. In the first linkage and date extraction in 2017, the percentage of survivors linked to the SNDS was 55.6% (n = 3,788). All SNIIRAM and PMSI databases were available from 1 January 2006 to 31 December 2016.

The FCCSS patient characteristics according to the SNDS linkage status are shown in Table 4. Among the eligible patients, survivors who died during 2006 and 2016 had a worse linkage to the SNDS data. To examine the factors driving variability in linkage, we performed a stepwise logistic regression with the outcome linked or not, and the factors listed in Table 4. The final model (data not shown) indicates that the only factors that drive the linkage are the age in 2006 (odds ratio [OR] 1.014, 95% CI 1.010–1.019) – older patients are more likely to be linked – and death (OR 0.392, 95% CI 0.329–0.466) – dead patients are less likely to be linked. We did not find any role of the following factors: gender, type of cancer or age at diagnosis.

This means that the identification variables (family and first name, sex and date and place of birth) probably included more error for dead patients than in the other ones. Indeed, before 2000 most of this information was not computerised and the errors had more chances to be corrected if the patients came frequently to the hospital, but no computerised information was transmitted to the hospital if the patient died.

Table 4. Characteristics of the FCCSS survivors by linkage to the SNDS data until 2016.

	Linked to SNDS	Not linked to SNDS	Chi2
Total	n= 3788 (%)	n= 3030 (%)	
Gender			
Male	2086 (55.07)	1639 (54.09)	0.4200
Female	1702 (44.93)	1391 (45.91)	
Age at January 2006 (Start date)			
<20	915 (24.16)	987 (32.57)	<.0001
20-30	1530 (40.39)	1009 (33.3)	
31-40	967 (25.53)	689 (22.74)	
>=41	376 (9.93)	345 (11.39)	
Status at December 2016 (Ending date)			
Alive	3650 (96.36)	2682 (88.51)	<.0001
Dead	138 (3.64)	348 (11.49)	
Year of diagnosis			
<1970	244 (6.44)	222 (7.33)	<.0001
1970-1979	712 (18.8)	559 (18.45)	
1980-1989	1350 (35.64)	894 (29.5)	
>=1990	1482 (39.12)	1355 (44.72)	
Age at first cancer			
0-1	839 (22.15)	775 (25.58)	0.0100
2-4	876 (23.13)	714 (23.56)	
5-9	860 (22.7)	643 (21.22)	
10-14	801 (21.15)	589 (19.44)	
≥15	412 (10.88)	309 (10.2)	
First primary cancer type			
Kidney tumours	576 (15.21)	467 (15.41)	0.0400
Neuroblastoma	508 (13.41)	453 (14.95)	
Lymphoma	664 (17.53)	502 (16.57)	
Soft tissue sarcomas	436 (11.51)	294 (9.7)	
Bone sarcomas	343 (9.05)	261 (8.61)	
Central nervous system tumour	482 (12.72)	377 (12.44)	
Gonadal/Germ cell tumours	235 (6.2)	177 (5.84)	
Thyroid tumour	37 (0.98)	24 (0.79)	
Retinoblastoma	295 (7.79)	291 (9.6)	
Other solid cancer	212 (5.6)	184 (6.07)	
Treatment received			
No radiation or chemotherapy	498 (13.15)	375 (12.38)	0.0900
Radiation	489 (12.91)	404 (13.33)	
Chemotherapy	1329 (35.08)	1142 (37.69)	
Radiation and chemotherapy	1472 (38.86)	1109 (36.6)	

II.3.2 Linkage until 2018

A few years later, the CNAM carried out a new probabilistic matching and an update of the SNDS data for the FCCSS, which was a considerable improvement on the previous one. In this second

linkage, the percentage of CCS linked to the SNDS data was 81.9% (n = 5,583/6,818), meaning that 1,795 (26.3%) survivors were found. In addition, the SNDS databases were updated up to December 2018. The FCCSS patient characteristics according to the second linkage status are shown in Table 5.

Table 5. Characteristics of the FCCSS survivors by linkage to the SNDS data until 2018.

	Linked to SNDS	Not Linked to SNDS	Chi2
Total	n= 5583 (%)	n= 1235 (%)	
Gender			
Male	3050 (54.63)	675 (54.66)	0.9900
Female	2533 (45.37)	560 (45.34)	
Age at January 2006 (Start date)			
<20	1593 (28.53)	309 (25.02)	<.0001
20-30	2115 (37.88)	424 (34.33)	
31-40	1342 (24.04)	314 (25.43)	
>=41	533 (9.55)	188 (15.22)	
Status at December 2018 (Ending date)			
Alive	5237 (93.8)	1001 (81.05)	<.0001
Dead	346 (6.2)	234 (18.95)	
Year of diagnosis			
<1970	354 (6.34)	112 (9.07)	<.0001
1970-1979	996 (17.84)	275 (22.27)	
1980-1989	1858 (33.28)	386 (31.26)	
>=1990	2375 (42.54)	462 (37.41)	
Age at first cancer			
0-1	1323 (23.7)	291 (23.56)	0.5700
2-4	1308 (23.43)	282 (22.83)	
5-9	1243 (22.26)	260 (21.05)	
10-14	1133 (20.29)	257 (20.81)	
≥15	576 (10.32)	145 (11.74)	
First primary cancer type			
Kidney tumours	848 (15.19)	195 (15.79)	0.5500
Neuroblastoma	775 (13.88)	186 (15.06)	
Lymphoma	954 (17.09)	212 (17.17)	
Soft tissue sarcomas	606 (10.85)	124 (10.04)	
Bone sarcomas	489 (8.76)	115 (9.31)	
Central nervous system tumour	717 (12.84)	142 (11.5)	
Gonadal/Germ cell tumours	343 (6.14)	69 (5.59)	
Thyroid tumour	49 (0.88)	12 (0.97)	
Retinoblastoma	478 (8.56)	108 (8.74)	
Other solid cancer	324 (5.8)	71 (5.75)	
Treatment Received			
No radiation or chemotherapy	731 (13.09)	142 (11.5)	0.0100
Radiation	711 (12.74)	182 (14.74)	
Chemotherapy	2062 (36.93)	409 (33.12)	
Radiation and Chemotherapy	2079 (37.24)	502 (40.65)	

A request for an extension and update of the SNDS data until December 2022 has been made by our team to the CepiDC to be carried out jointly with the CNAM. If realised, this would add 4 more years of monitoring, which would allow a global follow-up of the FCCSS of up to 16 years in the SNDS.

The following chapters present the analyses carried out on the data sources described in this chapter. It is important to point out that Chapter III uses data from the 2016 linkage, while Chapters IV and V are based on the linkage up to 2018.

Chapter III Health care expenditures among long-term survivors of paediatric solid tumours

III.1 Introduction

Advances in childhood cancer survival have been achieved by using treatments that can damage healthy tissues and, as a result, CCS carry a significant risk of late effects related to cancer treatments (Chapter I.3). Thus, CCS may require lifelong medical visits and testing to prevent and treat late effects (Chapter I.5). However, little is known about their long-term health care costs, especially in a publicly funded health care system, in particular in France.

It is estimated that there are between 300,000 and 500,000 CCS in Europe (104). In France, there are about 50,000 (105). The French health care system is mainly publicly funded and provides universal coverage to its citizens. It covers most medical expenses (106), especially for long-term conditions, but no studies have estimated the global health care expenditures among CCS. The FCCSS cohort, which includes CCS treated before 2000, provides an opportunity to detail the overall health care expenditures among very long-term cancer survivors. Nevertheless, FCCSS survivors were treated during their childhood in Centres for the fight against cancer (Centres de lutte contre le cancer, French acronym: CLCC), which are specialised cancer treatment hospitals in France. Therefore, we hypothesise that the FCCSS includes patients with more advanced and/or aggressive cancers, or they may have received more innovative treatments and, consequently, differ in terms of long-term outcomes and future health expenses from other CCS treated in other hospital settings.

In this chapter, we quantify and describe the health care expenditures among very long-term CCS in France. Subsequently, we compare the level of expenditures between FCCSS survivors with those from other settings included in existing French cancer registries during the FCCSS recruitment period.

III.2 Materials and methods

III.2.1 Study population

We used data from two sources, the FCCSS and the French Network of cancer registries (Réseau français des registres des cancers French acronym: FRANCIM). Detailed information on the data

collection methods for the FCCSS is provided in Chapter II.1. The FRANCIM includes all the population-based registries of cancer in France. This network records all newly diagnosed and confirmed cancer cases since 1975 in diverse areas of France (107,108). The population covered by the FRANCIM database represents 22% of the entire French population (109). Therefore, we considered the FCCSS survivors present in the FRANCIM to be FCCSS patients. We excluded leukaemia survivors from the FRANCIM for better comparability with the FCCSS, which did not include leukaemia.

From both databases, we selected all 5-year solid CCS diagnosed before January 2001 who were alive in January 2011 and who were linked to the SNDS. For this study we used the SNDS data obtained at the first linkage in 2016 (Chapter II.3.1), as these data were available at the time. Although the PMSI, MCO and HAD had cost information since 2006 (the SNDS start date), the availability of billing records for PSY and SSR systems began in 2011. Thus, we defined this year as the start date when data were available for all systems.

We followed survivors throughout the SNDS until 31 December 2016 or death, whichever occurred first. We excluded survivors who lived outside metropolitan France during follow-up due to the difference in the health insurance system, characteristics of the population and funding of care in French overseas territories (110).

III.2.2 Primary measures

We carried out this study from the CNAM perspective (payer). We estimated expenditures by considering all the reimbursements made by the CNAM in the mandatory reimbursement scheme between January 2011 and December 2016 or date of death. Therefore, we did not include reimbursements from private health insurance, special schemes or the final out-of-pocket costs.

Our primary outcome was the total direct health care expenditures for each calendar year and for each patient in both cohorts. We also classified direct expenditures for each year into 14 categories: general practitioner visits, other specialist visits, physiotherapy, nursing visits, other health professional visits, pharmacy, medical devices, laboratory tests, technical medical procedures, transport, hospitalisations, disability benefits, sick leave, and others. We expressed all expenditures in real terms by using the consumer price index provided by the INSEE with 2015 as the base year.

III.2.3 Covariates

Other covariates included age; sex; year of diagnosis; age at diagnosis; type of primary cancer (kidney tumour, neuroblastoma, lymphoma, soft tissue sarcoma, bone sarcoma, CNS tumour, gonadal/germ cell tumours, thyroid tumour, retinoblastoma and others); the French deprivation index in 2009, which is an area-based multidimensional index that measures socioeconomic differences (111) and where higher scores implies a higher ‘deprivation’ (categorised into quintiles); and death (alive or dead in December 2016).

III.2.4 Statistical analysis

The patient characteristics are described along with the estimation of annual mean expenditures for the 2011–2016 period. Categorical variables are expressed as numbers and percentages, and continuous variables as mean \pm standard deviation (SD). Direct total expenditures are described by categories and also according to the primary cancer.

Given the population studied, the frequency of people having no health care expenses during the 6-year follow-up period was less than 4% of the total patients within each cohort group; therefore, a two-stage model was not required. Instead, we used a repeated-measures generalised linear model (GLM) with a gamma distribution and a log link to estimate per-person annual medical expenditures for all patients to account for the skewness of the distribution. We added €1 to all expenditures to allow inclusion of individuals with no expenses (112). We chose neuroblastoma as the reference for type of primary cancer variable because it was one of the largest groups of cancer of the same histology. We compared the output of the model adjusted by all covariates (Model I), with models excluding the death variable (Model II) and patients who had died (Model III).

Finally, we performed several analyses by considering separately each type of expenditure and each type of cancer with and without interaction between the cohort (the FCCSS or the French cancer registries) and the type of cancer. Statistical significance was determined using $p < 0.05$. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

III.3 Results

III.3.1 Survivor characteristics and total health care expenditures

A total of 5,319 CCS were included in the study, among which 67.5% belong to the FCCSS (Table 6). Almost half of the patients were women and were diagnosed after 1990 (44.9% and 46.6%, respectively). More than 50% of the patients were over 30 years old at the beginning of the follow-up. The most common primary cancer was lymphoma (20.1%) followed by CNS tumours (14.2%). Between 2011 and 2016, around 3% of the patients died. The details of patient characteristics by cohort are shown in the Supplementary Tables 3 and 4.

The total direct health care expenditures for the 5,319 patients between 2011 and 2016 were € 134,523,643. The annual mean of health care expenditure for survivors were € 4,255 (Table 6). However, this variable was positively skewed due to a few very high values among survivors. In detail, 50% of patients had an annual mean health care expenditure of < € 1,000 and almost 10% had a mean expenditure of > € 10,000 (Supplementary Figure 1). In addition, the median health care expenditure was € 494 (interquartile range [IQR] € 105–2151).

The annual mean health care expenditure was higher in women than men (€ 4,795 and € 3,814), survivors diagnosed before 1980 (€ 6,970) who likely corresponded with survivors between 41 and 50 years old (€ 7,676), among those diagnosed with CNS tumours (€ 7,116), and in the FCCSS (€ 4,556 vs € 3,663 in the FRANCIM) (Table 6). It is noteworthy that the 167 survivors who died between 2011 and 2016 had an annual mean of expenditure of € 25,611 and accounted for 13.4% of the total expenditures.

Table 6. Survivor characteristics and health care expenditures.

	Patients	PY*	Annual health care expenditures	
	N (%)		Mean (SD)	Median (IQR)
Total	5319	31533.6	4255 (18790)	494 (105-2151)
Gender				
Male	2929 (55.1)	17351.9	3814 (19289)	338 (64-1554)
Female	2390 (44.9)	14181.7	4795 (18147)	721 (198-3290)
Age in January 2011 (start date)				
<20	550 (10.3)	3291.9	1475 (8143)	0 (0-309)
20-30	1979 (37.2)	11812.8	3561 (13189)	443 (113-1891)
31-40	1878 (35.3)	11142.6	4303 (20597)	592 (157-2312)
41-50	753 (14.2)	4355.4	7676 (29734)	1072 (265-5056)
≥51	159 (3)	930.9	6233 (14164)	1378 (398-5272)
French geographical deprivation index**				
1 Quintile	1063 (20)	6312.9	4569 (24995)	459 (92-1952)
2 Quintile	1061 (19.9)	6293.3	3688 (11473)	507 (118-2020)
3 Quintile	1066 (20)	6322.3	4034 (16209)	471 (103-1920)
4 Quintile	1064 (20)	6320.5	4699 (23783)	507 (97-2374)
5 Quintile	1065 (20)	6284.6	4283 (13374)	539 (119-2529)
Status in December 2016 (ending date)				
Alive	5152 (96.9)	30912.0	3770 (17677)	473 (101-2003)
Dead	167 (3.1)	621.6	25611 (40950)	10208 (1437-34703)
Year of childhood cancer diagnosis				
<1980	988 (18.6)	5760.3	6970 (28210)	995 (242-4552)
1980-1989	1852 (34.8)	10974.5	4731 (20024)	607 (149-2749)
≥1990	2479 (46.6)	14798.8	2841 (11813)	326 (52-1334)
Age at childhood cancer				
0-1	937 (17.6)	5575.0	2905 (9828)	257 (15-1337)
2-4	1034 (19.4)	6140.2	4926 (26253)	413 (69-2003)
5-9	1088 (20.5)	6433.3	4420 (14300)	552 (126-2743)
10-14	1130 (21.2)	6685.2	5072 (24480)	640 (170-2686)
≥15	1130 (21.2)	6699.8	3790 (12352)	600 (179-2135)
First primary cancer type				
Kidney tumours	668 (12.6)	3942.0	5021 (30330)	383 (78-1776)
Neuroblastoma	574 (10.8)	3434.2	2952 (12224)	285 (37-1301)
Lymphoma	1071 (20.1)	6350.7	3366 (10662)	442 (106-1770)
Soft tissue sarcomas	523 (9.8)	3117.3	4007 (14074)	471 (108-2219)
Bone sarcomas	445 (8.4)	2636.7	5207 (14193)	827 (188-4303)
Central nervous system tumour	756 (14.2)	4427.7	7116 (29617)	1130 (256-4925)
Gonadal/Germ cell tumours	389 (7.3)	2322.3	3575 (15215)	392 (93-1401)
Thyroid tumour	109 (2)	650.7	3202 (7882)	785 (348-2210)
Retinoblastoma	305 (5.7)	1815.5	2852 (9698)	235 (0-1161)
Other solid cancer	479 (9)	2836.5	3363 (12231)	495 (143-1797)
Cohort				
FCCSS	3589 (67.5)	21247.6	4556 (18830)	507 (97-2297)
French cancer registry	1730 (32.5)	10286.0	3633 (18692)	476 (122-1890)

* PY: Person-years of follow-up, SD: Standard deviation, IQR: Inter Quartile Range.

** : Ecological Index measuring the deprivation, and based on the median household income, the percentage high school graduates in the population aged 15 years and older, the percentage blue-collar workers in the active population, and the unemployment rate (111).

III.3.2 Health care expenditures

Health care expenditures by item are reported in Table 7. The leading expenditure item was hospitalisations, representing 45% of total expenses and experienced by 65% of survivors during the study period. Hospitalisations were more frequent in women than in men (73% vs 59%) (Supplementary Table 5). The annual mean expenditure for hospitalisation expenses was € 1,919. Pharmacy was also an important expenditure item representing 16% of total health care expenditures with an annual mean of € 676 per patient (€ 719 in men vs € 622 in women).

Around half of the survivors received sick leave during the 6-year follow-up and the annual mean per patient was € 410; notably, it was almost double for women compared with men (€ 557 vs € 289) (Supplementary Table 5). Only 6.5% of patients had expenditures related to disability benefits, but their total reached almost € 8 million, which is more than 5% of the total expenses. The distribution of health care expenditures by item was quite similar in both cohorts (Supplementary Table 6).

III.3.3 Health care expenditures by the type of primary cancer

Details on expenditures by the type of primary cancer are shown in Table 8. Survivors of CNS tumours experienced the highest annual mean of hospitalisation expenditure (€ 4,142), while kidney tumour survivors had the highest annual mean pharmacy expenditure (€ 1,578) compared with the other types of cancer. The annual mean expenditure for disability benefits was higher among bone sarcoma survivors (€ 479) while sick leave was the major source of expenditures for thyroid tumour survivors (€ 708).

Table 7. Health care expenditures by item.

	Number of patients (%)	Number of claims	Total expenditures in millions of € (%)	Annual mean expenditure per-patient in €* (SD)
General practitioner visits	5,055 (95)	144,107	3.1 (2.3)	97 (133)
Other specialist visits	4,935 (92.8)	161,998	5.4 (4)	170 (439)
Physiotherapy visits	2,195 (41.3)	123,828	2.1 (1.6)	67 (319)
Nursing visits	3,519 (66.2)	118,548	1.7 (1.3)	55 (650)
Other health professional visits †	597 (11.2)	12,548	0.4 (0.3)	12 (135)
Pharmacy	5,046 (94.9)	502,872	21.4 (15.9)	676 (9,736)
Medical devices	4,223 (79.4)	52,479	8.2 (6.1)	260 (1,800)
Laboratory tests	4,597 (86.4)	101,246	2.5 (1.9)	80 (302)
Technical medical procedures ‡	4,700 (88.4)	48,583	2.6 (1.9)	83 (287)
Transport	1,743 (32.8)	24,604	4.4 (3.3)	140 (979)
Hospitalizations	3,450 (64.9)	35,001	60.7 (45.1)	1,919 (13,730)
Disability Benefits §	345 (6.5)	13,863	7.9 (5.9)	251 (1,538)
Sick Leaves	2,731 (51.3)	41,722	13.0 (9.6)	410 (1,623)
Others	571 (10.7)	3,442	1.2 (0.9)	37 (1,039)
Total	5,319	1,384,841	134.5	4,255 (18,790)

SD: standard deviation.

* Annual mean expenditure per-patient in € were calculated for the entire population (=5,319).

† Other medical professional visits included expenditures related to visits to podiatrists, optometrists, speech therapists, and others.

‡ Technical medical procedures included expenditures mainly related to medical imaging techniques.

§ Disability benefits included all welfare payments or pensions made by the French Government to assistance people with disabilities.

Table 8. Annual mean health care expenditure (%) by item and the type of primary cancer.

	Kidney tumours (n = 668)	Neuroblastoma (n = 574)	Lymphoma (n = 1071)	Soft tissue sarcomas (n = 523)	Bone sarcomas (n = 445)	Central nervous system tumour (n = 756)	Gonadal tumours (n = 389)	Thyroid tumours (n = 109)	Retinoblastoma (n = 305)	Other solid cancer (n = 479)
General practitioner visits	84 (1.7)	70 (2.4)	96 (2.8)	94 (2.4)	116 (2.2)	130 (1.8)	81 (2.3)	128 (4)	72 (2.5)	102 (3)
Other specialist visits	172 (3.4)	134 (4.5)	185 (5.5)	162 (4.1)	179 (3.4)	181 (2.5)	160 (4.5)	250 (7.8)	126 (4.4)	182 (5.4)
Physiotherapy	37 (0.7)	35 (1.2)	49 (1.5)	55 (1.4)	90 (1.7)	182 (2.6)	37 (1)	40 (1.2)	21 (0.7)	59 (1.8)
Nursing visits	39 (0.8)	57 (1.9)	35 (1)	55 (1.4)	28 (0.5)	144 (2)	29 (0.8)	22 (0.7)	25 (0.9)	56 (1.7)
Other health professionals visits	5 (0.1)	8 (0.3)	7 (0.2)	9 (0.2)	4 (0.1)	39 (0.5)	4 (0.1)	15 (0.5)	1 (0)	16 (0.5)
Pharmacy	1578 (31.4)	350 (11.8)	498 (14.8)	469 (11.7)	564 (10.8)	864 (12.1)	777 (21.7)	944 (29.5)	220 (7.7)	397 (11.8)
Medical device	288 (5.7)	201 (6.8)	131 (3.9)	275 (6.9)	956 (18.4)	295 (4.2)	80 (2.2)	56 (1.7)	124 (4.3)	138 (4.1)
Laboratory test	99 (2)	63 (2.1)	85 (2.5)	67 (1.7)	80 (1.5)	87 (1.2)	74 (2.1)	130 (4)	49 (1.7)	81 (2.4)
Technical Medical Procedures	74 (1.5)	54 (1.8)	81 (2.4)	90 (2.3)	104 (2)	93 (1.3)	101 (2.8)	110 (3.4)	57 (2)	81 (2.4)
Transport	159 (3.2)	107 (3.6)	88 (2.6)	107 (2.7)	183 (3.5)	286 (4)	94 (2.6)	35 (1.1)	160 (5.6)	85 (2.5)
Hospitalizations	1827 (36.4)	1401 (47.5)	1345 (40)	1831 (45.7)	1863 (35.8)	4142 (58.2)	1500 (42)	658 (20.6)	1731 (60.7)	1384 (41.2)
Disability Benefits	245 (4.9)	152 (5.1)	276 (8.2)	287 (7.2)	479 (9.2)	303 (4.3)	205 (5.7)	91 (2.9)	69 (2.4)	176 (5.2)
Sick Leave	380 (7.6)	309 (10.5)	460 (13.7)	482 (12)	532 (10.2)	266 (3.7)	412 (11.5)	708 (22.1)	182 (6.4)	565 (16.8)
Others	34 (0.7)	12 (0.4)	30 (0.9)	23 (0.6)	30 (0.6)	103 (1.4)	19 (0.5)	15 (0.5)	15 (0.5)	39 (1.2)
Total	5 021 €	2 952 €	3 366 €	4 007 €	5 207 €	7 116 €	3 575 €	3 202 €	2 852 €	3 363 €

* The percentage (%) of each expenditure item was calculated for each primary cancer population.

III.3.4 Multivariate analysis of survivor characteristics associated with health care expenditures

Table 9 shows the estimations of the GLM model after adjusting for the survivor characteristics. Total health care expenditures were higher as age increased (beta = 0.04, $p < 0.0001$), in female gender (beta = 0.30, $p < 0.0001$), in patients with CNS tumours (beta = 0.70, compared with neuroblastoma, $p < 0.0001$), in patients treated between 2 and 4 years of age (beta = 0.36, compared with age 0–1 years, $p = 0.05$) and among survivors who died between 2011 and 2016 (beta = 1.85, $p < 0.0001$). Annual health care expenditures of survivors from the FCCSS were not significantly higher than expenditures of survivors from the FRANCIM (beta = 0.12, $p = 0.23$). These results did not vary when excluding the variable ‘death’ from the model or when excluding deceased survivors from the study population (Models II and III, respectively).

Table 9. Multivariate analysis of survivor characteristics associated with health care expenditures

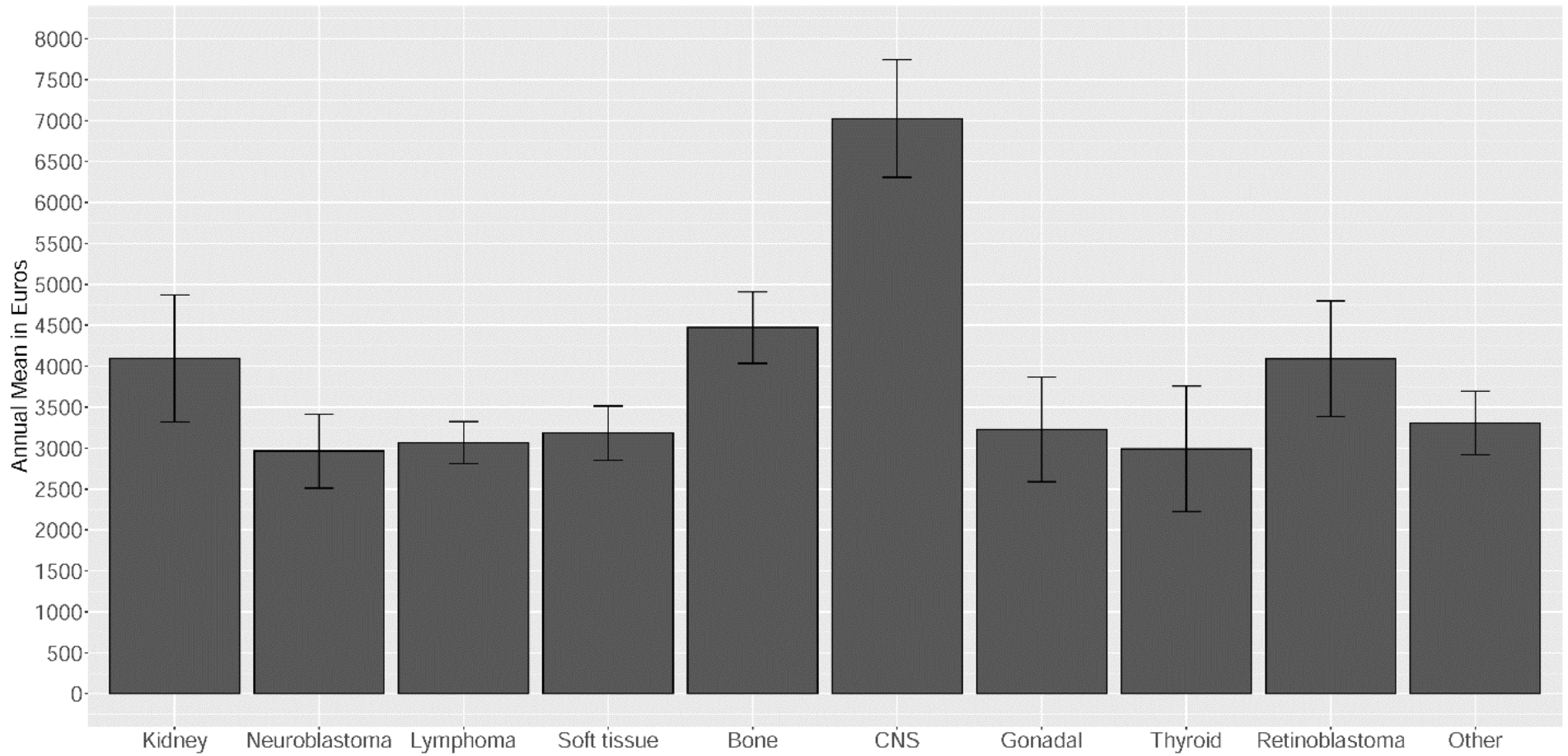
	Total Patients (n=5,319)				Patients Alive (n=5,152)	
	Model I		Model II		Model III	
	Beta	Pr > Z	Beta	Pr > Z	Beta	Pr > Z
Intercept	11.54	0.69	1.26	0.96	21.67	0.45
Female (Ref = Male)	0.30	<.0001	0.27	<.0001	0.31	<.0001
Age	0.04	<.0001	0.06	<.0001	0.04	<.0001
French Index Deprivation	0.02	0.47	0.04	0.27	0.03	0.40
Year of Diagnosis	0.00	0.85	0.00	0.86	-0.01	0.59
Age at first cancer (Ref = 0-1)						
2-4	0.36	0.05	0.33	0.06	0.37	0.05
5-9	0.08	0.64	0.07	0.69	0.10	0.56
10-14	0.16	0.50	0.08	0.72	0.20	0.38
≥15	-0.03	0.92	-0.16	0.57	0.04	0.90
First primary cancer type (Ref = Neuroblastoma)						
Kidney tumours	0.19	0.46	0.32	0.17	0.20	0.46
Lymphoma	-0.12	0.54	0.03	0.86	-0.13	0.50
Soft tissue sarcomas	-0.03	0.87	0.07	0.71	-0.04	0.83
Bone sarcomas	0.30	0.14	0.41	0.04	0.30	0.14
Central nervous system tumour	0.70	<.0001	0.86	<.0001	0.72	<.0001
Gonadal/Germ cell tumours	0.08	0.77	0.08	0.74	0.09	0.74
Thyroid tumour	0.01	0.98	0.01	0.98	0.02	0.95
Retinoblastoma	0.05	0.79	0.32	0.13	0.02	0.92
Other solid cancer	-0.05	0.81	0.11	0.59	-0.05	0.80
FCCSS Survivors	0.12	0.23	0.14	0.16	0.12	0.22
Dead	1.85	<.0001

* A generalised linear model using gamma distributions. Model I was adjusted using all variables. Model II excluded the ‘death’ variable. Model III excluded dead patients.

Figure 8 shows the adjusted annual mean health care expenditure from the gamma model by the type of primary cancer. CNS tumour survivors had the highest annual mean of € 7,000 per year. Survivors of neuroblastoma, lymphoma, soft tissue sarcomas, gonadal tumours, thyroid tumours and other solid tumours had the lowest values and a similar annual mean of health care expenditure between € 3,000–3,500, whereas survivors of kidney tumours, bone sarcomas and retinoblastoma had a similar mean expenditure of around € 4,000–4,500 per year.

Finally, we investigated each item of the health care expenditures separately and found that women had significantly higher adjusted expenditures than men, for all items, except for disability benefits, other health professional visits, pharmacy and medical devices (Supplementary Table 7). Male survivors from the FCCSS had higher adjusted expenses than the ones from the FRANCIM; this difference was not observed in women (interaction $p < 0.001$) (Supplementary Figure 2). Lastly, there was no global interaction between the type of primary cancer and whether CCS were from the FCCSS or the FRANCIM (Supplementary Figure 3).

Figure 8. Adjusted* annual mean health care expenditures by the type of primary cancer.



* Adjusted by age, sex, year of diagnosis, age at diagnosis, French index deprivation, cohort and type of primary cancer. Type of primary cancer: Kidney tumor, neuroblastoma, lymphoma, soft tissue sarcoma, bone sarcoma, central nervous system tumor (CNS), gonadal tumor, thyroid tumor, retinoblastoma and other solid cancer.

III.4 Discussion

To our knowledge, this is the first detailed study of the economic burden of CCS in France. We found that the annual mean health care expenditure among the 5,319 long-term CCS between 2011 and 2016 was € 4,255, mainly driven by expenditures on hospitalisations and pharmacy. Additionally, we showed that women had higher expenditures than men, and that CNS tumour survivors had the highest expenditures. Although the FCCSS survivors had higher expenditures than those from the FRANCIM, this difference was no longer significant when adjusting for the childhood cancer type, demographics and the geographical social deprivation index.

CCS have a high rate of illnesses due to chronic health conditions (113) and require significantly more health care resources than the general population (57). A previous study showed that their hospitalisation rates were almost twofold higher and their hospital stay was 35% longer than for patients without a cancer history (58). Consequently, their medical needs translate into substantial health care expenditures. In the United States, CCS were more likely to have out-of-pocket medical costs (114), and up to 33% of them were unable to see a doctor or go to the hospital due to financial issues (115).

Annual medical expenditures in adolescent or young adult cancer survivors (15–35 years old) has been estimated at \$7,417 (116), while annual productivity loss among adult survivors of childhood (< 14 years at diagnosis) cancer was estimated at \$8,169 (117). In Norway, survivors of cancer at a young age have a 4–5-fold increased risk of not being employed and receiving governmental financial assistance than general population (118). However, it is important to keep in mind that since the 1990s, the rate of iatrogenic events has decreased because of the reduction in the use of radiotherapy and, more recently, it could be anticipated that this risk will continue to decrease, in particular because of the emergence of proton therapy (119).

We also highlighted that only a few CCS, especially those who died during the follow-up period, were the main expenditure drivers. Most of these deaths were related to childhood cancer recurrence during the first two decades and to treatment-related sequelae including cardiovascular diseases and second malignant neoplasms (120). The mean expenditure during the last year of life in patients with lung and colorectal cancer has been estimated at up to € 43,000 in France (121,122), a finding that correlates with our results.

Our findings showing that female survivors have a higher annual mean total health care expenditure and several specific expenditures items are in agreement with several studies that have

shown that hospitalisations occur more often among females survivors (123,124), mostly due to endocrine, metabolic and nutritional disorders and subsequent neoplasms (125). Additionally, we included all the health care expenditures associated with pregnancies and perinatal conditions in our analysis. Moreover, female survivors have higher rates of miscarriage or preterm birth than the general population, including risks to both the mother and the foetus (126), which could at least partly explain the difference in the health care utilisation compared with male survivors.

As expected, expenditures were also higher in CNS tumour survivors. A previous study showed that the cumulative burden of chronic health conditions at age 50 years was higher in childhood CNS tumour survivors than in any other CCS (127). This, together with the evidence that survivors of CNS tumours have at least one disability condition (128), are less likely to progress in educational attainment (72) and have a higher risk of unemployment and reduced incomes compared with the cancer-free population (118,129), explains their high health care expenditures. Additionally, progressive disease or relapses more than 5 years after diagnosis of a brain tumour in children is common, particularly in slowly evolving, low-grade tumours (130).

Despite the fact that the FCCSS survivors had been treated in specialised cancer centres, and thus could have been more adverse cases or received a more intensive treatment, there was no significant difference in long-term expenses when adjusting for demographic factors and the type of childhood cancer compared with other CCS in France. Although the FCCSS survivors were younger at the time of diagnosis and were recruited in early years compared with survivors from French cancer registries, the FCCSS survivors were not particularly older than those from FRANCIM during the follow-up period of this study (Supplementary Table 4).

A strength of our study is the large sample of long-term survivors collected from two data sources (the FCCSS and the FRANCIM). The period of inclusion of our data started in 1945, which allowed us to evaluate the role of the period of diagnosis. We used a national administrative database, which allowed us to account for comprehensive health care expenditures over 6 years.

However, our study is subject to some limitations. First, the data for a cancer-free control group were not available, which limited our results to the CCS population. The processes to obtain this kind of data in France has been slowed and delayed by the COVID-19 pandemic. Second, the FRANCIM is a network of population-based registries that does not have national coverage. Third, we were unable to address the association between cancer treatments received by survivors and health care expenditures, due to the lack of therapeutic information in survivors from the

FRANCIM. Overall, our findings provide the first estimation of annual expenditures and the economic burden of CCS in France by type of childhood cancer, and demographic characteristics of survivors. Additionally, transferability to other contexts may be limited to the France territory.

In summary, we estimated and described the magnitude of health care expenditures related to consequences in adulthood of having had cancer treated in childhood. These high expenditures relative to the age of survivors were mainly driven by hospitalisation, pointing to the need for a more in-depth investigation into this item. Chapter IV presents a detailed overview of the high risks of hospitalisations in CCS compared with the general population for a better understanding of their particular needs.

Chapter IV Long-term hospitalisations in survivors of paediatric solid tumours

IV.1 Introduction

The late effects of treatments for childhood cancers may lead to severe and multiple health conditions requiring hospitalisation (58). Some studies that evaluated long-term risk of hospitalisation among CCS in the United States and Europe have reported an overall increased risk in survivors compared with general population (58,59,123–125,131). In addition, their average length of stay in the hospital was up to 35% longer than that of patients without cancer history (57). In Chapter III, we found that the leading expenditure item was hospitalisation, which represented 45% of total health care expenditure. In France, there are about 50,000 CCS, and this number continues to increase (132). However, no studies have analysed and detailed hospitalisation rates in long-term CCS.

The aim of this chapter was to estimate hospitalisation rates among CCS residing in France in comparison to those of the French general population. We also described the hospitalisation-related clinical diagnoses and investigated cancer-related factors associated with an increased rate of hospitalisation.

IV.2 Materials and methods

IV.2.1 Study population

The FCCSS is a retrospective cohort of CCS diagnosed for solid cancer. Detailed information on the methods for data collection and patients are presented in Chapter II.1. To study the FCCSS hospitalisation records, we selected survivors who were alive in January 2006, living in metropolitan France and who were linked to the SNDS. When we conducted this study, we obtained the updated SNDS data for the FCCSS from the second linkage that increased the number of FCCSS survivors followed through the SNDS to more than 5,500 (Chapter II.3.2) (Supplementary Figure 4).

IV.2.2 Reference sample

We obtained a reference sample for the FCCSS survivors from the EGB. Detailed information on the EGB is provided in Chapter II.2.4. Health care claims including the PMSI are available for the

EGB; however, hospitalisations from the PMSI SSR and PSY are not provided. We selected the reference sample by matching for sex, year of birth and region (French administrative area) of residence and randomly assigned them to each FCCSS survivor with the same characteristics. We did not limit the number of ‘controls’ included in the reference sample to ensure that each survivor had a good representation of the average hospitalisations in the general population.

IV.2.3 Hospitalisation measures

Using the PMSI, we obtained hospitalisation records in conventional hospital units (MCO) from January 2006 to December 2018 or death, whichever came first, for each CCS and individual of the reference population. Our endpoints of interest were (1) the total number of hospitalisations and (2) the total number of bed days spent in hospital, which is the number of days in which the patient stays overnight in hospital (in-patient) – that is, excluding day hospital visits. We grouped hospitalisations according to primary diagnosis into the 19 main groups of the ICD-10, excluding the following: certain conditions originating in the perinatal period (P00–P96), external causes of morbidity and mortality (V01–Y98) and codes for special purposes (U00–U99). This approach allowed us to focus on hospitalisation potentially linked to childhood cancer sequelae, and the pregnancy and childbirth codes (O00–O99), which require special considerations and will be investigated in other publications outside this thesis.

IV.2.4 Statistical analysis

We calculated the hospitalisation and bed-day rates for the FCCSS and reference populations as the total number of hospitalisations or bed days divided by the number of PY at risk and expressed them as a rate per 1,000 PY. We did not count the time during hospitalisation as time at risk when calculating the hospitalisation rates. To compare the hospitalisation rates of FCCSS survivors to the reference population, we calculated: (1) the absolute excess risk (AER) as the difference between the hospitalisation/bed-day rate of the FCCSS and the reference population expressed per 1,000 PY, and (2) the relative hospitalisation rates (RHR) and relative bed-day ratios (RBDR) with their corresponding 95% CI as the division of the hospitalisation/bed-day rates for the FCCSS and reference population based on the assumption that the observed number of hospitalisation/bed days followed a Poisson distribution. We calculated the AER, RHR and RBDR for overall hospitalisations and for each main ICD-10 group.

We used a GLM to model the number of hospitalisations and bed days. We used the expected number of hospitalisations or bed days as an offset to study the risk for the FCCSS survivors

relative to that for the reference population. We adjusted the models for sex, year of cancer diagnosis, age at cancer diagnosis, age in 2006, type of primary cancer, and cancer treatment(s) received (i.e., chemotherapy, radiotherapy and/or both). We chose neuroblastoma as the reference for type of primary cancer variable because it represents one of the larger groups of cancer of same histology. Risk estimates are reported as RR and 95% CI. Finally, we executed separate models for each main ICD-10 group to evaluate risk factors in the different types of hospitalisations. We used the SAS 9.4 software (SAS Institute, Cary, NC, USA) and considered $p < 0.05$ to be statistically significant.

IV.3 Results

We included a total of 5,439 FCCSS survivors and 386,073 reference people in the study. Each CCS was assigned an average of 71 (73.9) unique ‘controls’. Between 1 January 2006 and 31 December 2018, 3,756 CCS (69%) and 208,217 reference people (54%) had at least one hospitalisation. By the end of the follow-up, 383 (7%) CCS and 38,458 (10%) reference people had died. About 28% of FCCSS patients were less than 20 years old at time of start of the SNDS follow-up in 2006, and 10% were ≥ 40 years (Table 10). The average delay between childhood cancer treatment and 2006 was 19.9 years (IQR 12–26).

IV.3.1 Total numbers of hospitalisations and bed-days

The following results are summarised in Table 11. We identified 27,598 hospitalisations in FCCSS survivors, which accounted for 74,814 in-patient bed days. The hospitalisation rate was 401.2 per 1,000 PY while the bed-day rate was 1084.4 per 1,000 PY. In the matched reference population, the hospitalisation rate was 161.3 per 1,000 PY and the bed-day rate was 311.1 per 1,000 PY. Hence, for the FCCSS survivors the AER was 239.9 per 1,000 PY for hospitalisation and 773.2 per 1,000 PY for in-patient bed days. The RHR was 2.49 (95% CI 2.46–2.52, $p < 0.001$), meaning that FCCSS survivors were hospitalised more than twice as often as the matched reference population. Additionally, they had more than three times as many in-patient bed days as the reference population (RBDR 3.49, 95% CI 3.46–3.51, $p < 0.001$). When excluding hospitalisations for neoplasms, which could be linked both by long term relapses of childhood cancer and second neoplasms, the RHR was 2.12 (95% CI 2.08–2.15) and the RBDR was 3.36 (95% CI 3.33–3.38).

IV.3.2 Hospitalisations and bed-days by the main diagnostic groups

FCCSS survivors were more frequently hospitalised and had more in-patient bed days than the matched reference population for all diagnostic groups. The highest AER were observed in neoplasm-related hospitalisations (105.8), followed by diseases of the genitourinary system (34.4), factors influencing health status and contact with health services (other factors; 26.6), and diseases of the circulatory system (19.2). Mental and behavioural disorders and auditory-related hospitalisations had the lowest AER (0.6 and 0.7, respectively) (Figure 9 and Table 11). The details of the main diagnoses of the hospitalisations are reported in Supplementary Table 9.

As a general matter, for all diagnostic groups, hospitalisations were more frequent in FCCSS survivors than in the matched reference population and their stays were longer. The RBDR were higher than the RHR, except for endocrine and haematological diseases (Figure 10 and Table 11). The RBDR was particularly pronounced for hospitalisations related to the nervous system and the genitourinary system, with > 5 times as many in-patient bed-days as the reference population (RBDR: 5.74, 95% CI 5.57–5.91, and RBDR: 5.50, 95% CI 5.40–5.60, respectively).

Table 10. Survivor characteristics and hospitalisation and bed-day rates.

	Total Patients (%)	Patients Hospitalized (%)	N° Hospitalizations	Hospitalization rate in FCCSS (per 1,000 PY)	Hospitalization rate in EGB (per 1,000 PY)	AER per 1,000 PY	RHR (95% CI)	N° Bed-days	Bed-Days rate in FCCS (per 1,000 PY)	Bed-Days rate in EGB (per 1,000 PY)	AER per 1,000 PY	RBDR (95% CI)
All	5439	3756	27598	401.2	161.3	240.0	2.49 (2.46-2.52)	74814	1084.4	311.1	773.3	3.49 (3.46-3.51)
Gender												
Male	2970 (54.6)	1982 (52.8)	13646	363.5	145.4	218.1	2.5 (2.46-2.54)	35870	952.9	313.6	639.3	3.04 (3.01-3.07)
Female	2469 (45.4)	1774 (47.2)	13952	446.6	177.4	269.2	2.52 (2.48-2.56)	38944	1242.3	308.6	933.7	4.03 (3.99-4.07)
Age in January 2006 (start date)												
<20	1535 (28.2)	783 (20.8)	4012	202.0	85.9	116.1	2.35 (2.28-2.43)	7755	390.0	136.3	253.7	2.86 (2.8-2.93)
20-30	2066 (38)	1488 (39.6)	10665	407.1	111.4	295.7	3.66 (3.59-3.73)	27159	1033.7	182.7	851.0	5.66 (5.59-5.73)
31-40	1311 (24.1)	1038 (27.6)	8125	496.0	165.8	330.2	2.99 (2.93-3.06)	23168	1408.9	304.5	1104.4	4.63 (4.57-4.69)
>=41	527 (9.7)	447 (11.9)	4796	756.5	287.0	469.5	2.64 (2.56-2.71)	16732	2620.3	630.7	1989.6	4.15 (4.09-4.22)
Status in December 2018 (ending date)												
Alive	5056 (93)	3389 (90.2)	19606	298.9	163.7	135.2	1.83 (1.8-1.85)	44789	681.5	310.8	370.7	2.19 (2.17-2.21)
Dead	383 (7)	367 (9.8)	7992	2509.9	139.4	2370.5	18 (17.61-18.4)	30025	9192.1	314.3	8877.8	29.25 (28.92-29.58)
Year of diagnosis												
<1970	351 (6.5)	300 (8)	2925	688.3	300.9	387.4	2.29 (2.21-2.37)	10688	2498.0	677.7	1820.3	3.69 (3.62-3.76)
1970-1979	980 (18)	783 (20.8)	7387	611.4	197.1	414.3	3.1 (3.03-3.17)	19820	1633.2	375.3	1257.9	4.35 (4.29-4.41)
1980-1989	1809 (33.3)	1335 (35.5)	9905	433.3	129.5	303.8	3.34 (3.28-3.41)	29690	1294.1	227.8	1066.3	5.68 (5.62-5.75)
>=1990	2299 (42.3)	1338 (35.6)	7381	249.4	93.0	156.4	2.68 (2.62-2.74)	14616	493.2	150.3	342.9	3.28 (3.23-3.33)
Age at first cancer												
0-1	1288 (23.7)	770 (20.5)	5687	345.1	126.1	219.0	2.74 (2.67-2.81)	12031	728.7	227.3	501.4	3.21 (3.15-3.26)

2-4	1276 (23.5)	857 (22.8)	5864	362.9	146.6	216.3	2.48 (2.41- 2.54)	18753	1156.7	268.3	888.4	4.31 (4.25- 4.37)
5-9	1207 (22.2)	868 (23.1)	6617	437.5	164.5	273.0	2.66 (2.6- 2.73)	19619	1292.5	326.9	965.6	3.95 (3.9- 4.01)
10-14	1108 (20.4)	839 (22.3)	6839	492.1	193.7	298.4	2.54 (2.48- 2.6)	18031	1292.9	397.4	895.5	3.25 (3.21- 3.3)
≥15	560 (10.3)	422 (11.2)	2591	363.5	199.3	164.2	1.82 (1.75- 1.9)	6380	893.0	384.3	508.7	2.32 (2.27- 2.38)
First primary cancer type												
Other solid cancer	312 (5.7)	222 (5.9)	1622	414.1	152.8	261.3	2.71 (2.58- 2.84)	3645	928.2	285.9	642.3	3.25 (3.14- 3.35)
Kidney tumours	825 (15.2)	551 (14.7)	4712	453.1	172.1	281.0	2.63 (2.56- 2.71)	12249	1174.0	335.7	838.3	3.5 (3.44- 3.56)
Neuroblastoma	746 (13.7)	466 (12.4)	3124	327.1	126.7	200.4	2.58 (2.49- 2.67)	6727	703.1	219.9	483.2	3.2 (3.12- 3.27)
Lymphoma	931 (17.1)	669 (17.8)	4990	421.7	178.6	243.1	2.36 (2.3- 2.43)	12512	1054.3	363.2	691.1	2.9 (2.85- 2.95)
Soft tissue sarcomas	591 (10.9)	417 (11.1)	3098	410.7	184.1	226.6	2.23 (2.15- 2.31)	7680	1015.3	360.3	655.0	2.82 (2.76- 2.88)
Bone sarcomas	476 (8.8)	368 (9.8)	2428	400.9	187.0	213.9	2.14 (2.06- 2.23)	6129	1009.2	371.8	637.4	2.71 (2.65- 2.78)
Central nervous system tumour	708 (13)	567 (15.1)	4314	502.1	141.0	361.1	3.56 (3.45- 3.67)	15558	1801.7	286.3	1515.4	6.29 (6.2- 6.39)
Gonadal/Germ cell tumours	334 (6.1)	231 (6.2)	1441	337.2	182.7	154.5	1.85 (1.75- 1.94)	4731	1103.7	352.2	751.5	3.13 (3.04- 3.22)
Thyroid tumour	48 (0.9)	33 (0.9)	150	247.0	303.8	-56.8	0.81 (0.69- 0.95)	424	696.8	595.4	101.4	1.17 (1.06- 1.29)
Retinoblastoma	468 (8.6)	232 (6.2)	1719	285.8	105.0	180.8	2.72 (2.59- 2.85)	5159	855.8	165.7	690.1	5.17 (5.03- 5.31)
Treatment Received												
No radiotherapy or chemotherapy	720 (13.2)	394 (10.5)	1789	192.6	152.0	40.6	1.27 (1.21- 1.33)	3105	333.9	280.8	53.1	1.19 (1.15- 1.23)
Radiotherapy	696 (12.8)	549 (14.6)	4670	549.3	233.6	315.7	2.35 (2.28- 2.42)	15418	1804.4	500.9	1303.5	3.60 (3.55- 3.66)
Chemotherapy	1990 (36.6)	1236 (32.9)	7275	284.5	125.8	158.7	2.26 (2.21- 2.31)	19361	755.6	226.9	528.7	3.33 (3.28- 3.38)
Radiotherapy and Chemotherapy	2033 (37.4)	1577 (42)	13864	545.3	158.3	387.0	3.45 (3.39- 3.5)	36930	1446.8	297.7	1149.1	4.86 (4.81- 4.91)

FCCSS: French Childhood Cancer Survivor Study; EGB: General Sample of Beneficiaries; AER: absolute excess risk; PY: Person-Year; RHR: Relative Hospitalization Ratio; RBDR: Relative bed-days ratios.

Figure 9. The absolute excess risk (AER) of hospitalisation and bed day according to the International classification of diseases (ICD-10).

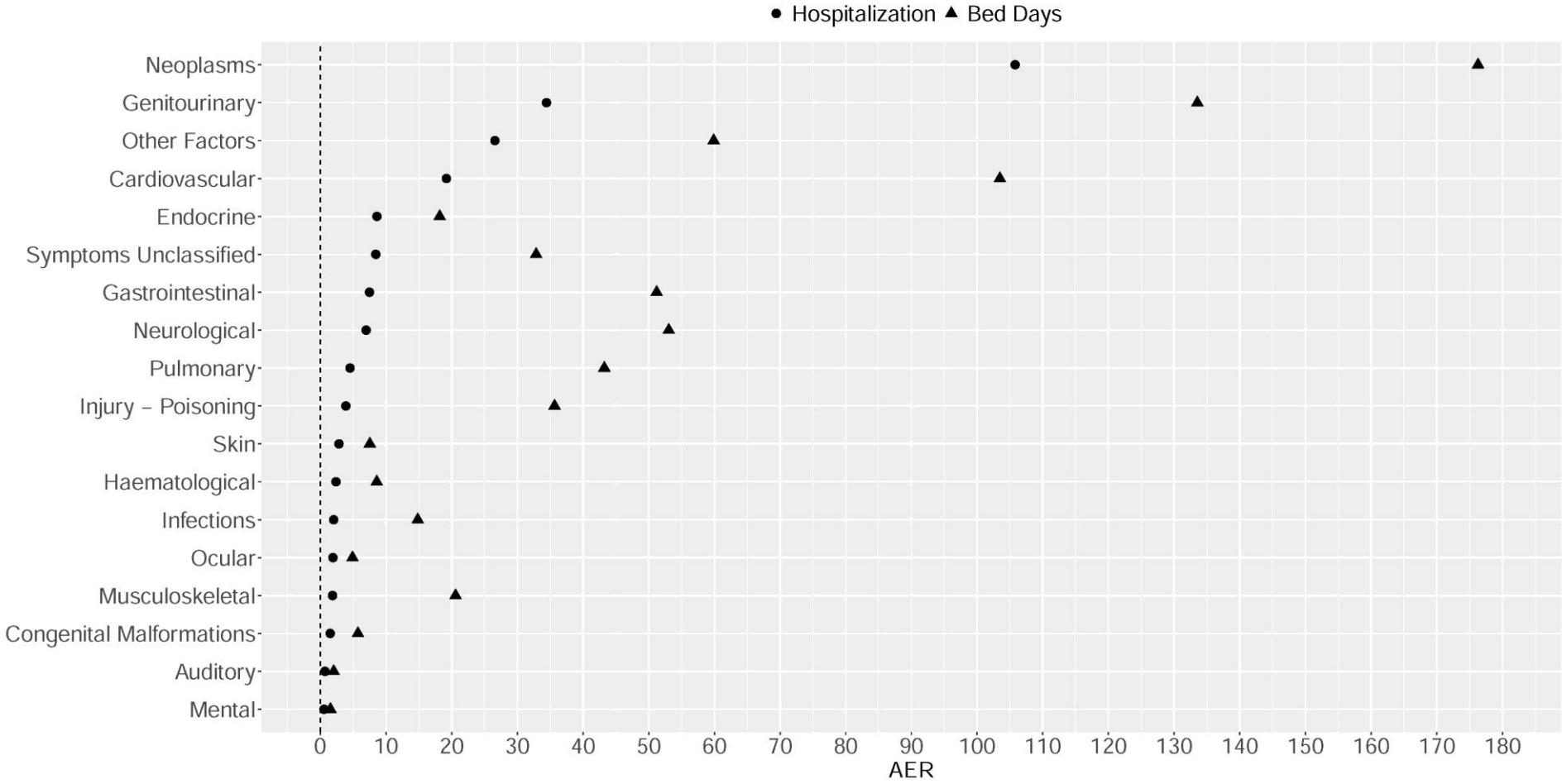
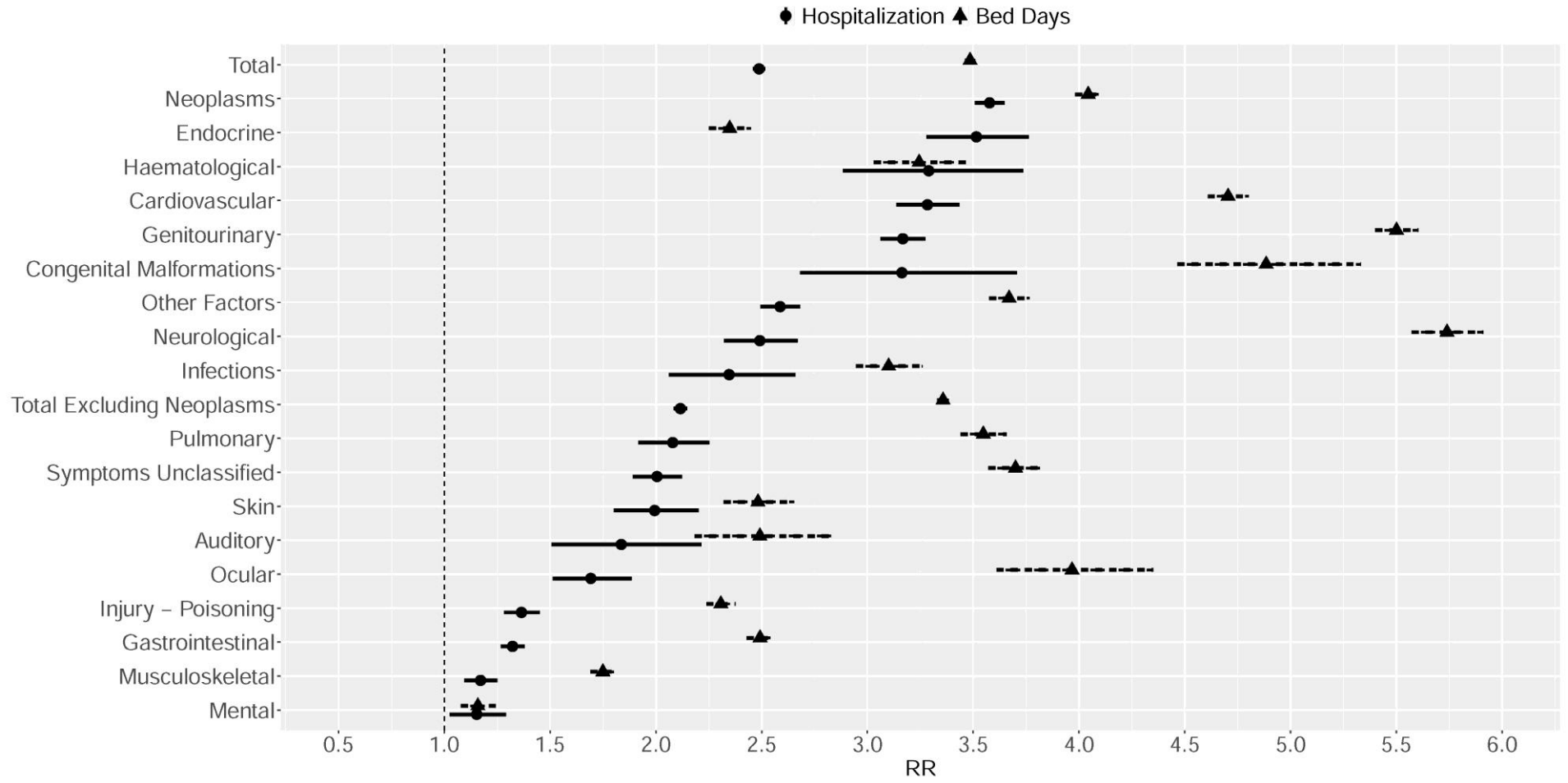


Figure 10. The relative hospitalisation and bed day ratios according to the International Classification of Diseases (ICD-10).



RR= Relative ratio

Table 11. Hospitalisations and bed days in the FCCSS survivors and the reference sample by the main ICD-10 groups.

	Hospitalizations							Bed-days in the hospital						
	N° Hospitalizations in FCCSS	Hospitalization rate in FCCSS (per 1,000 PY)	N° Hospitalizations in EGB	Hospitalization rate in EGB (per 1,000 PY)	AER per 1,000 PY	RHR	(95% CI)	N° Bed-Days in FCCSS	Bed-Days rate in FCCSS (per 1,000 PY)	N° Bed-Days in EGB	Bed-Days rate in EGB (per 1,000 PY)	AER per 1,000 PY	RBDR	(95% CI)
Total	27598	401.2	805758	161.3	240.0	2.49	(2.46 -2.52)	74814	1084.4	1555993	311.1	773.3	3.49	(3.46 -3.51)
Infections	245	3.6	7585	1.5	2.0	2.35	(2.06 -2.66)	1512	21.9	35350	7.1	14.8	3.10	(2.95 -3.26)
Neoplasms	10100	146.8	205097	41.0	105.8	3.58	(3.51 -3.65)	16156	234.2	289619	57.9	176.3	4.04	(3.98 -4.11)
Haematological	237	3.4	5233	1.0	2.4	3.29	(2.88 -3.74)	858	12.4	19169	3.8	8.6	3.24	(3.03 -3.47)
Endocrine	830	12.1	17153	3.4	8.6	3.51	(3.28 -3.76)	2185	31.7	67426	13.5	18.2	2.35	(2.25 -2.45)
Mental	300	4.4	18899	3.8	0.6	1.15	(1.03 -1.29)	782	11.3	48923	9.8	1.6	1.16	(1.08 -1.24)
Neurological	803	11.7	23414	4.7	7.0	2.49	(2.32 -2.67)	4433	64.3	55985	11.2	53.1	5.74	(5.57 -5.91)
Ocular	326	4.7	13992	2.8	1.9	1.69	(1.51 -1.89)	453	6.6	8277	1.7	4.9	3.97	(3.61 -4.35)
Auditory	109	1.6	4311	0.9	0.7	1.84	(1.51 -2.22)	236	3.4	6865	1.4	2.0	2.49	(2.18 -2.83)
Cardiovascular	1900	27.6	42035	8.4	19.2	3.28	(3.14 -3.43)	9065	131.4	139661	27.9	103.5	4.70	(4.61 -4.8)
Pulmonary	601	8.7	20994	4.2	4.5	2.08	(1.92 -2.25)	4155	60.2	84894	17.0	43.2	3.55	(3.44 -3.66)
Gastrointestinal	2113	30.7	116056	23.2	7.5	1.32	(1.27 -1.38)	5901	85.5	171616	34.3	51.2	2.49	(2.43 -2.56)
Skin	393	5.7	14316	2.9	2.8	1.99	(1.8 -2.2)	872	12.6	25460	5.1	7.5	2.48	(2.32 -2.65)
Musculoskeletal	881	12.8	54634	10.9	1.9	1.17	(1.1 -1.25)	3317	48.1	137421	27.5	20.6	1.75	(1.69 -1.81)
Genitourinary	3462	50.3	79401	15.9	34.4	3.17	(3.06 -3.27)	11259	163.2	148360	29.7	133.5	5.50	(5.4 -5.6)
Congenital Malformations	153	2.2	3514	0.7	1.5	3.16	(2.68 -3.71)	498	7.2	7390	1.5	5.7	4.88	(4.47 -5.33)
Symptoms	1160	16.9	42017	8.4	8.5	2.01	(1.89 -2.12)	3108	45.0	60888	12.2	32.9	3.70	(3.57 -3.83)
Unclassified														
Injury - Poisoning	1003	14.6	53385	10.7	3.9	1.36	(1.28 -1.45)	4344	63.0	136490	27.3	35.7	2.31	(2.24 -2.38)
Other Factors	2982	43.4	83722	16.8	26.6	2.59	(2.5 -2.68)	5680	82.3	112199	22.4	59.9	3.67	(3.57 -3.77)
Total Excluding Neoplasms	17498	254.4	600661	120.2	134.2	2.12	(2.08 -2.15)	58658	850.2	1266374	253.2	597.0	3.36	(3.33 -3.38)

FCCSS: French Childhood Cancer Survivor Study; EGB: General Sample of Beneficiaries; AER: Absolute Excess Risk; PY: Person-Year; RHR: Relative Hospitalization Ratio; RBDR: Relative bed-days ratios.

IV.3.3 Association between survivor characteristics and hospitalisations and bed days

Type of primary cancer

Figure 11 illustrates the RHR and the RBDR by the type of primary cancer. Hospitalisation rates were significantly higher in all types of primary cancer compared with the reference population, except in survivors of thyroid tumours (RHR 0.81, 95% CI 0.69–0.95) (Table 10). CNS tumour survivors had the highest RHR (3.56, 95% CI 3.45–3.67) and the highest RBDR (6.29, 95% CI 6.20–6.39) (Table 10). In detail, CNS survivors were most likely to be hospitalised for congenital malformations (RHR 14.34 95% CI 11.22–18.06), diseases of the nervous system (RHR 10.48, 95% CI 9.44–11.61) and endocrine-related diseases (RHR 10.45, 95% CI 9.29–11.7), with a very high RBDR for the first two groups of pathologies (33.88, 95% CI 30.27–37.81, and 32.19, 95% CI 31.02–33.39, respectively), but not for endocrine-related diseases (Supplementary Table 10).

In multivariate analysis, compared with neuroblastoma, survivors of thyroid tumours were at a lower risk of both hospitalisations and in-patient bed days (RR 0.66, 95% CI 0.56–0.78, and RR 0.73, 95% CI 0.66–0.80, respectively), while survivors of CNS tumours (RR 1.29, 95% CI 1.22–1.36), kidney tumours (RR 1.09, 95% CI 1.04–1.14) and other primary cancers (RR 1.39, 95% CI 1.30–1.48) were at higher risk (Table 12). The in-patient bed-day risk was higher among survivors of CNS tumours, gonadal tumours and retinoblastoma (Table 12).

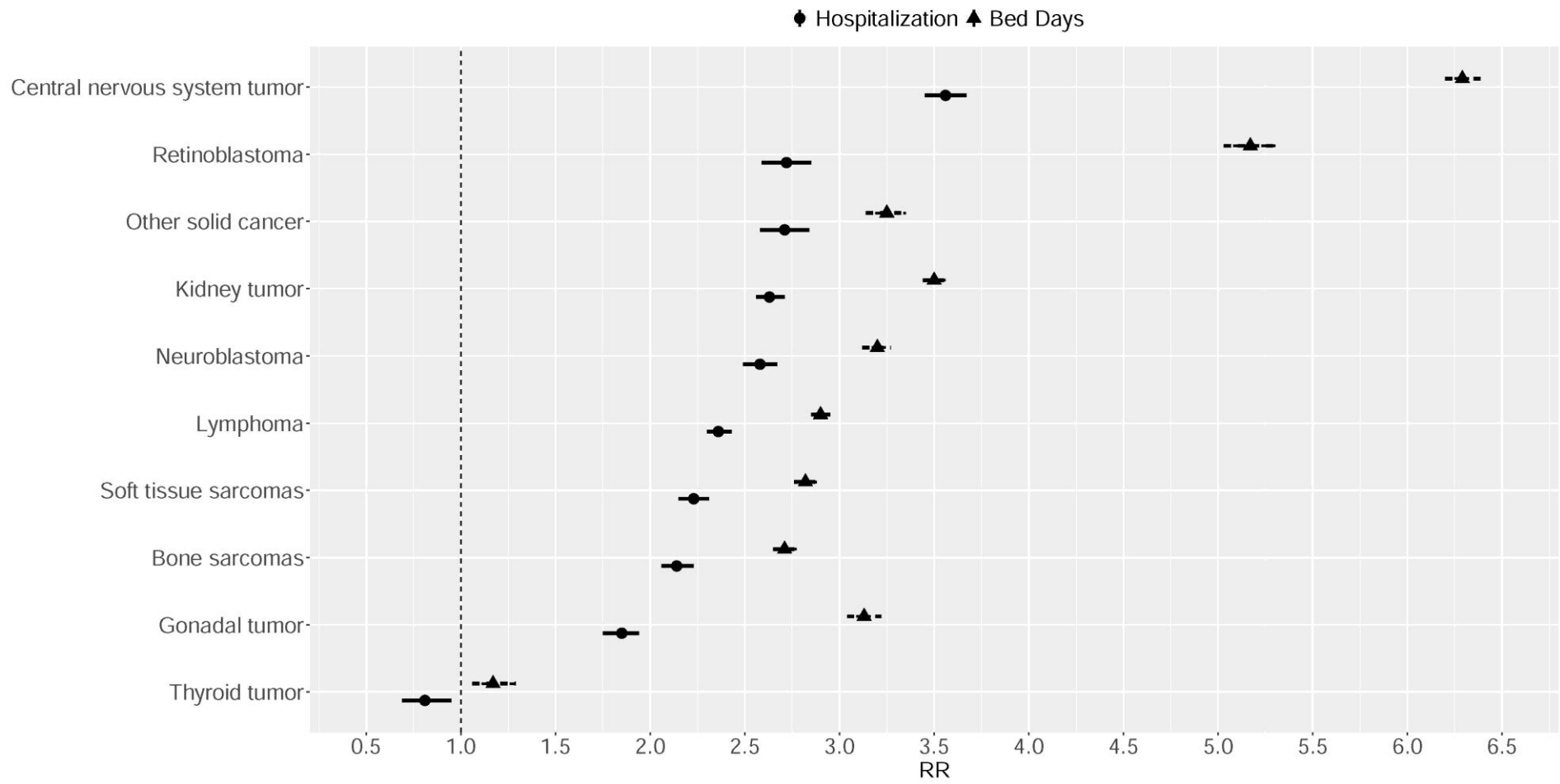
Gender

Women in the FCCSS were hospitalised slightly more frequently and accumulated more bed days than men (Table 10). In an adjusted analysis, compared with the reference population, female CCS had a lower relative hospitalisation risk (RR 0.97, 95% CI 0.95–0.99) than male CSS; however, they had a higher in-patient bed-day risk (RR 1.29, 95% CI 1.27–1.31) (Table 12).

Year of diagnosis, age at childhood cancer diagnosis, age in 2006

In a univariate analysis, there was no clear variation in the RHR according to the year of diagnosis and the age at childhood cancer diagnosis, nor with the age at time of start of the SNDS follow-up in 2006 (Table 10). There was an increase in the AER as the age in 2006 increased, showing that the increase in hospitalisation rates with increasing age was higher in the FCCSS than in the French general population. Similar results were observed for in-patient bed days (Table 10).

Figure 11. The relative hospitalisation and bed-day ratios by type of primary cancer.



In a multivariate analysis, the variations in the adjusted RBDR significantly decreased as the age at childhood cancer diagnosis increased (Table 12). In a more detailed multivariate analysis of the RHR (Supplementary Table 13) and the RBDR (Supplementary Table 14), we found no pattern of variation in the coefficients of age at childhood cancer in each hospitalisation category model, except for a decrease in RHR for genitourinary and skin diseases at childhood cancer diagnosis increased (Supplementary Table 13). On the other hand, the RHR and RBDR significantly decreased as the age in 2006 increased, and they were higher in patients treated between 1970 and 1990 than in the patients treated after 1990 (Table 12).

IV.3.4 Association between initial treatments and hospitalisations and bed days

Survivors treated with surgery or who did not receive treatment had a small increase in hospitalisation rates (RHR 1.27, 95% CI 1.21–1.33) (Table 10). However, both hospitalisation and bed-day risks increased in survivors treated with chemotherapy (RR 1.62, 95% CI 1.53–1.70, and RR 2.63, 95% CI 2.53–2.74, respectively) and radiotherapy (RR 2.11, 95% CI 1.98–2.22, and RR 2.72, 95% CI 2.61–2.83, respectively) and were higher in survivors treated with both (RR 2.60, 95% CI 2.46–2.73, and RR 3.72, 95% CI 3.58–3.86, respectively) compared with survivors who did not receive these treatments (Table 12). In the same way, chemotherapy was associated with a significant increase in hospitalisations related to neoplasms and endocrine and cardiovascular diseases, an increase that was reinforced by radiotherapy (Supplementary Table 13). Chemotherapy was the most important risk factor for hospitalisations related to diseases of the genitourinary system (RHR 6.53, 95% CI 5.34–7.99) and diseases of the blood (RR 3.59, 95% CI 1.69–7.66), while radiotherapy was a determinant for nervous system hospitalisations (RR 1.81, 95% CI 1.34–2.44) (Supplementary Table 13). The multivariate analyses yielded similar results for bed days in the different hospitalisation groups (Supplementary Table 14).

Table 12. Multivariate analysis of the total number of hospitalisations and bed days.

	Number of Hospitalizations	Number of Bed-Days
	RR (95% CI)	RR (95% CI)
Intercept	1.79 (1.66 -1.93) ***	0.93 (0.89 -0.98) ***
Female (Ref = Male)	0.97 (0.95 -0.99) ***	1.29 (1.27 -1.31) ***
Age in 2006	0.99 (0.99 -0.99) ***	0.99 (0.98 -0.99) ***
Year of Diagnosis (Ref = >1990)		
<1970	1.05 (0.93 -1.19)	1.86 (1.73 -2) ***
1970-1979	1.32 (1.22 -1.43) ***	1.82 (1.74 -1.9) ***
1980-1989	1.34 (1.27 -1.41) ***	2.07 (2.01 -2.13) ***
Age at first cancer (Ref = 0-1)		
2-4	0.89 (0.86 -0.93) ***	1.38 (1.35 -1.41) ***
5-9	0.99 (0.94 -1.03)	1.33 (1.29 -1.37) ***
10-14	1.04 (0.99 -1.11)	1.23 (1.19 -1.28) ***
≥15	0.83 (0.77 -0.9) ***	1 (0.96 -1.05)
First primary cancer type (Ref = Neuroblastoma)		
Other solid cancer	1.39 (1.3 -1.48) ***	1.4 (1.34 -1.47) ***
Kidney tumors	1.09 (1.04 -1.14) ***	0.98 (0.95 -1.01)
Lymphoma	0.99 (0.94 -1.04)	0.98 (0.95 -1.01)
Soft tissue sarcomas	0.97 (0.92 -1.03)	0.95 (0.91 -0.98) ***
Bone sarcomas	1.01 (0.95 -1.08)	1.03 (0.99 -1.07)
Central nervous system tumor	1.29 (1.22 -1.36) ***	1.97 (1.9 -2.03) ***
Gonadal/Germ cell tumours	1.02 (0.96 -1.1)	1.39 (1.34 -1.45) ***
Thyroid tumor	0.66 (0.56 -0.78) ***	0.73 (0.66 -0.8) ***
Retinoblastoma	0.98 (0.92 -1.04)	1.59 (1.54 -1.65) ***
Treatment (Ref = No radiotherapy or chemotherapy)		
Chemotherapy	1.62 (1.53 -1.70) ***	2.63 (2.53 -2.74) ***
Radiotherapy	2.10 (1.98 -2.22) ***	2.72 (2.61 -2.83) ***
Radiotherapy and Chemotherapy	2.60 (2.46 -2.73) ***	3.72 (3.58 -3.86) ***

RR: Risk ratio; CI: Confidence interval; *** p<0.01, ** p<0.05

IV.4 Discussion

In this cohort of 5,439 five-year solid CCS, we found that individuals treated for childhood cancer in 1940–2000 in France were hospitalised more than twice as often the general population during a 13-year follow-up (2006–2018). This increase in the hospitalisation rate was most important among cancer survivors treated with chemotherapy and/or radiotherapy. The hospitalisation rates were elevated for all the main ICD-10 groups of hospitalisation-related pathologies, especially for neoplasms and genitourinary system and cardiovascular diseases.

Our results are consistent with similar studies performed in the United States, Canada, the Nordic countries and the Netherlands in which CCS experienced higher hospitalisation rates compared with the general population of their countries (58,59,123–125,131). European studies have reported similar RHR to ours: around 2 in the Netherlands (131) and Nordic countries (59), and about 2.8 in Scotland. The RBDR in Scotland was similar to our study at 3.7 (133), but the RBDR was higher in the Nordic countries, namely 4.96 (59). On the other hand, a small Utah cohort and the large U.S. Childhood Cancer Survivor Study (CCSS) (58,124) reported lower hospitalisation rates, probably because most of the children in those studies were treated after the 1970s, i.e. treated more recently than the FCCSS, and hospitalisations were examined through questionnaires, i.e. accuracy of hospitalisations, or at earlier periods i.e. immediately after the end of treatment and not in the long term.

Previous studies have shown that survivors were more at risk of hospitalisation due to neoplasms, recurrences and/or subsequent neoplasms (58,59,125,133,134). These findings are similar to our findings in which both the AER and RHR were the highest in this category. Survivors were hospitalised because of blood disorders more often in two North American studies (58,134). However, our results indicate that although blood disorders have a higher RHR, the hospitalisation rate and the AER were among the lowest in this category. This outcome could be partially explained by the fact that our cohort did not include leukaemia survivors. One study from the United Kingdom reported that CCS had a 4-fold risk of being hospitalised for cardiovascular disease compared with the general population (135). Another study from the Netherlands (125) reported a high RHR but not a high AER for endocrine conditions, which is consistent with our findings. On the other hand, a study in the Nordic countries showed that excess hospitalisations were mainly due to nervous system diseases (59).

Researchers have reported significantly increased hospitalisation rates in Hodgkin lymphoma (124) and CNS (134) and bone (58,125) tumour survivors compared with other primary cancer types. Our results showed a few variations in the RHR according to primary cancer types, except for survivors of thyroid and CNS tumours. High hospitalisation rates for diseases of the CNS and congenital malformations have also been reported in survivors of CNS tumours (133); however, reclassification of neurofibromatosis from a tumour of uncertain behaviour in the ICD-9 to a congenital malformation in the ICD-10 partially explains their excess hospitalisation. On the contrary, in one study, kidney tumour survivors were not at additional risk of hospitalisation (58) and in another study they had among the lowest hospitalisation rate (124), which disagrees with our findings. This could be explained because we counted day-hospital admissions, which include dialysis. In fact, our results showed that kidney tumour survivors have a high risk of genitourinary-related hospitalisations, in which dialysis is classified.

Among the FCCSS survivors, women had slightly higher hospitalisation and bed-day rates than men (446.6 vs 363.5 and 1242.3 vs 952.9 per 1,000 PY, respectively). When compared with the reference population, there was a similar RHR for women and men but a higher AER in both hospitalisation and bed days, and a higher RBDR in women. These results are similar to those observed in the population-based cohort performed in Utah (58). However, they are not similar to another population-based cohort study performed in another U.S. state, in which both the RHR and AER were higher for women (123), or to the U.S. CCSS, in which women had a much lower RHR and AER than men (124). In the Netherlands, two studies evidenced a higher hospitalisation rate but a lower RHR in women than in men (125,131), whereas in the Scotland (133) the standardised bed days ratio was almost similar in women and men.

Our findings are consistent with those of earlier studies in the Netherlands in which survivors initially treated with radiotherapy had particularly increased hospitalisation rates for neoplasms, endocrine-related diseases and diseases of the circulatory system (125,136). Another study in British Columbia, Canada, reported that hospital-related morbidity was elevated for all combinations of primary treatment and was highest for those with previous radiation, chemotherapy and surgery (134). We identified chemotherapy as a factor associated with several types of hospitalisations especially for genitourinary system diseases, where cisplatin and ifosfamide have been established to cause treatment-related chronic renal damage in CCS (137).

Unexpectedly, we did not identify a variation in the RHR according to the age at childhood cancer (136). Our results regarding the variations in the RHR and RBDR according to year of childhood

cancer diagnosis and age in 2006 have to be cautiously considered because these two variables are linked – that is, survivors treated earlier are likely to be older at the start of the follow-up.

As a general matter, the differences in results between studies are hardly explained by difference in the demographic and clinical characteristics of the patients included in these studies. Their investigation probably needs to perform meta-analysis on individual data. Our results should be interpreted with caution because the SNDS data are only available for 2006–2018, which starts several years after the FCCSS recruitment period (1945–2000). Thus, a selection bias could occur in older patients at the time of onset of the SNDS data. Patients treated before 1970, for example, who survived until 2006 are not representative of all patients treated before 1970 and correspond to a different distribution of the types of treatments.

To our knowledge, this is the first detailed study of the hospitalisations of long-term CCS compared with the general population in France. We used a national administrative database, which allowed us to account for comprehensive information on hospitalisations over 13 years between both CCS and their reference population. One of the strengths of our study is that we accounted for hospitalisations in day-hospital units. In addition, our bed-day analysis, which excluded these hospitalisations, allowed us to focus on the more severe hospitalisations that require more medical care.

Our study is subject to some limitations. First of all, we were not able to identify hospitalisations related to relapse or metastasis of childhood cancer to the ones related to secondary neoplasms. Secondly, we considered only hospitalisations in conventional hospital units, due to the unavailability information of the rehabilitation and psychiatry institutions in the EGB sample, which constitutes our reference. We thus underestimated hospitalisations rates, especially mental-related hospitalisations. Nevertheless, the conventional hospital units treats more than 90% of all patients hospitalized in France (138). Moreover, giving that the EGB includes a population not consuming any health care and the data are stored for a period of 20 years (99), the EGB allows to carried out longitudinal studies of hospitalisations (139). Third, we could not address the association between specific types of hospitalisations and specific therapeutic modalities (e.g., chemotherapy and radiation doses) because this requires special considerations; we will investigate these issues in separate publications. Finally, FCCSS included only patients from five non-profit private cancer treatment centres in France, which are not representative of all French childhood cancer treatment centres. Nevertheless, we have evidenced that this did not impact the medical expenditures for long-term survivors (Chapter III) (140).

In summary, we showed that the hospitalisation and in-patient bed-day rates among CCS in France were more than twice as high than in the general population. In the next chapter, we focus on estimating the excess health care expenditures of CCS that results from this overuse of health services compared with the general population.

Chapter V Excess health care expenditures in survivors of paediatric solid tumours

V.1 Introduction

As presented in Chapter I, CCS carry a significant risk of developing long-term side effects from both the illness itself and cancer treatment, which may impact virtually any organ or organ system. In addition, the socioeconomic consequences in adulthood continue to pose challenges among long-term survivors and could increase the use of social security benefits, such as those for unemployment, sickness, disability or permanent invalidity (81,82), varying from country to country.

In Chapter III, we showed that the annual mean health care expenditure for adult CCS in France was more than € 4,200 (140). However, we were not able to compare their expenditure with that of the general population or estimate the cancer-attributable (excess) cost of care in the long term. This information is useful to understand the long-term consequences of survivorship, to improve follow-up programmes for CCS, to evaluate the long-term cost-effectiveness of cancer treatment and to plan budgets.

The objectives of this chapter were to estimate excess health care expenditure for long-term CCS in France compared with the general population, with the same sex, age and region of residence, and to investigate the associated factors leading to the excess.

V.2 Materials and methods

V.2.1 Study population

As in the previous chapters, we selected all survivors included in the FCCSS (Chapter II.1), who lived in metropolitan France and were linked to the SNDS until 2018 (Chapter II.3.2). However, we set the start date of the study for January 2011 to ensure we collected confirmed data on reimbursement for hospitalisations, similarly to the study design presented in Chapter III.2.1. Finally, the comparison group, set up for Chapter IV.2.2, comprised all patients from the EGB who fit with the FCCSS survivors for sex, age and region of residence.

V.2.2 Estimating excess healthcare expenditure

We conducted this analysis from the perspective of the public payer (the CNAM) in the compulsory reimbursement scheme. Based on the reimbursement's information, we summed direct health care expenditures for each calendar year and for each survivor and controls between January 2011 and December 2018, or date of death, whichever came first. We then estimated the annual excess health care expenditure as the difference between the expenditure for the CCS and the median expenditure for their controls. We used the median instead of the mean because the data on health care expenditures were strongly positively skewed, especially in the controls.

Our primary outcome variable was the total excess of direct healthcare expenditure for every calendar year for each CCS. We also stratified the excess by items and these were classified, for every year, into fourteen categories. All expenditures were expressed after correcting for the effect of inflation using the consumer price index with a 2015 base year provided by the INSEE.

V.2.3 Statistical analysis

First, the CCS characteristics are described, along with estimation of the annual mean excess expenditure over the 2011–2018 period. Categorical variables are expressed as numbers and percentages and continuous variables as the mean \pm SD and 95% CI. Excess health care expenditures are described by item and according to the type of primary cancer.

We used linear mixed models to assess the association between excess health care expenditures and the survivor characteristics. Because we computed the excess expenditures for each survivor with a different number of controls, we weighted the models according to the number of controls used for each survivor in each year. We adjusted the models for sex, age in 2011, the French deprivation index in 2009, the year of cancer diagnosis, the age at cancer diagnosis and the type of primary cancer and cancer treatment(s) received (i.e. no radiotherapy or chemotherapy, chemotherapy, radiotherapy or both). Finally, we performed several sub-analyses, estimating models for each expenditure item and each type of primary cancer. We used the SAS 9.4 software (SAS Institute, Cary, NC, USA) and considered $p < 0.05$ to be statistically significant.

V.3 Results

V.3.1 Survivor characteristics

We included a total of 5,353 FCCSS survivors and 382,757 controls in the study. The mean \pm SD

number of controls per survivor was 71.5 ± 73.6 . Approximately 46% were women and 51% were > 30 years old in 2011 (the start of follow-up). The most common childhood primary cancer in the cohort was lymphoma (17.2%), followed by kidney tumour (15.1%), neuroblastoma (13.8%) and CNS tumours (12.7%). Most survivors were treated after the 1980s and 37.2% received both radiotherapy and chemotherapy (Table 13). The mean time between childhood cancer treatment and 2011 was 24.7 years (IQR 17–31). By the end of the follow-up (December 2018), 254 (4.7%) of the CSS had died.

V.3.2 Excess healthcare expenditures

The weighted annual mean health care expenditure of CCS and the weighted median expenditure for their controls was € 4,203 and € 283, respectively (data not shown). Thus, the annual mean excess health care expenditure was € 3,920 (95% CI € 3539–4301). As expected, this variable was positively skewed due to a few very high values among the survivors (Supplementary Figure 5). The unadjusted annual mean excess was higher in women than in men (€ 4,058 vs € 3,783), in older patients (€ 5,948 in patients over 40 years old in 2011), in those treated before the 1970s (€ 5,836) and in survivors of CNS tumours (€ 6,712) (Table 13). Patients who were treated with chemotherapy alone had a 2.5 times lower annual mean excess than those who received only radiotherapy (€ 2,279 vs € 5,917) but a higher annual mean excess than patients not treated with radiotherapy or chemotherapy (€ 1,830). Those who died during follow-up had an annual mean excess of > 5 times higher than those who did not (€ 18,369 vs € 3,261).

The details of health care expenditures by health care item are reported in Table 14. Over the entire cohort, the highest expenditure was for hospitalisation (€ 1,552), which represented 39.6% of the total excess, followed by pharmacy (€ 668) with 17%. These two health care resources were used at least once during the follow-up period by more than 70% of the survivors. Other important items were medical devices (€ 324), sick leave (€ 377) and disability benefits (€ 387). It should be noted that health care expenditures for transportation were higher than for all types of medical visits.

Table 13. Survivor characteristics and excess health care expenditures.

	Number of patients (%)	Annual mean excess of healthcare expenditures per patient in Euros (95 % confidence interval)
All	5353	3920 (3539 ; 4301)
Gender		
Male	2919 (54.5)	3783 (3164 ; 4403)
Female	2434 (45.5)	4058 (3617 ; 4500)
Age in January 2011 (start date)		
<20	818 (15.3)	908 (670 ; 1145)
20-30	1814 (33.9)	3042 (2552 ; 3532)
31-40	1699 (31.7)	3938 (2927 ; 4950)
>=41	1022 (19.1)	5948 (5200 ; 6695)
French geographical deprivation index 2009		
1 Quintile	2192 (40.9)	4120 (3319 ; 4921)
2 Quintile	970 (18.1)	3757 (3078 ; 4436)
3 Quintile	764 (14.3)	3757 (2972 ; 4541)
4 Quintile	712 (13.3)	3484 (2737 ; 4230)
5 Quintile	715 (13.4)	4209 (3328 ; 5089)
Status in December 2018 (ending date)		
Alive	5099 (95.3)	3261 (2908 ; 3614)
Dead	254 (4.7)	18369 (15051 ; 21686)
Year of cancer diagnosis		
<1970	336 (6.3)	5836 (4662 ; 7010)
1970-1979	951 (17.8)	5798 (4540 ; 7056)
1980-1989	1780 (33.3)	4109 (3522 ; 4696)
>=1990	2286 (42.7)	1810 (1554 ; 2067)
Age at cancer diagnosis		
0-1	1277 (23.9)	2571 (2070 ; 3071)
2-4	1253 (23.4)	4495 (3280 ; 5709)
5-9	1183 (22.1)	3886 (3366 ; 4405)
10-14	1084 (20.3)	4918 (4080 ; 5757)
≥15	556 (10.4)	3892 (2969 ; 4815)
First primary cancer type		
Kidney tumours	810 (15.1)	4594 (2979 ; 6209)
Neuroblastoma	738 (13.8)	2498 (1842 ; 3155)
Lymphoma	920 (17.2)	3962 (3240 ; 4683)
Soft tissue sarcomas	583 (10.9)	4030 (3122 ; 4938)
Bone sarcomas	471 (8.8)	4283 (3471 ; 5094)
Central nervous system tumours	679 (12.7)	6712 (5267 ; 8158)
Gonadal tumours	331 (6.2)	3750 (2410 ; 5089)
Thyroid tumours	47 (0.9)	3511 (1268 ; 5754)
Retinoblastoma	467 (8.7)	1798 (1242 ; 2354)
Other solid cancers	307 (5.7)	2609 (1519 ; 3698)
Treatment Received		
No radiotherapy or chemotherapy	717 (13.4)	1830 (1256 ; 2404)
Radiotherapy	672 (12.6)	5917 (4807 ; 7028)
Chemotherapy	1974 (36.9)	2279 (1912 ; 2645)
Radiotherapy and chemotherapy	1990 (37.2)	5143 (4359 ; 5928)

*: Ecological Index measuring the deprivation, and based on the median household income, the percentage of high school graduates in the population aged 15 years and older, the percentage of blue-collar workers in the active population, and the unemployment rate. The fifth quintile represents the most disadvantaged area.

Table 14. Excess health care expenditures by item.

	Number of patients (%)	Number of claims	Total excess of health care expenditure over the follow-up period in million euros (%)	Annual mean excess healthcare expenditure per -patient in euros (95 % CI) *
General practitioner visits	5082 (94.9)	170039	2.2 (1.5)	60 (56 ; 64)
Specialist visits	5030 (94.0)	208804	5.3 (3.6)	142 (133 ; 152)
Physiotherapy visits	2428 (45.4)	166592	3.2 (2.2)	87 (74 ; 99)
Nursing visits	3797 (70.9)	154089	2.8 (1.9)	74 (54 ; 95)
Other health professional visits †	811 (15.2)	19879	0.6 (0.4)	17 (11 ; 23)
Pharmacy	5107 (95.4)	699570	24.8 (17)	668 (450 ; 886)
Medical devices	4447 (83.1)	72039	12.1 (8.3)	324 (272 ; 377)
Laboratory tests	4683 (87.5)	130378	2.9 (2)	77 (71 ; 83)
Technical Medical Procedures ‡	4790 (89.5)	65872	3.6 (2.5)	96 (85 ; 108)
Transport	1976 (36.9)	34006	6.0 (4.1)	162 (140 ; 185)
Hospitalizations	3773 (70.5)	42670	57.8 (39.6)	1552 (1355 ; 1749)
Disability Benefits §	384 (7.2)	17854	14.4 (9.9)	387 (305 ; 470)
Sick Leave	2731 (51)	49507	14.0 (9.6)	377 (337 ; 417)
Others	709 (13.2)	5076	1.9 (1.3)	49 (28 ; 70)
Total	5353	1836375	145,90 €	3920 (3539 ; 4301)

* Annual mean expenditure per-patient in € were calculated for the entire population (n=5,353). † Other health professional visits included expenditures related to visits to podiatrists, optometrists, speech therapists, and others. ‡ Technical medical procedures included expenditures mainly related to medical imaging techniques. § Disability benefits included all welfare payments or pensions made by the French Government to assist people with disabilities.

V.3.3 Excess healthcare expenditures by type of primary cancer

Figure 12 shows the distribution of excess health care expenditures by item according to the type of primary cancer. Although hospitalisations were the main driver for the excess in most cancer groups, pharmacy was the most important item among thyroid tumour survivors (€ 1,346), representing 35.7% of their total annual excess (Supplementary Table 16). Pharmacy was also a major item for kidney tumour survivors (€ 1,408) and gonadal tumour survivors (€ 1,037), representing 29.6% and 26.4% of the total annual excess, respectively. Sick leave was a major item among neuroblastoma, lymphoma, soft tissue sarcoma, bone sarcoma and thyroid tumour survivors, representing > 11% of the total annual excess, while medical devices were an important item for bone sarcoma survivors (€ 986), representing 22% of their total annual excess.

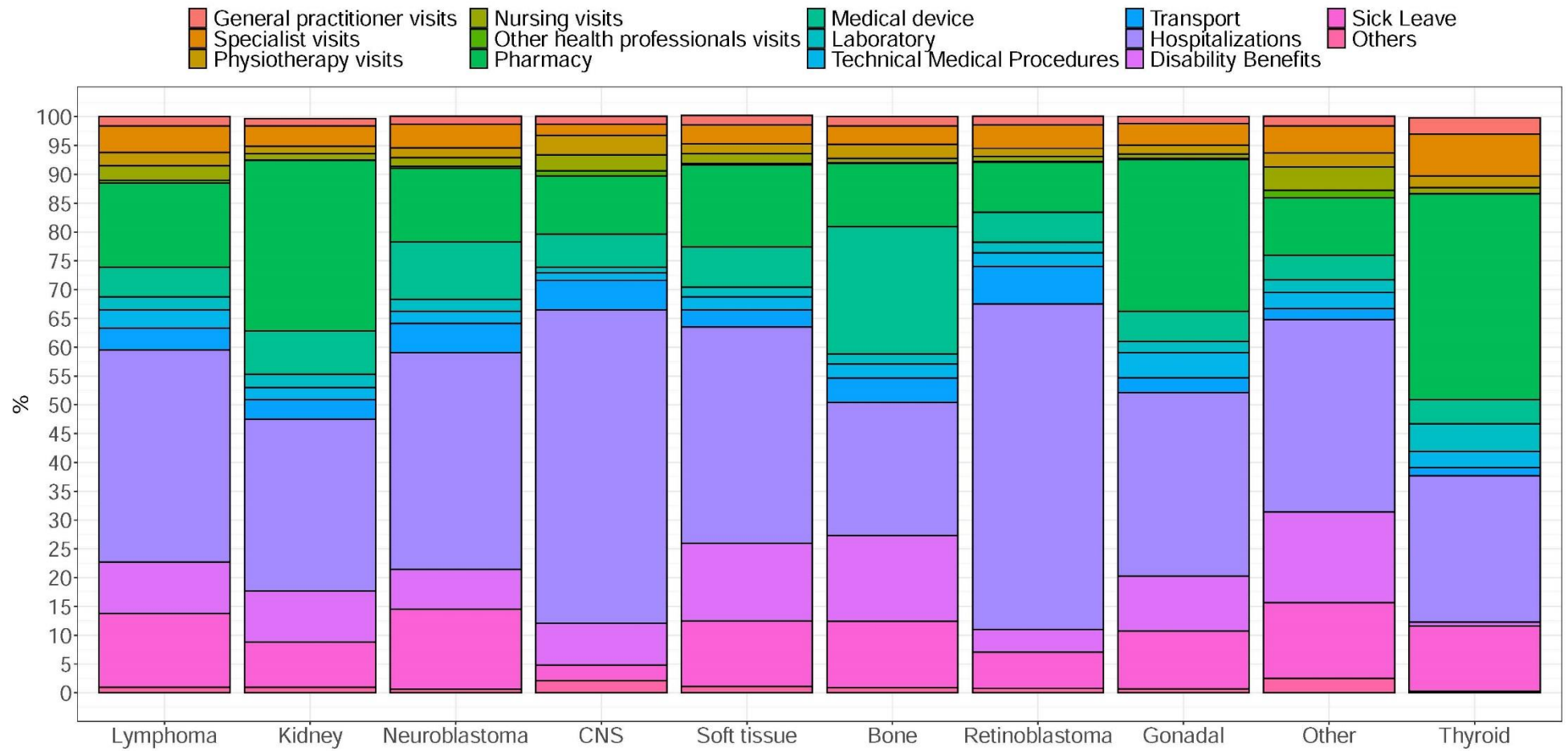
Regarding CNS tumour survivors, almost 55% of the total annual excess was due to hospitalisations (€ 3,732). In addition, these patients had, on average, a higher annual excess for physiotherapy, nursing and other health professional visits and transportation compared with the other primary cancer types. However, the annual excess on sick leave among these patients was among the lowest of the other cancer types, with a mean of € 186 (Supplementary Table 16).

V.3.4 Factors associated with excess healthcare expenditures

Table 15 presents estimates of the linear mixed model after adjusting for survivor characteristics. The increase in excess health care expenditure with each passing year among survivors was € 231 ($p \leq 0.01$). The annual mean excess health care expenditure was higher among the survivors treated in the 1980s (€ 2306; $p \leq 0.01$), the 1970s (€ 3848; $p \leq 0.01$) and before the 1970s (€ 4389; $p \leq 0.05$) compared with the survivors treated after the 1990s (Table 15). CNS tumour survivors also had a higher annual expenditure compared with survivors of other types of primary cancers.

The total annual excess was not significantly higher among female compared with male survivors (€ 231; $p = 0.48$) (Table 15), except in lymphoma and soft tissue sarcoma survivors (Supplementary Table 17). However, in the sub-analysis of each health care expenditure item, being a woman was associated with a higher excess for specialist, physiotherapy and nursing visits; laboratory tests; technical medical procedures; and sick leave (Supplementary Table 18).

Figure 12. Distribution of excess health care expenditure by item and the type of primary cancer*.



* Type of primary cancer: lymphoma, kidney tumours, neuroblastoma, central nervous system (CNS) tumours, soft tissue sarcomas, bone sarcomas, retinoblastoma, gonadal tumours, other solid cancers and thyroid tumours.

Table 15. Multivariate analysis: predictors of annual excess health care expenditures.

	Beta	Pr > Z
Intercept	4217.94	< 0.01 ***
Time in years	231.63	< 0.01 ***
Female (Ref = Male)	231.95	0.5
Age at January 2011	-13.01	0.8
French geographical deprivation index (Ref = 1 Quintile)		
2 Quintile	-294.42	0.54
3 Quintile	-629.98	0.22
4 Quintile	-839.07	0.12
5 Quintile	-312.09	0.55
Year of Diagnosis (Ref = >1990)		
<1970	4389.18	0.01 ***
1970-1979	3848.18	< 0.01 ***
1980-1989	2306.94	< 0.01 ***
Age at first cancer	88.46	0.17
First primary cancer type (Ref = Central nervous system tumour)		
Kidney tumours	-2274.48	< 0.01 ***
Neuroblastoma	-3237.60	< 0.01 ***
Lymphoma	-3166.94	< 0.01 ***
Soft tissue sarcomas	-2555.28	< 0.01 ***
Bone sarcomas	-2681.82	< 0.01 ***
Gonadal tumour	-2930.01	< 0.01 ***
Thyroid tumour	-4325.84	0.01 ***
Retinoblastoma	-2936.16	< 0.01 ***
Other solid cancer	-3454.80	< 0.01 ***
Treatment (Ref = Radiotherapy)		
No radiotherapy or chemotherapy	-1910.54	0.01 ***
Chemotherapy	-1464.65	0.02 ***
Radiotherapy and chemotherapy	513.71	0.36

*** p<0.05

CNS tumour survivors had a significantly higher annual mean excess expenditure for general practitioner, physiotherapy and nursing and other health professional visits; transport; and hospitalisation compared with survivors of other types of primary cancers (Supplementary Table 18). However, sick leave expenditure in CNS tumour survivors was significantly lower. Bone sarcoma survivors had a significantly higher annual mean excess expenditure for medical device and disability benefits, whereas thyroid tumour and kidney tumour survivors had a significantly higher annual mean excess expenditure for specialist visits and laboratory tests compared with CNS tumour survivors (Supplementary Table 18).

Regarding treatment, survivors not treated with radiotherapy or chemotherapy (−€ 1910; $p \leq 0.01$) and survivors treated with chemotherapy alone (−€ 1464; $p < 0.05$) had a significantly lower annual mean excess health care expenditure compared with those treated with only radiotherapy (Table 15). Survivors treated with radiotherapy and chemotherapy had a higher annual excess, although it was not significant, than those treated with only radiotherapy, but it was significant for general practitioner visits, technical medical procedures and sick leave (Supplementary Table 18). Moreover, survivors treated with chemotherapy alone were associated with a lower annual mean excess expenditure for general practitioner, specialist and physiotherapy visits; medical devices; laboratory tests; hospitalisations; and disability benefits (Supplementary Table 18).

V.4 Discussion

In this study, we were able to compare health care expenditures in CCS with the general population and to detail the long-term costs attributable to childhood cancer. We found that the annual mean excess health care expenditure for CCS was € 3,920. Of note, this excess was mainly composed of hospitalisation and pharmacy expenses. CCS treated before the 1990s and CNS tumour survivors had a higher annual excess, while CCS who had not received treatment with radiotherapy had a lower annual excess. This work fills an important gap in the literature regarding the economic burden of childhood cancer survivorship in a publicly funded health care system.

Given the risk of developing late effects, CCS require significantly more health care resources over their lifetime than the general population (57). Several studies have shown that in high-income countries, CCS have a higher risk of hospitalisation (58,59,123–125,141), contacting their primary care physician (61,142) and being economically dependent (143) and unemployed (77), particularly CNS tumour survivors (69), than the general population. Consequently, CCS are more likely to experience financial hardship (e.g. higher out-of-pocket payments) as a result of medical costs more specifically in health care systems that are not publicly funded (89,90). While the cost attributable to adolescent and young adult cancer survivors in the long term (age 15–35 years at their first cancer diagnosis) has been estimated at \$3,170 (116) in the United States, to our knowledge this is the first study that has estimated the long-term costs attributable to childhood cancer.

Although we found in a previous study that female survivors had a higher annual health care expenditure than male survivors (140), our current findings suggest that the excess is not significantly higher. However, this overall result masks the fact that being a female survivor is

associated with a higher excess for physiotherapy and nursing visits, technical medical procedures, disability benefits and sick leave, extending the results of Streefkerk et al. (142), who showed that female sex is a determinant for more primary care physician-based health care use.

We also showed that CNS tumour survivors had the highest annual mean excess expenditure. This result is consistent with several studies that have shown that CNS tumour survivors have a higher risk of having poor health and socioeconomic conditions, including having at least one disability indication condition (128), lower educational attainment (72) and a higher risk of unemployment (77) and social security benefit uptake (81) than the cancer-free population. Sick leave expenditure was significantly lower in CNS survivors, suggesting that they are not part of the working population.

Regarding the influence of the period during which the patient was treated for cancer, we observed that having been treated before 1980 (before 1970 and between 1970 and 1979) compared with being treated after 1990 increased the excess expenditure (about € 4,300 and € 3,800, respectively). It was also the case, but to a lesser extent, for those treated between 1980 and 1989 (about € 2,300). This may reflect the therapeutic progress that has been made. Treatment of solid tumours has moved from a purely surgical approach to the addition of radiotherapy and then to multimodal treatment based primarily on chemotherapy after the 1980s (14,144). In the 1970s and 1980s, studies began to emerge documenting the long-term health effects of childhood cancer treatment and suggesting the need for LTFU (145).

All other things being equal, the type of treatment received influences the annual excess expenditure. CCS treated with radiotherapy had an excess of more than € 1,400 compared with those treated with chemotherapy and a higher excess compared with those not treated with either (€ 1,900). These findings are consistent with studies from the Netherlands in which survivors treated with radiotherapy had a particularly increased hospitalisation rate for neoplasms, endocrine diseases and circulatory system diseases (125,136) and were nearly 1.5 times more likely to contact their primary care physician compared with CCS treated with chemotherapy only (142).

Efforts to reduce the cumulative doses (e.g. protection of healthy tissues during radiotherapy or decreased chemotherapy doses) and to improve monitoring are needed to reduce long-term toxicity and therefore costs. Newer types of radiotherapy, such as proton therapy, have been introduced to treat cancer with increasing promise to reduce both short- and long-term toxicities (119,146). In France, proton therapy is shown to be a priority for children and young adults in all three of its

centres (147). Although establishing and operating proton therapy centres is very expensive, the opportunity cost of expanding the care of such centres should be considered if the reduction in late effects and future health care costs is greater than the long-term costs of these centres.

There are some limitations to this study. First, we considered only hospitalisation in conventional hospital units because information regarding the PMSI SSR and PSY was not available in the EGB sample. Thus, we have underestimated hospitalisation costs, especially those related to mental health, where, for example, survivors of CNS tumours are likely to be treated. Nevertheless, the conventional hospital units treat more than 90% of all patients hospitalised in France (138). Second, we could not address the association between the annual mean excess health care expenditure and specific therapeutic modalities (e.g. chemotherapy regimens and/or radiation doses) because this requires special considerations; we will investigate this issue in separate publications. Lastly, the FCCSS included only patients from five non-profit private cancer treatment centres in France, which are not representative of all French childhood cancer treatment centres. However, in a previous study we found that this did not impact the medical expenditures of long-term survivors (Chapter III) (140).

In this chapter, we showed that long-term CCS had a high annual mean health care expenditure compared with the general population of the same age and sex, resulting in an important excess, especially among CNS tumour survivors and those who received radiotherapy. As the number of CCS is expected to increase, health authorities could use our findings to improve the organisation of care, in terms of medical follow-up and prevention of complications, in order to better anticipate the long-term effects and their associated medical expenses. Future research should focus on addressing the long-term cost effectiveness of new approaches to childhood cancer treatment, especially those related to radiotherapy.

Chapter VI General conclusion

This chapter summarises the main findings of the thesis and provides their potential implications for clinical care and our proposal for future research.

VI.1 Main findings

CCS are at long-term risk for a variety of serious late physical and mental health effects related to the disease and its treatment. This raises concerns about their long-term health care needs, including the utilisation of health care services and the costs of these services. In this thesis we studied the economic burden of long-term survivors of paediatric solid tumours in France.

In the three studies that we have presented in this thesis, 1) we quantified and detailed the health care expenditures of solid CCS in France; 2) we estimated the hospitalisation rates among CCS and described the hospitalisation-related clinical diagnoses compared with those of the French general population with the same sex, age and region of residence; and 3) we estimated the annual mean excess health care expenditure for long-term solid CCS in France compared with the general population mentioned above. We investigated cancer-related and socioeconomic factors associated with the outcomes of interest in all three studies. The research presented in this thesis is based on data from the FCCSS cohort, which includes 5-year survivors from five specialised anticancer centres before 2001 and the SNDS.

Our main findings can be summarised as seven key points:

1. *Health care expenditures in CCS are high.* In Chapter III, we found that the total direct health care expenditure for 5,300 CCS from two data source (the FCCSS and the FRANCIM) in France were € 134,523,643 over 6 years (2011–2016) of follow-up. The annual mean health care expenditure among solid CCS was € 4,255; it was slightly higher among FCCSS survivors ($n \approx 3500$) at € 4,556. Then, in Chapter V, when we were able to compare the health care expenditure of even more FCCSS patients ($n \approx 5300$) with that of the French general population. We found that the annual mean excess health care expenditure for CCS compared with the median of the general population was € 3,920 over 8 years (2011–2018) of follow-up.

However, it is important to mention that both the health care expenditure and the excess were positively skewed due to some very high values among a small number of CCS. The

median health care expenditure in our first study was € 494 (IQR 105–2151) (Chapter III). This could be partially explained by the intensive use of end-of-life health care services by survivors who died during the follow-up period in the SNDS. In Chapter III, we observed that the 167 survivors who died accounted for 13.4% of the total expenditures and had an annual mean expenditure of € 25,000.

2. *Health care expenditures in CCS mainly comprise hospitalisations and pharmacy.* We found that 61% of total health care expenditures among CCS were due to hospitalisations (45%) and pharmacy (16%) (Chapter III). Similarly, hospitalisation represented 39.6% of the total excess, followed by pharmacy at 17% (Chapter V). We found that 70% of CCS had hospital expenses during the 8 years (2011–2018) of follow-up. Finally, the annual mean excess among CCS for hospitalisation and pharmacy was € 1,552 and € 668, respectively (Chapter V).

3. *CCS experience significantly more hospitalisations over their lifetime than the general population.* In Chapter IV, we found that CCS were hospitalised more than twice as often as the matched reference population, and they had more than three times as many in-patient bed days during a 13-year follow-up (2006–2018). Even when excluding hospitalisations for neoplasms, which could be related to both long-term relapses of childhood cancer and second neoplasms, survivors were hospitalised twice as often as the general population.

In addition, we found the highest absolute excess risks in both the number of hospitalisations and in-patient bed days occurred for neoplasm-related hospitalisation, followed by diseases of the genitourinary system and the circulatory system, factors influencing health status and contact with health services.

4. *There are few differences in expenditures, but different patterns of health care use between male and female CCS.* In Chapter III, we found that health care expenditures were higher in women than in men (€ 4,795 and € 3,814), and adjusted analysis confirmed that being a woman was associated with a higher expenditure. In this study we considered all reimbursements, including those associated with pregnancies and perinatal conditions, potentially high due to the risk of infertility among female CCS caused by the treatment (148). In Chapter V, we showed that total excess health care expenditure was not significantly higher among female compared with male survivors (€ 231; $p = 0.48$).

The relative hospitalisation rate of female CCS was similar to that of men, but they had a

higher in-patient bed-day rate (Chapter IV). In addition, our detailed analysis of health care expenditure by item showed that being a woman was associated with a higher excess for specialist, physiotherapy and nursing visits; laboratory tests; technical medical procedures; and sick leave (Chapter V).

5. Health care expenditures are higher in CCS treated a long time ago. We reported that CCS diagnosed before 1980 had the highest annual mean health care expenditure of € 6,900 (Chapter III). Survivors treated long ago likely correspond with the older survivors at the start of the follow-up in the SNDS. However, in adjusted analysis, we observed a significant association between the decade of treatment and the annual excess health care expenditure among survivors treated in the 1980s (€ 2306; $p \leq 0.01$), the 1970s (€ 3848; $p \leq 0.01$) and before the 1970s (€ 4389; $p \leq 0.05$) compared with survivors treated after the 1990s (Chapter V).

6. Health care use and expenditures are higher in CNS tumour survivors. In all our studies we found that survivors of CNS tumours had worse outcomes compared with CCS of other primary cancers. This group of survivors had the highest hospitalisation and in-patient bed-day rates (Chapter IV). Specifically, CNS tumour survivors were more likely to be hospitalised for congenital malformations, nervous system diseases and endocrine diseases, with a very high bed-day rate in the first two groups.

Moreover, CNS tumour survivors had the highest annual mean health care expenditure of € 7,100 (Chapter III). Almost 55% of the total annual excess in this group of survivors was due to hospitalisations (Chapter V). CNS tumour survivors had a higher annual mean excess compared with survivors of other types of primary cancers. Specifically, the annual excess expenditure from general practitioner, physiotherapy, nursing and other health professional visits; transport; and hospitalisation were significantly higher among CNS tumour survivors than among survivors of other primary cancers (Chapter V).

7. Health care use and expenditures are higher among CCS treated with radiotherapy. We found that the hospitalisation and bed-day risks increased in survivors treated with radiotherapy, and even more in survivors treated with radiotherapy and chemotherapy (Chapter IV). Radiotherapy was associated with a significant increase in hospitalisations related to neoplasms and endocrine, neurological, ocular, pulmonary, genitourinary and cardiovascular diseases.

Furthermore, we found that survivors treated with only radiotherapy had a significantly higher annual excess health care expenditure compared with survivors not treated with radiotherapy or chemotherapy and survivors treated with chemotherapy alone (Chapter V). In detail, survivors treated with radiotherapy alone had a higher annual excess expenditure for general practitioner, specialist and physiotherapy visits; medical devices; laboratory tests; hospitalisations; and disability benefits compared with those treated with chemotherapy.

We have already compared our main results with the international literature and have discussed the strengths and limitations of our data in the previous chapters.

VI.2 Clinical implications

The findings of this thesis provide evidence of a higher risk of health care use and expenditure among CCS, leading to considerable excess compared with the median health care expenditure of the general population of the same sex and age. This high expenditure is related to multimorbidity, which is more common in survivors than in the general population. Therefore, our results lead us to recommend that special attention be paid to this population, especially in terms of follow-up and prevention of complications. Reducing the late effects of cancer treatment in CCS is a key to reducing healthcare spending. This requires a coordinated follow-up plan that provides the comprehensive and specialised care they need, along with early intervention strategies at key transition ages to overcome possible late effects and to improve the health and quality of life of survivors in adulthood.

In addition, identifying survivors at high risk of high health expenditures is necessary to implement interventions. Our results suggest special attention to survivors treated: 1) before the 1980s, 2) for a CNS tumour and 3) with radiotherapy. Older survivors, or those who have a longer interval since treatment completion, have been associated as predictors of not attending follow-up care (149). Efforts are needed to reach out and help these survivors access this specialised care. Regarding CNS tumours, both physicians and survivors and their families should be aware of the physical and socioeconomic late effects to facilitate early detection of health problems and to obtain the necessary social support. Lastly, our results suggest that one lever of action is the type of treatment administered, in particular radiotherapy, although the survivors examined in this thesis had been treated decades ago and treatment has evolved over time. Radiotherapists must consider the cost of the long-term effects of radiotherapy within their parameters and treatment plans to reduce

cumulative doses and toxicity.

Finally, health policymakers are encouraged to use the results of this thesis as a starting point, in economic terms, to improve the organisation of care, to better anticipate long-term effects and their associated medical costs and to guide health policies for childhood cancer in France.

VI.3 Perspectives for future research

The long-term health care utilisation and costs of childhood cancer remain poorly studied, especially in publicly funded health care systems. Understanding this will be an important pillar in developing strategies that better serve CCS and potentially reduce the costs to treat this population. Therefore, a careful prospective analysis and reports of all costs and utilisation patterns from childhood cancer diagnosis to the end of life in different cohorts at the national and international levels is needed. This could be followed by the creation of harmonised, evidence-based guidelines that consider the differences between health systems; these guidelines could be an important tool for health policymakers. In France, the interest in a systematic and permanent epidemiological surveillance of CCS has led to the creation of the national COHOPER cohort. This cohort is based on the National Registry of Childhood Cancer, includes all cases diagnosed in France since 2000 and is linked to the SNDS, which may present an opportunity to do so in the future.

Moreover, we want to emphasise that future research must consider the indirect costs that remain hidden, especially those incurred by family members who must receive education and support to help them manage the physical and emotional effects of cancer survivorship. This can include counselling, support groups and resources for managing chronic health conditions, which must be considered in the economic burden of the disease.

Although harmonised guidelines for surveillance of the late effects and subsequent neoplasms have been developed, it is essential to assess the cost-effectiveness of these guidelines. More research is needed to determine whether guidelines and programmes such as colorectal cancer screening in survivors exposed to abdominal radiotherapy and mammograms and breast magnetic resonance imaging in women exposed to thoracic radiotherapy are cost effective. Even if they are, it is important to think about non-adherence to these guidelines and its costs. Many older CCS are no longer followed in a cancer centre and may be unaware of their health risks and surveillance recommendations.

Finally, the association between excess health care expenditures and treatment, especially radiotherapy, needs to be investigated further. We are currently studying the association between specific therapeutic modalities (e.g., chemotherapy regimens and/or radiation doses) and health care expenditures, which may be useful in establishing the long-term cost effectiveness of childhood cancer treatment. Our aim is to model the excess health expenditures presented in this thesis as a function of both volume and whole-body dose distribution received during radiotherapy. This will help establish whether radiotherapy is cost effective in the long term among CCS. It will also help to anticipate costs that could be avoided with new radiotherapy techniques that reduce the volume of healthy tissue irradiated, in particular proton therapy.

The cost effectiveness of proton therapy compared with other cancer treatments has been a topic of debate among health care providers, insurers and policymakers (150). Proton therapy is generally more expensive than traditional radiotherapy or other cancer treatments, largely due to the high cost of the equipment and infrastructure. However, extending this treatment could be recommended if such centres reduce late effects, and thus health care expenditures, incurred by long-term survivors. Future research addressing these issues will provide useful information to onco-paediatricians and radiotherapists, as well as to medical and health policy authorities.

Appendices

Appendix 1 Late effects

A.1.1 Selected examples of treatment-specific adverse outcomes.

Supplementary Table 1. Selected examples of established radiation-associated late effects.

Radiation Exposure	Established Late Effects
Cardiovascular	<ul style="list-style-type: none"> Cardiomyopathy Carotid/subclavian artery disease Coronary artery disease Dysrhythmias/conduction disorders Heart valve abnormalities Pericardial fibrosis/pericarditis
Central nervous system	<ul style="list-style-type: none"> Neurocognitive deficits including diminished IQ, learning deficits, executive function, sustained attention, memory processing speed, and visual motor integration. Cerebrovascular disease including stroke, moyamoya, occlusive cerebral vasculopathy Clinical leukoencephalopathy including spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures Neurologic and neurosensory deficits
Endocrine	<ul style="list-style-type: none"> Pituitary dysfunction including altered pubertal timing, growth hormone, TSH, ACTH, LH and FSH deficiency, altered body composition (reduced lean muscle mass, overweight/obesity), metabolic syndrome Thyroid abnormalities including hypothyroid, hyperthyroid, thyroid nodules Diabetes mellitus
Gastrointestinal	<ul style="list-style-type: none"> Esophageal stricture Chronic enterocolitis Bowel obstruction Gastrointestinal fistula/stricture
Gonadal/reproductive (females)	<ul style="list-style-type: none"> Uterine vascular insufficiency predisposing to spontaneous abortion, neonatal death, low-birth weight infant, fetal

	malposition, and premature labor Ovarian dysfunction resulting in delayed/arrested puberty, premature menopause, infertility
Gonadal/reproductive (males)	Leydig cell dysfunction resulting in delayed/arrested puberty androgen insufficiency Germ cell failure oligospermia, azoospermia, Infertility
Hepatobiliary	Hepatic fibrosis Cholelithiasis
Musculoskeletal	Hypoplasia/Fibrosis Reduced or uneven growth (resulting in shortened trunk height, limb length discrepancy, kyphoscoliosis)
Pulmonary	Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease
Urinary tract	Bladder fibrosis Dysfunctional voiding Vesicoureteral reflux Hydronephrosis Renal insufficiency Hypertension
Any organ system	Subsequent neoplasms including skin (predominantly basal cell carcinoma), breast, thyroid, bone, brain. Increasing data on risk of radiation-associated colorectal cancers.

Reprinted from Robison LL et al. 2014 (35).

Supplementary Table 2. Selected examples of established chemotherapy-associated late effects

Class of Chemotherapy	Chemotherapeutic Agents	Established Late Effects
Alkylating agents	Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin, Cyclophosphamide, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Procarbazine, Thiotepa; plus the non-classical alkylators Dacarbazine and Temozolomide	<p>Secondary myelodysplasia or acute myeloid leukemia</p> <p>Gonadal dysfunction and Infertility</p> <p>Pulmonary fibrosis (with exposure to Busulfan, Carmustine or Lomustine)</p> <p>Urinary tract abnormalities (with exposure to Cyclophosphamide or Ifosfamide)</p> <p>Renal dysfunction (with exposure to Cisplatin/Carboplatin and Ifosfamide)</p> <p>Ototoxicity (with exposure to Cisplatin or very high dose Carboplatin)</p> <p>Dyslipidemia (with exposure to Cisplatin)</p>
Anthracyclines	Daunorubicin, Doxorubicin, Epirubicin, and Idarubicin	<p>Left ventricular dysfunction</p> <p>Cardiomyopathy</p> <p>Dysrhythmias</p>
Corticosteroids	Dexamethasone, Prednisone	<p>Reduced bone mineral density</p> <p>Osteonecrosis</p> <p>Cataracts</p>
Vinca Alkaloids	Vincristine, Vinblastine	Peripheral sensory and motor neuropathy
Antimetabolites	Methotrexate	<p>Neurocognitive impairment</p> <p>Leukoencephalopathy</p> <p>Liver dysfunction</p> <p>Renal toxicity</p> <p>Decreased bone mineral density</p>
Epipodophyllotoxins	Etoposide Teniposide	Acute myeloid leukemia

Reprinted from Robison LL et al. 2014 (35).

Appendix 2 Supplementary results for Chapter III

A.2.1 Population characteristics

Supplementary Table 3. Participating French administrative areas in the FRANCIM.

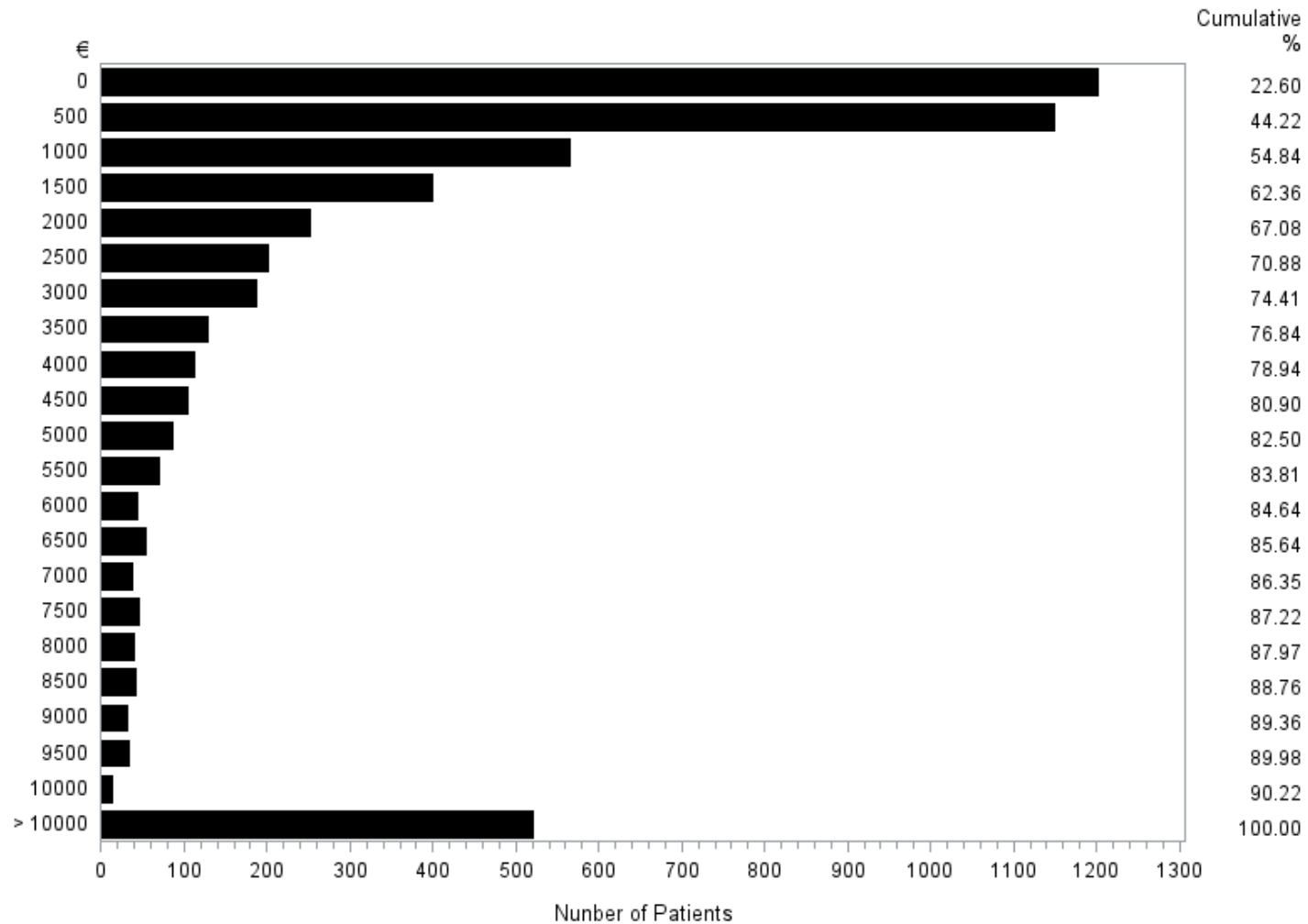
"Departement" (French administrative areas)	Year of Started	N	Already in- cluded in FCCSS
Ardennes	1980	31	0
Bas-Rhin	1975	396	12
Calvados	1978	149	36
Côte-d'Or	1981	16	0
Doubs	1978	140	6
Haut-Rhin	1981	102	3
Hérault	1986	120	2
Isère	1979	217	7
Lorrain	1983	337	10
Manche	1994	59	6
Martinique	1981	16	6
Somme	1982	155	38
Tarn	1981	62	10
Loire-Atlantique & Vendée	1991	69	3
Total	-	1869	139

Supplementary Table 4. Survivor characteristics by cohort.

	FCCSS		French cancer registry		Chi2
	n (%)	PY	n (%)	PY	
Total	3589	21247.6	1730	10286.0	
Gender					
Male	1972 (54.95%)	11672.7	957 (55.32%)	5679.1	0.80
Female	1617 (45.05%)	9574.9	773 (44.68%)	4606.9	
Age at January 2011					
<20	392 (10.92%)	2345.7	158 (9.13%)	946.1	<.0001
20-30	1311 (36.53%)	7825.4	668 (38.61%)	3987.4	
31-40	1200 (33.44%)	7110.7	678 (39.19%)	4031.9	
41-50	546 (15.21%)	3147.4	207 (11.97%)	1208.0	
≥51	140 (3.9%)	818.4	19 (1.1%)	112.6	
French geographical deprivation index					
1 Quintile	833 (23.21%)	4940.9	230 (13.29%)	1372.0	<.0001
2 Quintile	742 (20.67%)	4392.3	319 (18.44%)	1901.0	
3 Quintile	648 (18.06%)	3828.6	418 (24.16%)	2493.7	
4 Quintile	667 (18.58%)	3959.0	397 (22.95%)	2361.5	
5 Quintile	699 (19.48%)	4126.8	366 (21.16%)	2157.8	
Status at December 2016					
Alive	3462 (96.46%)	20772.0	1690 (97.69%)	10140.0	<.0001
Death	127 (3.54%)	475.6	40 (2.31%)	146.0	
Year of diagnosis					
<1980	926 (25.8%)	5391.9	62 (3.58%)	368.4	<.0001
1980-1989	1292 (36%)	7660.0	560 (32.37%)	3314.5	
≥1990	1371 (38.2%)	8195.7	1108 (64.05%)	6603.1	
Age at first cancer					
0-1	781 (21.76%)	4639.0	156 (9.02%)	936.0	<.0001
2-4	826 (23.01%)	4899.9	208 (12.02%)	1240.3	
5-9	821 (22.88%)	4842.0	267 (15.43%)	1591.3	
10-14	767 (21.37%)	4535.6	363 (20.98%)	2149.7	
≥15	394 (10.98%)	2331.1	736 (42.54%)	4368.7	
First primary cancer type					
Kidney tumours	549 (15.3%)	1159.6	119 (6.88%)	1676.9	
Neuroblastoma	471 (13.12%)	3228.4	103 (5.95%)	713.6	
Lymphoma	631 (17.58%)	2816.2	440 (25.43%)	618.0	
Soft tissue sarcomas	414 (11.54%)	3753.3	109 (6.3%)	2597.3	
Bone sarcomas	325 (9.06%)	2465.6	120 (6.94%)	651.6	
Central nervous system tumour	466 (12.98%)	1927.8	290 (16.76%)	709.0	
Gonadal/Germ cell tumours	230 (6.41%)	2708.7	159 (9.19%)	1719.0	
Thyroid tumour	36 (1%)	1375.7	73 (4.22%)	946.6	
Retinoblastoma	269 (7.5%)	212.7	36 (2.08%)	438.0	
Other solid cancer	198 (5.52%)	1599.5	281 (16.24%)	216.0	

A.2.2 Health care expenditures

Supplementary Figure 1. Histogram of the survivors mean of healthcare expenditures.



Supplementary Table 5. Health care expenditures by sex.

Type of Expenditure	Men				Women			
	N° Patients (%)	N° Claims	Total Expenditures in Millions € (%)	Annual mean Per-Patient in € (SD)	N° Patients (%)	N° Claims	Total Expenditures in Millions € (%)	Annual mean Per-Patient in € (SD)
General practitioner visits	2762 (94.3)	66 396	1.4 (2.13)	81 (131)	2293 (95.94)	77 711	1.6 (2.41)	115 (133)
Other specialist visits	2672 (91.23)	60 268	2.2 (3.34)	127 (435)	2263 (94.69)	101 730	3.2 (4.64)	223 (438)
Physiotherapy visits	1002 (34.21)	55 174	0.9 (1.42)	54 (298)	1193 (49.92)	68 654	1.2 (1.72)	83 (341)
Nursing visits	1711 (58.42)	52 764	0.7 (1.07)	41 (520)	1808 (75.65)	65 784	1.0 (1.52)	73 (781)
Other health professionals visits	267 (9.12)	6 560	0.2 (0.32)	12 (151)	330 (13.81)	5 988	0.2 (0.24)	11 (112)
Pharmacy	2742 (93.62)	216 045	12.5 (18.86)	719 (12906)	2304 (96.4)	286 827	8.8 (12.98)	622 (2644)
Medical device	2157 (73.64)	25 558	4.6 (6.98)	266 (1913)	2066 (86.44)	26 921	3.6 (5.25)	252 (1650)
Laboratory Test	2376 (81.12)	35 703	0.9 (1.41)	54 (348)	2221 (92.93)	65 543	1.6 (2.35)	113 (228)
Technical medical procedures**	2530 (86.38)	21 283	1.1 (1.64)	62 (218)	2170 (90.79)	27 300	1.5 (2.23)	107 (351)
Transport	895 (30.56)	11 575	1.9 (2.89)	110 (782)	848 (35.48)	13 029	2.5 (3.67)	176 (1174)
Hospitalizations	1717 (58.62)	16 670	30.0 (45.16)	1722 (11488)	1733 (72.51)	18 331	30.7 (45.06)	2160 (16049)
Disability Benefits***	175 (5.97)	7 223	4.2 (6.32)	241 (1516)	170 (7.11)	6 640	3.7 (5.46)	262 (1564)
Sick Leave	1485 (50.7)	17 832	5.0 (7.58)	289 (1280)	1246 (52.13)	23 890	7.9 (11.62)	557 (1953)
Others	300 (10.24)	1 786	0.6 (0.87)	33 (1088)	271 (11.34)	1 656	0.6 (0.86)	41 (975)
Total	2929	594 837	66,3	3814 (19289)	2390	790 004	68,2	4795 (18147)

** Technical medical procedures include expenditures mainly related to medical imaging techniques. *** Disability benefits include all welfare payments or pensions made by the French Government to assistance people with disabilities.

Supplementary Table 6. Health care expenditures by cohort.

Type of Expenditure	FCCSS				French Cancer Registry			
	N° Patients (%)	N° Claims	Total Expenditures in Millions € (%)	Annual mean Per-Patient in € (SD)	N° Patients (%)	N° Claims	Total Expenditures in Millions € (%)	Annual mean Per-Patient in € (SD)
General practitioner visits	3396 (94.62)	93 607	2.0 (2.07%)	94 (132)	1659 (95.9)	50 500	1.0 (2.79%)	102 (136)
Other specialist visits	3318 (92.45)	105 762	3.6 (3.68%)	168 (476)	1617 (93.47)	56 236	1.8 (4.83%)	176 (350)
Physiotherapy visits	1441 (40.15)	81 451	1.4 (1.45%)	66 (323)	754 (43.58)	42 377	0.7 (1.88%)	68 (310)
Nursing visits	2337 (65.12)	77 885	1.1 (1.15%)	52 (615)	1182 (68.32)	40 663	0.6 (1.68%)	61 (718)
Other health professionals visits	426 (11.87)	8 653	0.3 (0.27%)	12 (130)	171 (9.88)	3 895	0.1 (0.3%)	11 (143)
Pharmacy	3398 (94.68)	335 479	16.2 (16.65%)	758 (11720)	1648 (95.26)	167 393	5.2 (13.89%)	505 (2597)
Medical device	2848 (79.35)	36 957	5.9 (6.11%)	278 (1847)	1375 (79.48)	15 522	2.3 (6.09%)	221 (1697)
Laboratory Test	3074 (85.65)	69 462	1.7 (1.8%)	82 (351)	1523 (88.03)	31 784	0.8 (2.1%)	76 (158)
Technical medical procedures**	3153 (87.85)	32 862	1.8 (1.88%)	86 (317)	1547 (89.42)	15 721	0.8 (2.1%)	76 (208)
Transport	1225 (34.13)	17 742	3.3 (3.42%)	156 (1037)	518 (29.94)	6 862	1.1 (2.95%)	107 (844)
Hospitalizations	2397 (66.79)	25 748	44.6 (45.99%)	2095 (11694)	1053 (60.87)	9 253	16.0 (42.82%)	1556 (17186)
Disability Benefits***	238 (6.63)	9 609	5.8 (5.93%)	270 (1590)	107 (6.18)	4 254	2.2 (5.78%)	210 (1423)
Sick Leave	1789 (49.85)	26 540	8.4 (8.62%)	393 (1592)	942 (54.45)	15 182	4.6 (12.23%)	444 (1686)
Others	420 (11.7)	2 503	1.0 (0.98%)	45 (1240)	151 (8.73)	939	0.2 (0.56%)	20 (358)
Total	3589	924 260	97,1	4556 (18830)	1730	460 581	37,4	3633 (18692)

** Technical medical procedures include expenditures mainly related to medical imaging techniques. *** Disability benefits include all welfare payments or pensions made by the French Government to assistance people with disabilities.

A.2.3 Multivariate analysis

Supplementary Table 7. Multivariate analysis of survivor characteristics associated with each expenditure item. β for the GLM model.

	General practitioner visits	Other specialist visits	Physiotherapy visits	Nursing visits	Other health professionals visits	Pharmacy	Medical device
Intercept	9.26	-6.04	-7.44	-164.83 **	-16.58	1.68	25.55
Female (Ref=Male)	0.37 ***	0.64 ***	0.49 ***	0.58 ***	-0.15	0.13	0.2
Age	0.03 ***	0.05 ***	0.07 ***	0.16 ***	0.08 ***	0.06 ***	0.06 ***
Year of Diagnosis	0	0	0	0.08 **	0.01	0	-0.01
Age at first cancer (Ref = 0-1)							
2-4	0.1 **	0.1	-0.15	0.2	0.16	0.88 **	0.14
5-9	0.1 *	0.02	-0.33	-0.19	0.01	0.41 *	-0.23
10-14	0.11	-0.04	-0.5 *	-0.24	-0.32	0.44	-0.23
≥15	0.03	-0.12	-0.63 **	-0.98	-1.11 **	0.03	-0.82 *
French Index Deprivation	0.08 ***	-0.01	-0.01	0.16 **	-0.03	0.01	0
First primary cancer type (Ref = Neuroblastoma)							
Kidney tumor	0.04	0.11	-0.12	0.12	-0.5	0.99 **	0.1
Lymphoma	0.17 ***	0.21 ***	0.31	-0.93 ***	-0.25	0.23	-0.49
Soft tissue sarcoma	0.18 ***	0.12	0.58 **	-0.58	-0.2	0.08	0.36
Bone sarcoma	0.33 ***	0.13	0.96 ***	-0.86 **	-0.65	0.23	1.63 ***
Central nervous system tumor	0.56 ***	0.29 ***	1.78 ***	0.74 **	1.66 ***	0.93 ***	0.54 *
Gonadal tumor	-0.01	0.01	0.09	-0.92 **	-0.19	0.89 *	-0.72
Thyroid tumor	0.3 ***	0.27	-0.13	-1.66 ***	1.28 *	1.02	-1.11 ***
Retinoblastoma	0.16 **	0.07	-0.1	-0.07	-1.18 ***	-0.08	-0.24
Other solid cancer	0.21 ***	0.12	0.54 **	-0.16	0.74	0.14	-0.26
FCCSS	-0.09 **	-0.1 **	-0.15	-0.06	0.21	0.05	-0.18

*** p<0.01, ** p<0.05, * p<0.10

Supplementary Table 7. Multivariate analysis for each type of expenditure. Continued.

	Laboratory Test	Technical Medical Procedures**	Transport	Hospitalizations	Disability Benefits***	Sick Leave	Others
Intercept	19.63	-34.37 *	-67.01 *	9.24	-1.85	18.77	81.49
Female (Ref=Male)	0.85 ***	0.5 ***	0.69 ***	0.24 **	0.18	0.7 ***	0.1
Age	0.03 ***	0.06 ***	0.09 ***	0.04 **	0.18 ***	0.03 ***	0.06
French Index Deprivation	-0.01	0.03	0.31 ***	0.06	0.17 **	0.02	0.09
Year of Diagnosis	-0.01	0.02 *	0.03 *	0	0	-0.01	-0.04
Age at first cancer (Ref = 0-1)							
2-4	0.25 ***	0.08	0.43 *	0.19	-0.12	0.25 **	0.85 **
5-9	0.21 **	-0.08	-0.19	0.01	-0.11	0.25 *	0.62
10-14	0.18	0.01	-0.73 **	-0.05	-0.26	0.45 ***	1.34 **
≥15	0.08	-0.35 *	-1.35 ***	-0.29	0.02	0.51 **	0.92
First primary cancer type (Ref = Neuroblastoma)							
Kidney tumor	0.23 **	0.14	0.4	0.16	-0.59	0.04	0.55
Lymphoma	0.21 **	0.19 *	0.1	-0.01	-0.22	0.09	-0.15
Soft tissue sarcoma	-0.07	0.32 ***	0.02	0.06	-0.1	0.21	0.07
Bone sarcoma	0.05	0.31 ***	1.06 ***	0.29	0.31	0.16	0.29
Central nervous system tumor	0.23 **	0.55 ***	1.59 ***	1.1 ***	0.25	-0.23	0.79 *
Gonadal tumor	0	0.37 **	0.01	-0.01	-0.99	-0.11	0.18
Thyroid tumor	0.37 ***	0.26	-0.6	-0.74 **	-1.55 *	0.16	-0.29
Retinoblastoma	-0.14	0.2	1.05 ***	0.52 *	-0.21	-0.38 *	0.69
Other solid cancer	0.12	0.26 *	0.5	0.07	-1.18 **	0.12	1.2
FCCSS	-0.01	0.05	0.33 **	0.25 *	-0.19	-0.07	0.3

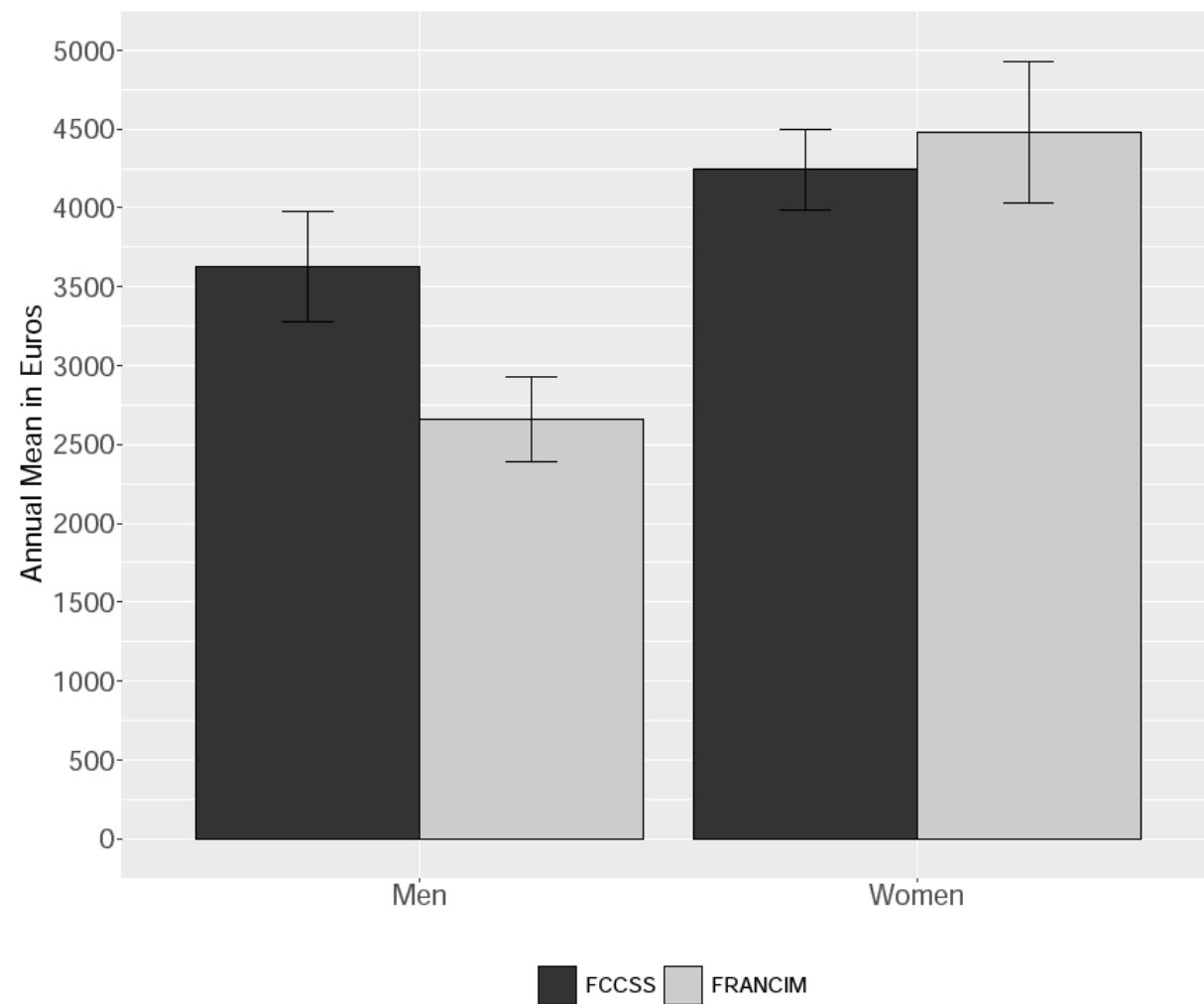
*** p<0.01, ** p<0.05, * p<0.10

Supplementary Table 8. . Multivariate analysis of survivor characteristics associated total health care expenditures by the type of cancer. β for the GLM model.

	Kidney tumour (n = 668)	Neuroblastom a (n = 574)	Lymphom a (n = 1,071)	Soft tissue sarcom a (n = 523)	Bone sarcoma (n = 445)	Central nervous system tumour (n = 756)	Gonadal/Ger m cell tumours (n = 389)	Thyroi d tumour (n = 109)	Retinoblastom a (n = 305)	Other solid cancer (n = 479)
Intercept	-27.71	-119.94	29.08	30.02	-19.04	72.79	-114.51	-101.69	25.45	45.49
Female(Ref=Male)	0.16	0.11	0.73 ***	0.69 ***	0.37 **	0.13	0.7 **	0.08	0.25	-0.11
Age	0.07 *	0.12 ***	0.05 **	0.05	0.05 **	0.02	0.1 ***	0.05	0.06 *	0.04
French Index	-0.17 *	0.18 **	0.13 ***	-0.05	0	-0.01	0.31 **	-0.04	-0.12	0.05
Deprivation										
Year of Diagnosis	0.02	0.06	-0.01	-0.01	0.01	-0.03	0.06	0.05	-0.01	-0.02
Age at first cancer (Ref = ≥ 15)										
0-1	-0.12	1.3	0.04	0.13	-0.63	0.24	1.01		3.17 ***	-0.2
2-4	0.32	1.51	0.27	0.78	-0.28	0.41	0.44	-3.25 ***	3 ***	0.88 *
5-9	-0.21	1.44	-0.05	0.35	0.36	0.36	0.8	0.33	2.27 ***	0.34
10-14	-0.79	0.78	-0.12	0.45	0.15	0.69 **	0.34	0.59	3.36 ***	0.42
FCCSS	-0.12	0.48 *	0.03	0.06	-0.1	-0.11	0.47	0.51	0.3	0.13

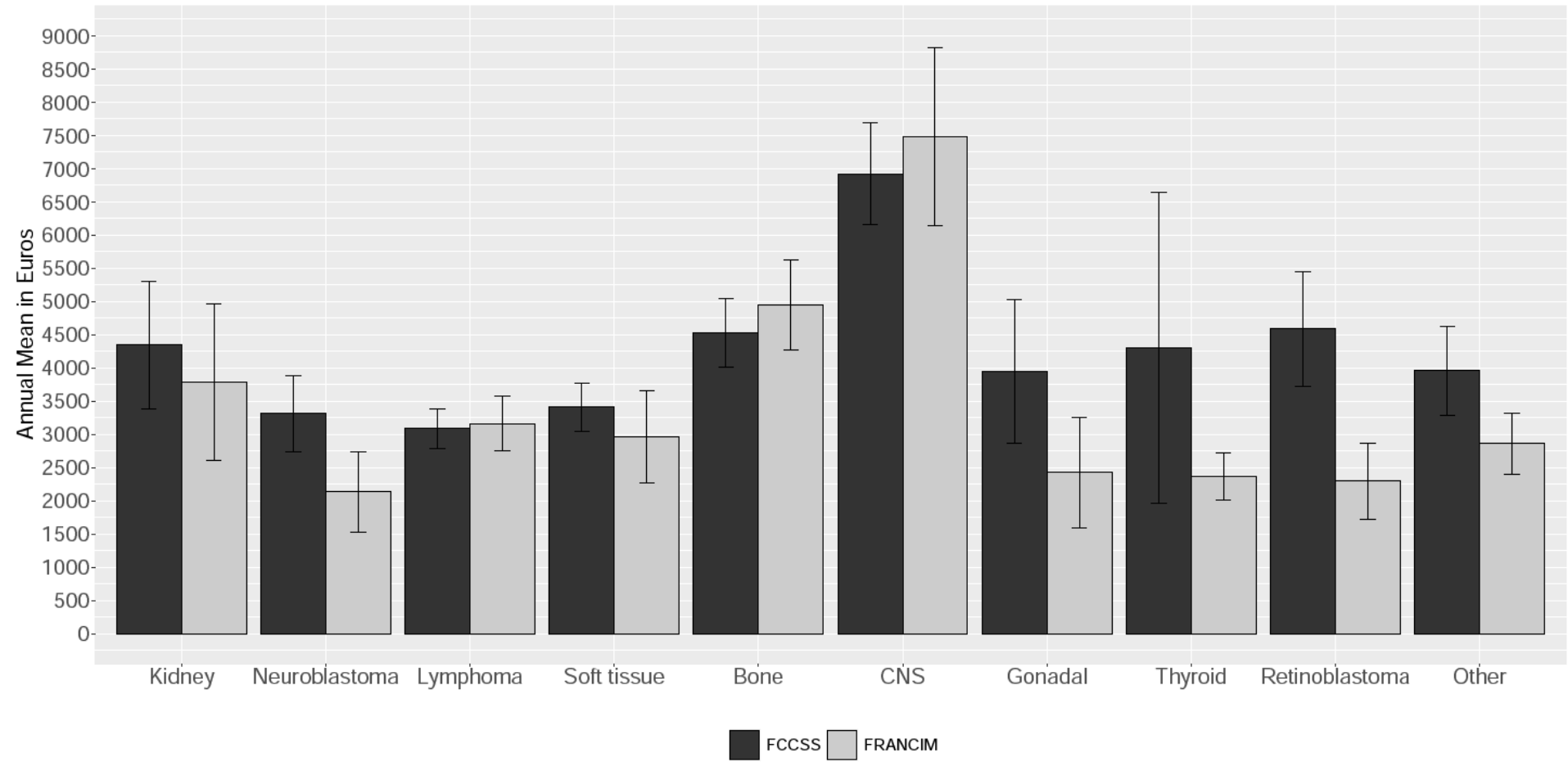
*** p<0.01, ** p<0.05, * p<0.10

Supplementary Figure 2. Adjusted* annual health care expenditures by sex and cohort



* Adjusted by age, sex, year of diagnosis, age at diagnosis, French index deprivation, cohort and type of primary cancer.

Supplementary Figure 3. Adjusted* annual health care expenditures by type of primary cancer and cohort

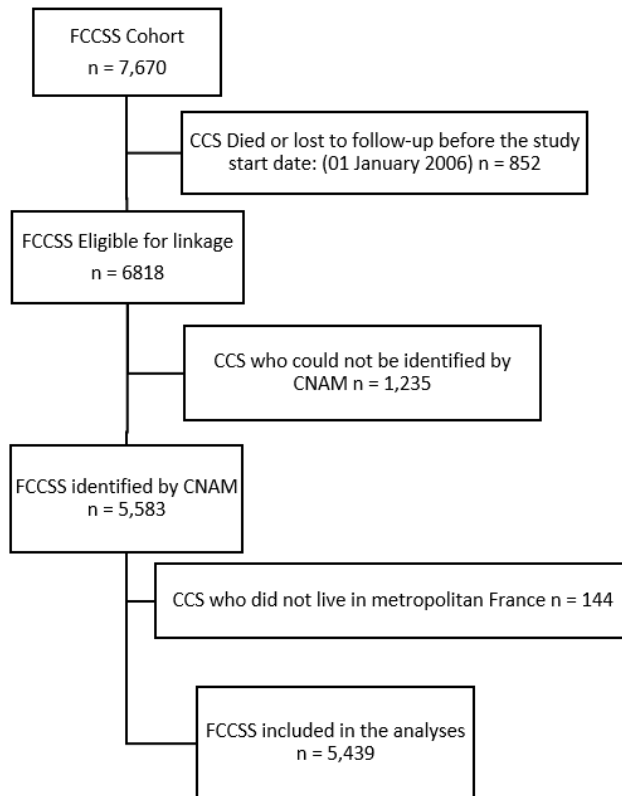


* Adjusted by age, sex, year of diagnosis, age at diagnosis, French index deprivation, cohort and type of primary cancer. Type of primary cancer: Kidney tumor, neuroblastoma, lymphoma, soft tissue sarcoma, bone sarcoma, central nervous system tumour (CNS), gonadal tumour, thyroid tumour, retinoblastoma and other solid cancer.

Appendix 3 Supplementary results for Chapter IV

A.3.1 Flowchart

Supplementary Figure 4. Study flowchart of the FCCSS.



A.3.2 Hospital admission diagnosis

Supplementary Table 9. The main primary diagnosis of childhood cancer survivors based on the International Classification of Diseases, 10th revision (ICD-10) codes.

	n	%
Chapter I Certain infectious and parasitic diseases		
Infectious gastroenteritis and colitis, unspecified	41	16.73
Erysipelas	31	12.65
Anogenital (venereal) warts	26	10.61
Chronic viral hepatitis B without delta-agent	12	4.90
Sepsis due to Staphylococcus aureus	9	3.67
Sepsis, unspecified organism	9	3.67
Sepsis due to other Gram-negative organisms	8	3.27
Chronic viral hepatitis C	7	2.86
Other and unspecified infectious diseases	7	2.86
Others	95	38.78
Chapter II Neoplasms		
Encounter for antineoplastic chemotherapy and immunotherapy	3269	32.37
Encounter for antineoplastic radiation therapy	2595	25.69
Personal history of malign neoplasms of organs and systems	672	6.65
Encounter for other aftercare	609	6.03
Encounter for follow-up examination after completed treatment for malignant neoplasm	237	2.35
Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues	187	1.85
Personal history of malignant neoplasm of urinary tract	144	1.43
Malignant neoplasm of thyroid gland	108	1.07
Benign neoplasm of thyroid gland	97	0.96
Others	2182	21.60
Chapter III Diseases of the blood and blood-forming organs		
Drug-induced aplastic anemia	41	17.30
Anemia in other chronic diseases classified elsewhere	20	8.44
Iron deficiency anemia secondary to blood loss (chronic)	15	6.33
Anemia in neoplastic disease	13	5.49
Iron deficiency anemia, unspecified	12	5.06
Other specified anemias	12	5.06
Acute posthemorrhagic anemia	10	4.22
Immunodeficiency, unspecified	10	4.22
Secondary thrombocytopenia	10	4.22
Others	94	39.66
Chapter IV Endocrine, nutritional and metabolic diseases		
Hypopituitarism	153	18.43
Postprocedural hypopituitarism	58	6.99
Nontoxic multinodular goiter	56	6.75
Type 1 diabetes mellitus without complications	52	6.27
Type 2 diabetes mellitus without complications	51	6.14
Nontoxic single thyroid nodule	40	4.82
Obesity due to excess calories	29	3.49
Morbid (severe) obesity due to excess calories	28	3.37
Drug-induced hypopituitarism	24	2.89

Others	339	40.84
<hr/>		
Chapter V Mental and behavioural disorders		
<hr/>		
Alcohol related disorders	123	41.00
Adjustment disorders	16	5.33
Alcohol dependence	11	3.67
Major depressv disord, single epsd, sev w/o psych features	9	3.00
Anorexia nervosa	8	2.67
Other mental disorders due to known physiological condition	8	2.67
Generalized anxiety disorder	7	2.33
Major depressive disorder, single episode, unspecified	7	2.33
Other anxiety disorders	6	2.00
Others	105	35.00
<hr/>		
Chapter VI Diseases of the nervous system		
<hr/>		
Carpal tunnel syndrome	70	8.72
Local-rel (focal) symptc epilepsy w complex partial seizure	57	7.10
Epilepsy, unspecified	52	6.48
Spastic hemiplegia	41	5.11
Generalized idiopathic epilepsy and epileptic syndromes	31	3.86
Nerve root and plexus compressions in diseases classd elsw	27	3.36
Paraplegia (paraparesis) and quadriplegia (quadriparesis)	24	2.99
Cluster headaches and oth trigeminal autonm cephalgias (TAC)	19	2.37
Multiple sclerosis	18	2.24
Others	464	57.78
<hr/>		
Chapter VII Diseases of the eye and adnexa		
<hr/>		
Infantile and juvenile cataract	35	10.74
Enophthalmos	30	9.20
Ptosis of eyelid	22	6.75
Other disorders of globe	21	6.44
Unspecified cataract	16	4.91
Other specified cataract	13	3.99
Exotropia	10	3.07
Other disorders of orbit	10	3.07
Esotropia	8	2.45
Others	161	49.39
<hr/>		
Chapter VIII Diseases of the ear and mastoid process		
<hr/>		
Cholesteatoma of middle ear	13	11.93
Chronic serous otitis media	12	11.01
Sensorineural hearing loss, bilateral	9	8.26
Other peripheral vertigo	8	7.34
Sudden idiopathic hearing loss	8	7.34
Unspecified sensorineural hearing loss	7	6.42
Other chronic nonsuppurative otitis media	4	3.67
Other perforations of tympanic membrane	4	3.67
Benign paroxysmal vertigo	3	2.75
Others	41	37.61
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Chapter IX Diseases of the circulatory system		
<hr/>		
Heart transplant status	345	18.16
Encounter for adjustment and management of VAD	213	11.21

Heart failure	125	6.58
Dilated cardiomyopathy	71	3.74
Asymptomatic varicose veins of lower extremities	68	3.58
Left ventricular failure	57	3.00
Atherosclerotic heart disease of native coronary artery	37	1.95
Unstable angina	36	1.89
Cerebral infarction, unspecified	31	1.63
Others	917	48.26
<hr/>		
Chapter X Diseases of the respiratory system		
<hr/>		
Acute respiratory failure	47	7.82
Chronic respiratory failure	45	7.49
Pneumonitis due to inhalation of food and vomit	38	6.32
Unspecified bacterial pneumonia	26	4.33
Deviated nasal septum	21	3.49
Pneumonia, unspecified organism	21	3.49
Pleural effusion, not elsewhere classified	20	3.33
Acute bronchitis, unspecified	18	3.00
Bronchopneumonia, unspecified organism	15	2.50
Others	350	58.24
<hr/>		
Chapter XI Diseases of the digestive system		
<hr/>		
Embedded teeth	159	7.52
Polyp of colon	87	4.12
Other and unspecified intestinal obstruction	73	3.45
Other gastritis	62	2.93
Diverticular disease of lg int w/o perforation or abscess	54	2.56
Dental caries	44	2.08
Calculus of gallbladder without cholecystitis	42	1.99
Intestinal adhesions w obst (postprocedural) (postinfection)	42	1.99
Unilateral inguinal hernia, without obstruction or gangrene	41	1.94
Others	1509	71.42
<hr/>		
Chapter XII Diseases of the skin and subcutaneous tissue		
<hr/>		
Pilonidal cyst and sinus with abscess	39	9.92
Scar conditions and fibrosis of skin	34	8.65
Cutaneous abscess, furuncle and carbuncle of limb	32	8.14
Cutaneous abscess, furuncle and carbuncle of trunk	32	8.14
Cellulitis and acute lymphangitis of finger and toe	30	7.63
Ingrowing nail	27	6.87
Pilonidal cyst and sinus without abscess	22	5.60
Epidermal cyst	21	5.34
Oth local infections of the skin and subcutaneous tissue	18	4.58
Others	138	35.11
<hr/>		
Chapter XIII Diseases of the musculoskeletal system and connective tissue		
<hr/>		
Low back pain	47	5.33
Thor, thrcm & lumbosacr intvrt disc disord w radiculopathy	35	3.97
Hallux valgus (acquired)	29	3.29
Disorder of continuity of bone	25	2.84
Other dorsalgia	20	2.27
Other specified disorders of muscle	19	2.16

Unilateral primary osteoarthritis of hip	17	1.93
Chronic instability of knee, right knee	16	1.82
Radiculopathy, lumbar region	15	1.70
Others	658	74.69
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Chapter XIV Diseases of the genitourinary system		
Encounter for care involving renal dialysis	1848	53.38
Kidney transplant status	151	4.36
Acute tubulo-interstitial nephritis	107	3.09
Calculus of kidney	90	2.60
Calculus of ureter	73	2.11
Unspecified renal colic	65	1.88
Chronic kidney disease (CKD)	60	1.73
Polyp of corpus uteri	53	1.53
Other and unspecified ovarian cysts	41	1.18
Others	974	28.13
<hr/>		
Chapter XVII Congenital malformations, deformations and chromosomal abnormalities		
Neurofibromatosis (nonmalignant)	70	45.75
Prominent ear	6	3.92
Congenital malformations of other endocrine glands	4	2.61
Other atresia and stenosis of urethra and bladder neck	4	2.61
Arteriovenous malformation (peripheral)	3	1.96
Arteriovenous malformation of cerebral vessels	3	1.96
Congenital facial asymmetry	3	1.96
Other congenital malformations of breast	3	1.96
Other phakomatoses, not elsewhere classified	3	1.96
Others	54	35.29
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Chapter XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified		
Abdominal and pelvic pain	140	12.07
Pain, unspecified	93	8.02
Pain in throat and chest	74	6.38
Malaise and fatigue	68	5.86
Pain localized to upper abdomen	64	5.52
Ascites	53	4.57
Headache	44	3.79
Fever, unspecified	43	3.71
Dyspnea	32	2.76
Others	549	47.33
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Chapter XIX Injury, poisoning and certain other consequences of external causes		
Mechanical complication of internal joint prosthesis	66	6.58
Benzodiazepines	52	5.18
Concussion	32	3.19
Open wound of thumb without damage to nail	25	2.49
Unspecified fracture of the lower end of radius	23	2.29
Traumatic subdural hemorrhage	22	2.19
Mechanical comp of cardiac and vascular devices and implant	21	2.09
Sprain of cruciate ligament of knee	21	2.09
Inj extensor musc/fasc/tend and unsp finger at wrs/hnd lv	19	1.89

Others	722	71.98
<hr/>		
Chapter XXI Factors influencing health status and contact with health services		
Encounter for follow-up examination after completed treatment for conditions other than malignant neoplasm	728	24.41
Encounter for other aftercare	330	11.07
Encounter for examination and observation for oth reasons	280	9.39
Encounter for other specified aftercare	279	9.36
Encounter for palliative care	164	5.50
Encntr for plast/recnst surg fol med proc or healed injury	142	4.76
Orthopedic aftercare	105	3.52
Encounter for adjustment and management of implanted device	103	3.45
Encounter for breast reconstruction following mastectomy	66	2.21
Others	785	26.32

A.3.3 Relative hospitalisation and bed-days ratios

Supplementary Table 10. Relative hospitalisation and bed-day ratios by the type of hospitalisation and primary cancer.

	Hospitalizations									
	Other solid cancer	Kidney tumours	Neuroblastoma	Lymphoma	Soft tissue sarcomas	Bone sarcomas	Central nervous system tumour	Gonadal/Germ cell tumours	Thyroid tumour	Retinoblastoma
Total	2.71 (2.58-2.84)	2.63 (2.56-2.71)	2.58 (2.49-2.67)	2.36 (2.3-2.43)	2.23 (2.15-2.31)	2.14 (2.06-2.23)	3.56 (3.45-3.67)	1.85 (1.75-1.94)	0.81 (0.69-0.95)	2.72 (2.59-2.85)
Infections	2.53 (1.38-4.24)	4 (3.07-5.11)	2.05 (1.36-2.97)	2.34 (1.69-3.15)	2 (1.28-2.98)	2.5 (1.6-3.72)	2.34 (1.58-3.34)	1.49 (0.72-2.74)	1.98 (0.24-7.16)	0.79 (0.32-1.64)
Neoplasms	3.85 (3.54-4.19)	2.68 (2.54-2.83)	3.36 (3.13-3.61)	3.85 (3.69-4.02)	2.96 (2.79-3.14)	3.73 (3.52-3.94)	5.15 (4.9-5.41)	2.18 (1.99-2.38)	0.55 (0.38-0.77)	10.32 (9.65-11.03)
Haematological	4.23 (2.37-6.97)	4.35 (3.2-5.76)	3.42 (2.36-4.81)	5.16 (3.96-6.61)	1.24 (0.62-2.22)	2.77 (1.67-4.33)	3.02 (1.99-4.39)	1.26 (0.46-2.75)	0 (-2.59)	3.48 (1.99-5.65)
Endocrine	2.1 (1.42-3)	2.78 (2.27-3.37)	2.61 (2.06-3.27)	2.95 (2.46-3.5)	2.27 (1.74-2.91)	1.55 (1.08-2.15)	10.45 (9.29-11.7)	3.78 (2.91-4.81)	1.47 (0.4-3.75)	2.02 (1.33-2.94)
Mental	2.39 (1.59-3.45)	1.2 (0.89-1.57)	0.79 (0.53-1.14)	0.94 (0.68-1.26)	1.81 (1.35-2.36)	0.38 (0.18-0.71)	1.7 (1.28-2.23)	0.65 (0.33-1.13)	4.45 (1.92-8.76)	0.77 (0.42-1.3)
Neurological	2.79 (2.06-3.7)	1.09 (0.83-1.41)	2.56 (2.06-3.15)	1.38 (1.11-1.7)	1.11 (0.81-1.49)	0.93 (0.64-1.32)	10.48 (9.44-11.61)	1.6 (1.11-2.22)	2.18 (1.05-4.01)	1.72 (1.12-2.51)
Ocular	0.83 (0.36-1.63)	0.77 (0.49-1.16)	1.3 (0.76-2.09)	0.81 (0.55-1.15)	1.4 (0.98-1.94)	0.43 (0.21-0.8)	3 (2.29-3.87)	0.51 (0.23-0.97)	0.7 (0.23-1.65)	23.41 (19.52-27.86)
Auditory	4.62 (2.64-7.51)	0.9 (0.39-1.78)	0.13 (0-0.72)	1.51 (0.84-2.48)	1.7 (0.85-3.04)	1.2 (0.44-2.61)	6.4 (4.63-8.62)	1.6 (0.59-3.48)	1.34 (0.03-7.47)	0.32 (0.04-1.14)
Cardiovascular	2.75 (2.21-3.38)	3.06 (2.73-3.43)	4.33 (3.75-4.97)	3.6 (3.28-3.96)	4.86 (4.38-5.39)	2.46 (2.09-2.86)	2.69 (2.31-3.13)	2.32 (1.88-2.83)	0.44 (0.14-1.03)	3.89 (3-4.97)
Pulmonary	2.3 (1.61-3.19)	2.58 (2.12-3.11)	1.01 (0.72-1.38)	2.62 (2.19-3.1)	1.48 (1.1-1.96)	1.13 (0.77-1.6)	4.89 (4.17-5.7)	0.75 (0.41-1.26)	1.21 (0.33-3.09)	0.83 (0.5-1.3)
Gastrointestinal	2 (1.72-2.32)	1.58 (1.43-1.75)	1.05 (0.91-1.2)	1.44 (1.3-1.58)	1.3 (1.14-1.48)	1.08 (0.92-1.26)	1.32 (1.15-1.5)	1.49 (1.27-1.74)	0.93 (0.56-1.45)	0.86 (0.72-1.04)
Skin	2.71 (1.8-3.91)	1.32 (0.93-1.81)	1.84 (1.39-2.41)	2.2 (1.73-2.76)	2.4 (1.81-3.14)	2.61 (1.89-3.52)	1.85 (1.34-2.49)	3.23 (2.29-4.43)	0.62 (0.02-3.43)	1.03 (0.63-1.59)
Musculoskeletal	0.97 (0.7-1.31)	1.21 (1.02-1.42)	1.87 (1.59-2.2)	0.97 (0.82-1.15)	1.04 (0.85-1.27)	1.41 (1.17-1.7)	1.13 (0.92-1.38)	0.87 (0.64-1.16)	1.36 (0.78-2.21)	0.83 (0.56-1.19)
Genitourinary	3.36 (2.89-3.89)	6.66 (6.29-7.05)	7.44 (6.96-7.95)	1.31 (1.16-1.46)	2.12 (1.89-2.36)	1.01 (0.83-1.23)	1.23 (1.02-1.48)	3.08 (2.68-3.52)	0.34 (0.15-0.64)	1.96 (1.64-2.32)
Congenital Malformations	0.96 (0.12-3.47)	2.39 (1.37-3.89)	1.43 (0.76-2.45)	1.88 (0.94-3.36)	2.57 (1.33-4.49)	1.29 (0.35-3.3)	14.34 (11.22-18.06)	5.36 (2.86-9.17)	4.95 (0.6-17.89)	0.92 (0.4-1.81)
Symptoms Unclassified	2.53 (2-3.15)	2.48 (2.17-2.81)	1.57 (1.29-1.89)	1.99 (1.72-2.28)	1.73 (1.43-2.06)	1.39 (1.1-1.74)	3.62 (3.18-4.12)	1.02 (0.73-1.38)	1.38 (0.66-2.53)	1.08 (0.77-1.46)
Injury - Poisoning	1.3 (0.97-1.72)	1.14 (0.94-1.36)	1.13 (0.94-1.36)	1.44 (1.24-1.66)	1.33 (1.1-1.6)	2.36 (2.01-2.75)	1.77 (1.5-2.07)	1.12 (0.83-1.48)	1.16 (0.5-2.28)	0.69 (0.5-0.91)
Other Factors	3.02 (2.63-3.45)	2.72 (2.49-2.97)	2.15 (1.91-2.41)	2.32 (2.12-2.53)	2.55 (2.29-2.83)	1.97 (1.73-2.24)	4.49 (4.13-4.87)	1.77 (1.49-2.08)	0.89 (0.46-1.56)	2.4 (2.04-2.81)

Supplementary Table 10. Relative hospitalisation and bed-day ratios by the type of hospitalisation and primary cancer. Continued.

	Other solid cancer	Bed-days								
		Kidney tumours	Neuroblastoma	Lymphoma	Soft tissue sarcomas	Bone sarcomas	Central nervous system tumour	Gonadal/Germ cell tumours	Thyroid tumour	Retinoblastoma
Total	3.25 (3.14-3.35)	3.5 (3.44-3.56)	3.2 (3.12-3.27)	2.9 (2.85-2.95)	2.82 (2.76-2.88)	2.71 (2.65-2.78)	6.29 (6.2-6.39)	3.13 (3.04-3.22)	1.17 (1.06-1.29)	5.17 (5.03-5.31)
Infections	2.32 (1.75-3.03)	7.66 (7.06-8.3)	1.11 (0.84-1.43)	2.07 (1.81-2.36)	2.02 (1.69-2.4)	5.61 (4.91-6.37)	2.46 (2.05-2.93)	1.58 (1.2-2.04)	2.73 (1.49-4.58)	0.53 (0.29-0.89)
Neoplasms	4.47 (4.18-4.76)	3.02 (2.9-3.15)	3.1 (2.9-3.3)	4.33 (4.18-4.48)	2.84 (2.7-2.99)	3.39 (3.22-3.57)	6.92 (6.68-7.15)	3.1 (2.9-3.3)	1.52 (1.27-1.81)	12.2 (11.55-12.88)
Haematological	14.84 (12.47-17.53)	3.26 (2.72-3.87)	2.58 (2.1-3.15)	3.71 (3.19-4.3)	1 (0.68-1.43)	2.2 (1.65-2.87)	3.37 (2.76-4.07)	3.77 (2.95-4.75)	0 (-0.66)	2.95 (2.19-3.89)
Endocrine	1.38 (1.09-1.72)	2.26 (2.02-2.51)	2.02 (1.76-2.31)	1.62 (1.44-1.81)	2.27 (2-2.58)	1.05 (0.85-1.29)	6.09 (5.63-6.57)	2.46 (2.1-2.87)	1.19 (0.65-1.99)	1.62 (1.26-2.04)
Mental	0.78 (0.49-1.18)	1.37 (1.16-1.62)	1.01 (0.82-1.24)	1.55 (1.34-1.78)	0.83 (0.64-1.06)	0.18 (0.09-0.31)	2.25 (1.94-2.59)	0.54 (0.34-0.82)	2.59 (1.34-4.52)	0.5 (0.32-0.75)
Neurological	4.51 (3.87-5.24)	1.66 (1.44-1.91)	2.92 (2.57-3.31)	2.54 (2.3-2.8)	1.41 (1.19-1.66)	0.97 (0.77-1.21)	32.19 (31.02-33.39)	2.37 (1.96-2.84)	3.09 (2.15-4.3)	4.88 (4.16-5.69)
Ocular	0.33 (0.04-1.21)	2.73 (2-3.63)	2.05 (1.25-3.16)	1.96 (1.43-2.63)	5.65 (4.47-7.04)	0 (-0.28)	7.57 (6.11-9.27)	1.77 (1.03-2.84)	0 (-1.53)	25.04 (21.19-29.38)
Auditory	3.99 (2.63-5.81)	0.85 (0.47-1.43)	0 (-0.38)	1.93 (1.34-2.68)	1.93 (1.16-3.02)	0.79 (0.32-1.62)	12.34 (10.19-14.82)	1.49 (0.74-2.67)	7.12 (3.07-14.03)	0 (-0.54)
Cardiovascular	4.55 (4.14-4.99)	3.64 (3.43-3.85)	8.4 (7.91-8.91)	5.68 (5.46-5.91)	5.5 (5.22-5.81)	2.31 (2.12-2.52)	6.45 (6.12-6.8)	2.46 (2.2-2.73)	0.57 (0.35-0.87)	3.24 (2.76-3.79)
Pulmonary	4.33 (3.85-4.86)	3.73 (3.45-4.03)	1.98 (1.73-2.26)	3.64 (3.4-3.89)	1.52 (1.33-1.73)	4.11 (3.77-4.49)	9 (8.5-9.51)	0.45 (0.32-0.62)	0.55 (0.26-1.01)	1.4 (1.12-1.73)
Gastrointestinal	3.03 (2.74-3.34)	3.62 (3.43-3.81)	1.76 (1.6-1.94)	2.11 (1.98-2.25)	3.42 (3.21-3.65)	1.23 (1.09-1.38)	2.14 (1.98-2.32)	3.42 (3.15-3.71)	1.33 (0.98-1.75)	1.63 (1.42-1.86)
Skin	1.44 (0.92-2.17)	1.85 (1.5-2.26)	2.13 (1.73-2.6)	2.57 (2.2-2.99)	3.02 (2.53-3.59)	3.57 (2.95-4.27)	3.19 (2.67-3.78)	2.14 (1.66-2.71)	0 (-1.06)	1.89 (1.33-2.6)
Musculoskeletal	0.63 (0.49-0.8)	1.62 (1.48-1.78)	2.7 (2.47-2.95)	1.24 (1.13-1.36)	1.36 (1.22-1.52)	4.23 (3.96-4.52)	1.3 (1.15-1.46)	0.88 (0.73-1.05)	2.3 (1.84-2.83)	1.19 (0.96-1.46)
Genitourinary	2.03 (1.76-2.33)	9.85 (9.51-10.19)	9.63 (9.18-10.1)	2.38 (2.23-2.52)	3.41 (3.19-3.63)	0.74 (0.63-0.86)	2.32 (2.12-2.53)	11.67 (11.08-12.29)	0.21 (0.1-0.38)	19.39 (18.54-20.27)
Congenital Malformations	0.76 (0.31-1.58)	3.51 (2.63-4.57)	2.31 (1.67-3.13)	1.64 (1.02-2.51)	1.2 (0.64-2.05)	1.05 (0.39-2.29)	33.88 (30.27-37.81)	2.42 (1.21-4.33)	2.07 (0.05-11.54)	1.55 (1-2.31)
Symptoms Unclassified	3.88 (3.31-4.52)	4.07 (3.74-4.43)	2.16 (1.86-2.48)	3.07 (2.8-3.35)	3.82 (3.46-4.2)	2.64 (2.31-3)	8.17 (7.6-8.77)	3.41 (2.93-3.94)	0.99 (0.53-1.69)	1.95 (1.59-2.37)
Injury - Poisoning	2.47 (2.16-2.81)	1.11 (0.99-1.25)	1.57 (1.41-1.74)	1.54 (1.42-1.67)	1.94 (1.77-2.13)	5.39 (5.06-5.74)	5.7 (5.38-6.03)	1.27 (1.08-1.49)	0.33 (0.13-0.68)	0.59 (0.47-0.72)
Other Factors	4.85 (4.38-5.36)	2.23 (2.06-2.42)	2.23 (2.01-2.47)	2.29 (2.13-2.46)	3.31 (3.06-3.59)	2.44 (2.21-2.69)	8.88 (8.44-9.33)	3.5 (3.16-3.87)	0.7 (0.39-1.16)	10.31 (9.51-11.16)

Supplementary Table 11. Relative hospitalisation rates and AER by attained age in 2006.

	attained age <20		attained age 20-30		attained age 31-40		attained age ≥41	
	RHR	AER	RHR	AER	RHR	AER	RHR	AER
Gender								
Male	2.26 (2.16-2.37)	105.6	3.81 (3.71-3.91)	273.8	3.14 (3.04-3.23)	295.7	2.54 (2.44-2.65)	414.4
Female	2.44 (2.34-2.55)	127.5	3.62 (3.52-3.72)	328.9	2.95 (2.86-3.04)	378.9	2.74 (2.63-2.84)	528.6
Status at December 2018 (Ending date)								
Alive	1.8 (1.74-1.87)	69.5	2.67 (2.61-2.73)	191.1	2.24 (2.18-2.29)	212.6	1.71 (1.64-1.77)	224.6
Dead	43.62 (40.92-46.46)	2988.6	53.44 (51.53-55.41)	3207.4	20.12 (19.29-20.97)	2068.5	11 (10.5-11.51)	1787.1
Year of diagnosis								
<1970	2.16 (1.95-2.38)	238.9	2.41 (2.31-2.5)	440.3
1970-1979	.	.	4.7 (4.44-4.97)	494.6	3.3 (3.2-3.4)	376.8	3.15 (3.02-3.28)	533.8
1980-1989	4.39 (4.03-4.78)	286.9	3.73 (3.63-3.83)	303.6	2.98 (2.88-3.08)	319.3	2.12 (1.66-2.68)	214.7
≥1990	2.19 (2.12-2.27)	102.6	3.33 (3.22-3.44)	248.2	1.9 (1.66-2.17)	133.7	.	.
Age at first cancer								
0-1	2.15 (2.04-2.26)	97.6	4.14 (3.97-4.31)	368.3	2.8 (2.65-2.97)	323.9	2.74 (2.51-2.98)	473.7
2-4	2.08 (1.96-2.20)	94.4	3.74 (3.6-3.89)	304.8	3.04 (2.88-3.21)	328.4	2.7 (2.52-2.89)	528.8
5-9	2.81 (2.62-2.99)	154.4	4.17 (4.01-4.34)	334.9	3.48 (3.34-3.63)	396.7	2.29 (2.15-2.44)	358.0
10-14	3.61 (3.26-3.98)	225.4	3.27 (3.13-3.41)	254.4	2.99 (2.87-3.12)	332.8	3.26 (3.12-3.4)	628.8
≥15	.	.	2.64 (2.47-2.81)	180.5	2.48 (2.34-2.62)	243.3	1.62 (1.47-1.78)	190.9
First primary cancer type								
Kidney tumours	1.87 (1.7-2.05)	72.5	4.05 (3.86-4.25)	362.1	2.98 (2.82-3.14)	339.5	3.61 (3.4-3.82)	705.9
Neuroblastoma	1.36 (1.24-1.49)	30.6	4.17 (3.97-4.37)	368.6	2.37 (2.19-2.56)	238.1	3.2 (2.86-3.58)	565.2
Lymphoma	2.1 (1.87-2.36)	95.7	2.93 (2.79-3.08)	205.7	2.92 (2.79-3.06)	331.1	3.32 (3.14-3.51)	648.6
Soft tissue sarcomas	2.8 (2.53-3.08)	157.1	3.92 (3.7-4.16)	329.4	2.7 (2.54-2.86)	278.0	1.67 (1.52-1.83)	216.7
Bone sarcomas	3.52 (3.08-4.01)	202.2	3.33 (3.13-3.54)	259.6	2.39 (2.21-2.58)	222.3	2.15 (1.97-2.34)	347.2
Central nervous system tumour	4.09 (3.83-4.36)	266.1	4.72 (4.5-4.96)	381.9	4.99 (4.72-5.28)	560.6	2.72 (2.48-2.97)	417.3
Gonadal/Germ cell tumours	3.05 (2.58-3.58)	149.8	2.02 (1.84-2.21)	120.5	3.01 (2.77-3.25)	334.4	1.49 (1.3-1.7)	157.6
Thyroid tumour	0.97 (0.36-2.11)	-2.4	1.89 (1.43-2.45)	102.6	1.56 (1.01-2.3)	114.6	0.86 (0.66-1.1)	-53.5
Retinoblastoma	2.21 (2.07-2.37)	108.6	4.23 (3.92-4.56)	377.9	4.02 (3.43-4.69)	483.3	0.61 (0.33-1.02)	-140.5
Other solid cancer	2.35 (2.03-2.72)	113.7	3.8 (3.52-4.1)	281.7	2.89 (2.62-3.17)	326.0	3.79 (3.39-4.23)	725.4
Treatment Received								
No radiotherapy or chemotherapy	1.52 (1.39-1.66)	45.0	1.86 (1.73-2)	97.9	1.41 (1.27-1.56)	71.2	1.01 (0.88-1.17)	4.5
Radiotherapy	4.05 (3.69-4.43)	279.2	3.96 (3.74-4.19)	309.5	4.38 (4.15-4.61)	537.8	2.22 (2.11-2.33)	372.0
Chemotherapy	1.8 (1.71-1.89)	67.7	2.95 (2.85-3.04)	222.2	2.37 (2.26-2.49)	214.5	2.2 (2-2.42)	371.8
Radiotherapy and Chemotherapy	3.44 (3.27-3.61)	209.1	5.18 (5.04-5.32)	456.0	3.29 (3.2-3.39)	393.6	3.77 (3.62-3.91)	677.2

Supplementary Table 12. Relative bed days ratio and AER by attained age in 2006.

	attained age <20		attained age 20-30		attained age 31-40		attained age >=41	
	RBDR	AER	RBDR	AER	RBDR	AER	RBDR	AER
Gender	2.49 (2.41-2.58)	206.8	4.85 (4.77-4.93)	678.5	4.24 (4.17-4.32)	959.5	3.74 (3.65-3.82)	1812.2
Male	3.27 (3.17-3.37)	304.0	6.71 (6.6-6.82)	1080.5	5.1 (5.01-5.2)	1286.4	4.62 (4.53-4.72)	2173.4
Female								
Status at December 2018 (Ending date)								
Alive	2.05 (1.99-2.1)	143.3	3.7 (3.65-3.76)	506.4	2.98 (2.93-3.03)	625.0	1.94 (1.9-1.99)	649.2
Dead	62.82 (60.27-65.46)	6927.5	105.49 (103.39-107.63)	10240.4	41.09 (40.23-41.97)	8140.5	22.38 (21.93-22.83)	9286.1
Year of diagnosis								
<1970	2.42 (2.26-2.58)	558.2	4.06 (4.00-4.16)	2194.3
1970-1979	.	.	3.26 (3.09-3.43)	513.7	5.52 (5.42-5.62)	1317.2	4.62 (4.51-4.73)	1819.9
1980-1989	4.61 (4.32-4.91)	507.1	7.33 (7.22-7.43)	1142.1	4.48 (4.39-4.56)	1051.9	4.40 (3.93-4.90)	1448.7
>=1990	2.72 (2.65-2.78)	233.4	4.01 (3.92-4.11)	529.7	2.05 (1.86-2.24)	296.0	.	.
Age at first cancer								
0-1	2.47 (2.38-2.57)	188.5	4.33 (4.2-4.46)	650.4	3.73 (3.59-3.86)	899.8	4.73 (4.53-4.93)	2381.4
2-4	2.58 (2.47-2.68)	223.8	8.91 (8.74-9.09)	1419.9	4.97 (4.82-5.13)	1118.5	4.17 (4.02-4.34)	2094.6
5-9	3.46 (3.31-3.61)	364.1	7.06 (6.89-7.22)	1045.2	6.12 (5.98-6.27)	1454.8	3.92 (3.79-4.04)	1827.8
10-14	4.36 (4.06-4.67)	475.4	3.67 (3.56-3.79)	488.2	4.47 (4.36-4.58)	1123.2	4.84 (4.72-4.95)	2367.7
≥15	.	.	3.19 (3.06-3.34)	407.3	3.5 (3.38-3.63)	758.1	2.38 (2.25-2.51)	871.2
First primary cancer type								
Kidney tumours	1.95 (1.81-2.1)	120.2	6.46 (6.27-6.65)	1121.0	4.54 (4.4-4.69)	1095.5	4.2 (4.05-4.35)	1892.1
Neuroblastoma	1.5 (1.4-1.61)	68.1	4.03 (3.87-4.19)	559.1	2.96 (2.81-3.12)	602.7	8.89 (8.49-9.3)	4215.7
Lymphoma	2.32 (2.13-2.53)	185.5	3.38 (3.26-3.5)	431.4	3.83 (3.72-3.94)	893.3	5.07 (4.92-5.22)	2625.1
Soft tissue sarcomas	2.43 (2.25-2.62)	240.6	5.63 (5.43-5.84)	888.6	3.73 (3.6-3.88)	807.1	2.5 (2.37-2.63)	1029.0
Bone sarcomas	7.84 (7.25-8.46)	717.6	4.55 (4.36-4.74)	617.7	4.6 (4.42-4.79)	1103.2	1.6 (1.5-1.71)	398.2
Central nervous system tumour	5.58 (5.34-5.83)	616.7	10.36 (10.09-10.63)	1506.5	9.52 (9.25-9.81)	2249.7	7.58 (7.33-7.84)	3973.3
Gonadal/Germ cell tumours	5.36 (4.86-5.89)	517.7	2.47 (2.31-2.64)	277.6	6.16 (5.92-6.41)	1681.4	3.05 (2.85-3.25)	1371.4
Thyroid tumour	1.21 (0.58-2.22)	21.8	4.15 (3.58-4.8)	545.5	1.1 (0.75-1.56)	36.9	1.34 (1.16-1.53)	255.0
Retinoblastoma	2.49 (2.37-2.62)	206.9	12.03 (11.62-12.46)	2099.1	4.55 (4.11-5.04)	1161.2	2.49 (1.97-3.09)	745.1
Other solid cancer	2.7 (2.42-2.99)	232.0	6.04 (5.77-6.33)	838.2	3.36 (3.14-3.59)	706.5	3.47 (3.21-3.76)	1369.2
Treatment Received								
No radiotherapy or chemotherapy	1.21 (1.12-1.3)	30.9	2.02 (1.91-2.14)	187.0	1.39 (1.28-1.5)	121.3	1.26 (1.15-1.37)	181.1
Radiotherapy	3.45 (3.19-3.74)	356.7	8.15 (7.9-8.41)	1195.7	7.02 (6.82-7.23)	1829.7	3.97 (3.88-4.07)	2044.4
Chemotherapy	2.49 (2.4-2.58)	194.8	4.64 (4.54-4.73)	663.3	3.6 (3.51-3.7)	783.7	4.18 (4-4.37)	2307.3
Radiotherapy and Chemotherapy	4.56 (4.4-4.71)	480.8	7.49 (7.36-7.62)	1221.7	5.23 (5.14-5.32)	1290.6	5.35 (5.23-5.47)	2259.0

A.3.4 Multivariate analysis

Supplementary Table 13. Multivariate analysis of the number of hospitalisations by the type of hospitalisation.

	Infections	Neoplasms	Haematological	Endocrine	Mental	Neurological	Ocular	Auditory†	Cardiovascular
Intercept	0.51 (0.24 -1.11)	7.32 (6.35 -8.44) ***	0.55 (0.22 -1.39)	1.49 (0.93 -2.38)	0.86 (0.44 -1.66)	2.96 (1.92 -4.57) ***	1.63 (0.78 -3.39)	0.33 (0.07 -1.43)	3.05 (2.13 -4.37) ***
Female (Ref = Male)	1.14 (0.88 -1.47)	0.81 (0.78 -0.84) ***	0.95 (0.73 -1.24)	0.77 (0.67 -0.88) ***	1.14 (0.9 -1.45)	1.06 (0.92 -1.22)	1.04 (0.83 -1.3)	0.95 (0.65 -1.39)	1.19 (1.09 -1.31) ***
Age in 2006	1.04 (1 -1.08) **	0.95 (0.95 -0.96) ***	1.01 (0.98 -1.05)	1 (0.98 -1.02)	0.96 (0.92 -1) **	0.99 (0.97 -1.01)	0.97 (0.94 -1)	0.97 (0.92 -1.03)	0.93 (0.91 -0.94) ***
Year of Diagnosis (Ref = >1990)									
<1970	0.42 (0.11 -1.56)	1.39 (1.14 -1.7) ***	1.28 (0.37 -4.39)	0.66 (0.32 -1.33)	5.42 (1.57 -18.72) ***	0.59 (0.29 -1.22)	1.04 (0.33 -3.31)	2.76 (0.35 -21.71)	7.72 (4.86 -12.27) ***
1970-1979	0.91 (0.39 -2.1)	1.12 (0.98 -1.27)	1.05 (0.47 -2.37)	0.86 (0.55 -1.33)	5.93 (2.64 -13.31) ***	0.93 (0.59 -1.47)	1.43 (0.69 -2.96)	3.63 (1.02 -13.01) **	6.19 (4.54 -8.45) ***
1980-1989	1.29 (0.78 -2.14)	1.12 (1.03 -1.21) ***	1.2 (0.73 -1.99)	1.23 (0.93 -1.62)	2.21 (1.32 -3.69) ***	1.16 (0.87 -1.53)	1.39 (0.88 -2.21)	2.05 (0.92 -4.58)	3.65 (2.96 -4.51) ***
Age at first cancer (Ref = 0-1)									
2-4	1.33 (0.87 -2.02)	0.9 (0.84 -0.97) ***	1.26 (0.82 -1.94)	1.56 (1.2 -2.04) ***	0.77 (0.53 -1.12)	1.07 (0.84 -1.38)	1.45 (1.07 -1.98) **	1.57 (0.63 -3.9)	1.49 (1.26 -1.75) ***
5-9	0.97 (0.59 -1.59)	1.17 (1.08 -1.27) ***	1.86 (1.11 -3.11) **	1.66 (1.24 -2.22) ***	1.44 (0.94 -2.19)	1.24 (0.94 -1.65)	1.3 (0.86 -1.95)	2.88 (1.12 -7.43) **	2.12 (1.77 -2.54) ***
10-14	0.83 (0.44 -1.58)	1.59 (1.44 -1.75) ***	1.23 (0.63 -2.4)	1.17 (0.81 -1.68)	1.81 (1.05 -3.12) **	0.81 (0.57 -1.15)	0.8 (0.45 -1.4)	2.66 (0.87 -8.11)	1.47 (1.16 -1.86) ***
≥15	0.49 (0.21 -1.15)	1.09 (0.96 -1.24)	0.48 (0.18 -1.28)	0.95 (0.6 -1.5)	1.45 (0.7 -3.01)	0.75 (0.48 -1.18)	0.85 (0.42 -1.73)	3.01 (0.8 -11.37)	1.58 (1.18 -2.11) ***
First primary cancer type (Ref = Neuroblastoma)								0.22 (0.03 -1.81)	
Kidney tumours	1.63 (1.01 -2.63) **	1.06 (0.97 -1.17)	0.99 (0.61 -1.61)	0.7 (0.51 -0.97) **	1.3 (0.8 -2.11)	0.5 (0.35 -0.7) ***	0.75 (0.4 -1.43)	Ref	0.73 (0.6 -0.88) ***
Lymphoma	1 (0.57 -1.74)	1.24 (1.12 -1.36) ***	1.32 (0.77 -2.25)	0.78 (0.56 -1.09)	1.14 (0.66 -1.97)	0.63 (0.45 -0.88) ***	1.09 (0.57 -2.07)	1.39 (0.56 -3.45)	1.2 (0.99 -1.45)
Soft tissue sarcomas	0.85 (0.48 -1.53)	1.11 (1.01 -1.23) **	0.39 (0.19 -0.82) ***	0.63 (0.44 -0.91) ***	2.25 (1.38 -3.67) ***	0.53 (0.37 -0.78) ***	1.75 (0.95 -3.2)	1.88 (0.74 -4.77)	1.57 (1.3 -1.89) ***
Bone sarcomas	1.18 (0.63 -2.22)	1.54 (1.38 -1.71) ***	0.81 (0.42 -1.55)	0.52 (0.34 -0.8) ***	0.5 (0.23 -1.07)	0.49 (0.32 -0.77) ***	0.73 (0.32 -1.68)	1.35 (0.44 -4.16)	0.99 (0.79 -1.25)
Central nervous system tumour	1.28 (0.71 -2.31)	1.41 (1.28 -1.56) ***	0.71 (0.41 -1.23)	2.06 (1.52 -2.79) ***	2.44 (1.45 -4.11) ***	3.79 (2.84 -5.06) ***	2.7 (1.5 -4.87) ***	5.7 (2.48 -13.07) ***	0.74 (0.58 -0.93) ***
Gonadal tumour	0.79 (0.37 -1.67)	1.12 (0.99 -1.27)	0.54 (0.22 -1.37)	1.53 (1.07 -2.21) **	0.97 (0.48 -1.94)	0.84 (0.55 -1.27)	0.97 (0.42 -2.26)	2.29 (0.76 -6.91)	1.19 (0.92 -1.54)
Thyroid tumour	1.53 (0.34 -6.82)	0.43 (0.31 -0.62) ***	0 (0 -)	0.86 (0.31 -2.41)	6.44 (2.76 -15.02) ***	1.35 (0.68 -2.69)	2.27 (0.78 -6.62)	1.64 (0.19 -14.23)	0.4 (0.16 -0.97) **
Retinoblastoma	0.47 (0.2 -1.09)	1.75 (1.58 -1.94) ***	1.72 (0.93 -3.2)	0.57 (0.36 -0.89) ***	1.27 (0.66 -2.44)	0.48 (0.31 -0.76) ***	11.51 (6.82 -19.43) ***	0.61 (0.12 -3.03)	0.78 (0.58 -1.03)

Other solid cancer	1.58 (0.79 -3.19)	1.4 (1.24 -1.58) ***	1.67 (0.86 - 3.25)	0.74 (0.47 - 1.17)	3.82 (2.18 - 6.68) ***	1.4 (0.95 - 2.05)	1.12 (0.47 -2.7)	6.05 (2.39 -15.35) ***	1.35 (1.04 - 1.76) **
Treatment (Ref = No radiation or chemotherapy)									
Chemotherapy	1.45 (0.88 -2.4)	1.75 (1.58 -1.94) ***	3.59 (1.69 - 7.66) ***	1.52 (1.07 - 2.17) **	0.96 (0.64 - 1.43)	1.27 (0.94 - 1.71)	1.34 (0.85 - 2.11)	1.09 (0.44 -2.7)	2.56 (1.95 - 3.36) ***
Radiation	0.71 (0.37 -1.37)	2.54 (2.28 -2.82) ***	2.71 (1.2 - 6.08) **	2.93 (2.05 - 4.18) ***	0.61 (0.38 - 0.98) **	1.81 (1.34 - 2.44) ***	2.27 (1.42 - 3.62) ***	1.97 (0.86 -4.53)	2.91 (2.18 - 3.88) ***
Radiation and Chemotherapy	1.5 (0.92 -2.45)	3.47 (3.15 -3.83) ***	4.41 (2.08 - 9.38) ***	3.38 (2.42 - 4.72) ***	1.15 (0.79 - 1.68)	1.29 (0.97 - 1.71)	2.17 (1.41 - 3.35) ***	2.46 (1.12 -5.4) **	4.37 (3.36 - 5.69) ***

*** p<0.01, ** p<0.05, † Reference in First primary Cancer "Kidney Tumours"

Supplementary Table 13. Multivariate analysis of the number of hospitalisations by the type of hospitalisation. Continued.

	Pulmonary	Gastrointestinal	Skin	Musculoskeletal	Genitourinary	Congenital Mal- formations	Symptoms Un- classified	Injury - Poison- ing	Other Factors
Intercept	0.33 (0.19 -0.57) ***	0.74 (0.58 -0.95) **	1.16 (0.68 -1.97)	1.78 (1.22 -2.59) ***	1.81 (1.41 -2.33) ***	0.78 (0.31 -1.96)	0.89 (0.61 -1.29)	0.43 (0.3 -0.62) ***	4.01 (3.23 -4.97) ***
Female (Ref = Male)	1.38 (1.17 -1.62) ***	1.02 (0.93 -1.11)	1.11 (0.9 -1.35)	1.22 (1.06 -1.39) ***	0.45 (0.42 -0.49) ***	0.75 (0.54 -1.04)	1.03 (0.92 -1.16)	1.4 (1.23 -1.6) ***	0.7 (0.65 -0.75) ***
Age in 2006	1.01 (0.99 -1.04)	1.01 (1 -1.02)	1.02 (0.99 -1.05)	0.99 (0.97 -1.01)	1.02 (1.01 -1.03) ***	1.05 (1 -1.1)	0.99 (0.98 -1.01)	1.04 (1.02 -1.06) ***	0.98 (0.97 -0.99) ***
Year of Diagnosis (Ref = >1990)									
<1970	0.92 (0.4 -2.1)	1.04 (0.68 -1.6)	0.9 (0.32 -2.49)	0.82 (0.42 -1.62)	0.25 (0.18 -0.35) ***	0.5 (0.09 -2.76)	1.17 (0.65 -2.12)	0.51 (0.27 -0.97) **	1.26 (0.87 -1.81)
1970-1979	1.69 (1.01 -2.82) **	1.06 (0.8 -1.39)	0.62 (0.32 -1.2)	1.2 (0.78 -1.85)	1.04 (0.83 -1.3)	0.59 (0.2 -1.73)	1.69 (1.16 -2.47) ***	0.81 (0.54 -1.21)	1.18 (0.93 -1.49)
1980-1989	1.32 (0.95 -1.83)	1.2 (1.01 -1.42) **	1.07 (0.73 -1.57)	1.27 (0.97 -1.66)	1.21 (1.04 -1.4) ***	1.52 (0.78 -2.96)	1.24 (0.98 -1.58)	0.96 (0.75 -1.22) ***	1.19 (1.03 -1.38) **
Age at first cancer (Ref = 0-1)									
2-4	1.35 (1 -1.84) **	1.02 (0.88 -1.17)	0.66 (0.48 -0.9) ***	0.92 (0.74 -1.15)	0.34 (0.31 -0.37) ***	2.02 (1.1 -3.71) **	1.35 (1.11 -1.65) ***	0.95 (0.77 -1.17)	1.1 (0.97 -1.24)
5-9	1.74 (1.25 -2.43) ***	1.11 (0.94 -1.31)	0.69 (0.48 -1) **	0.78 (0.6 -1.01)	0.36 (0.32 -0.4) ***	1.89 (0.94 -3.79)	1.3 (1.03 -1.64) **	0.85 (0.66 -1.09)	1.04 (0.9 -1.21)
10-14	1.26 (0.83 -1.93)	1.06 (0.86 -1.31)	0.47 (0.29 -0.75) ***	0.65 (0.46 -0.91) ***	0.2 (0.17 -0.25) ***	1.5 (0.65 -3.46)	1.53 (1.14 -2.05) ***	0.8 (0.59 -1.09)	1.2 (1 -1.43) **
≥15	1.25 (0.74 -2.1)	0.82 (0.63 -1.07)	0.43 (0.23 -0.77) ***	1.16 (0.78 -1.72)	0.13 (0.11 -0.17) ***	0.69 (0.22 -2.18)	1.17 (0.8 -1.69)	0.75 (0.52 -1.1)	1.06 (0.85 -1.34)
First primary cancer type (Ref = Neuroblastoma)									
Kidney tumours	1.74 (1.19 -2.54) ***	1.42 (1.19 -1.7) ***	0.74 (0.48 -1.14)	0.78 (0.61 -0.99) **	1.22 (1.11 -1.34) ***	1.18 (0.54 -2.57)	1.34 (1.05 -1.71) **	0.85 (0.65 -1.11)	1.42 (1.21 -1.65) ***
Lymphoma	1.8 (1.21 -2.68) ***	1.3 (1.07 -1.58) ***	1.52 (0.99 -2.32) **	0.68 (0.52 -0.9) ***	0.41 (0.36 -0.48) ***	0.81 (0.33 -1.95)	1.04 (0.79 -1.36)	1.07 (0.81 -1.42)	1.13 (0.96 -1.34)
Soft tissue sarcomas	1.03 (0.66 -1.59)	1.19 (0.98 -1.45)	1.59 (1.05 -2.4) **	0.67 (0.51 -0.89) ***	0.57 (0.5 -0.65) ***	0.96 (0.42 -2.23)	0.97 (0.74 -1.28)	1.02 (0.77 -1.35)	1.28 (1.08 -1.51) ***
Bone sarcomas	0.86 (0.52 -1.42)	1.01 (0.8 -1.28)	2 (1.25 -3.22) ***	1.05 (0.78 -1.41)	0.35 (0.28 -0.43) ***	0.4 (0.12 -1.3)	0.76 (0.55 -1.05)	1.64 (1.22 -2.19) ***	1.17 (0.96 -1.42)
Central nervous system tumour	2.61 (1.76 -3.87) ***	1.07 (0.87 -1.32)	1.13 (0.71 -1.79)	0.65 (0.48 -0.88) ***	0.28 (0.23 -0.35) ***	2.37 (1.17 -4.82) **	1.89 (1.45 -2.45) ***	1.37 (1.03 -1.82) **	1.69 (1.43 -1.99) ***
Gonadal tumour	0.67 (0.36 -1.26)	1.53 (1.23 -1.9) ***	2.26 (1.45 -3.54) ***	0.59 (0.42 -0.85) ***	1.36 (1.16 -1.6) ***	1.75 (0.77 -3.99)	0.69 (0.47 -1.01) **	0.79 (0.55 -1.12)	1.01 (0.82 -1.24)
Thyroid tumour	1.09 (0.38 -3.14)	0.98 (0.6 -1.6)	0.43 (0.06 -3.18)	1.17 (0.67 -2.06)	0.84 (0.43 -1.64)	0.75 (0.16 -3.56)	1.22 (0.62 -2.38)	0.76 (0.36 -1.61)	0.58 (0.32 -1.05)
Retinoblastoma	0.81 (0.46 -1.41)	0.88 (0.7 -1.11)	0.59 (0.35 -1) **	0.37 (0.25 -0.56) ***	0.38 (0.31 -0.46) ***	0.61 (0.25 -1.52)	0.67 (0.46 -0.97) **	0.68 (0.48 -0.96) **	0.79 (0.64 -0.96) **
Other solid cancer	1.91 (1.17 -3.09) ***	1.95 (1.57 -2.42) ***	1.97 (1.2 -3.23) ***	0.65 (0.45 -0.95) **	1.45 (1.22 -1.71) ***	0.24 (0.05 -1.12)	1.66 (1.21 -2.27) ***	1.08 (0.76 -1.55) ***	1.59 (1.31 -1.93) ***

Treatment (Ref = No radiation or chemotherapy)

Chemotherapy	1.17 (0.78 -1.75)	0.97 (0.83 -1.14)	1.1 (0.79 -1.54)	1.08 (0.84 -1.38)	6.53 (5.34 -7.99)	0.52 (0.28 -1) **	1.66 (1.28 -2.16)	1.34 (1.06 -1.69)	0.74 (0.64 -0.85)
	***				***		***	**	***
Radiation	2.41 (1.61 -3.61)	1.23 (1.02 -1.47)	1.3 (0.85 -1.99)	1.45 (1.09 -1.94)	5.35 (4.23 -6.77)	2.96 (1.62 -5.4)	1.62 (1.22 -2.15)	1.27 (0.97 -1.67)	1.46 (1.25 -1.7)
	***	**		***	***	***	***		***
Radiation and Chemotherapy	2.31 (1.59 -3.37)	1.24 (1.06 -1.45)	1.13 (0.8 -1.6)	1.32 (1.03 -1.68) **	9.98 (8.17 -12.19)	0.56 (0.3 -1.03)	2.16 (1.68 -2.78)	1 (0.79 -1.28)	1.32 (1.16 -1.51)
	***	***		***	***		***		***

*** p<0.01, ** p<0.05, † Reference in First primary Cancer "Kidney Tumours"

Supplementary Table 14. Multivariate analysis of the number of bed days by the type of hospitalisation.

	Pulmonary	Gastrointestinal	Skin	Musculoskeletal	Genitourinary	Congenital Malformations	Symptoms Unclassified	Injury - Poisoning	Other Factors
Intercept	0.17 (0.13 -0.22) ***	1.02 (0.87 -1.21)	0.71 (0.46 -1.09)	2.6 (2.11 -3.21) ***	0.23 (0.19 -0.27) ***	3.65 (2.09 -6.39) ***	0.54 (0.41 -0.7) ***	0.43 (0.35 -0.53) ***	1.03 (0.85 -1.25)
Female (Ref = Male)	2.09 (1.96 -2.23) ***	1.23 (1.16 -1.29) ***	1.01 (0.88 -1.17)	1.21 (1.13 -1.3) ***	0.73 (0.7 -0.76) ***	0.69 (0.57 -0.84) ***	1.32 (1.22 -1.41) ***	2.01 (1.89 -2.13) ***	1.32 (1.25 -1.39) ***
Age in 2006	1.05 (1.04 -1.06) ***	1 (1 -1.01)	1 (0.98 -1.03)	0.97 (0.96 -0.98) ***	0.96 (0.96 -0.97) ***	0.92 (0.89 -0.95) ***	0.98 (0.97 -0.99) ***	1 (0.99 -1.01)	1.01 (1 -1.02) **
Year of Diagnosis (Ref = >1990)									
<1970	0.32 (0.23 -0.44) ***	1.31 (1.03 -1.68) **	1.62 (0.84 -3.14)	2.87 (2.04 -4.02) ***	16.56 (13.65 -20.1) ***	217.92 (73.55 -645.69) ***	2.47 (1.71 -3.57) ***	1.46 (1.08 -1.98) ***	0.66 (0.51 -0.86) ***
1970-1979	0.88 (0.72 -1.07)	1.1 (0.94 -1.3)	1.02 (0.66 -1.57)	1.51 (1.2 -1.89) ***	9.07 (7.94 -10.36) ***	21.56 (10.18 -45.67) ***	3.39 (2.67 -4.3) ***	1.72 (1.42 -2.08) ***	0.94 (0.8 -1.11)
1980-1989	1.5 (1.32 -1.72) ***	1.05 (0.94 -1.16)	1.59 (1.22 -2.07) ***	1.79 (1.55 -2.06) ***	9.54 (8.69 -10.48) ***	10.11 (6.22 -16.44) ***	3.03 (2.6 -3.53) ***	1.81 (1.61 -2.03) ***	0.91 (0.82 -1.01)
2-4	1.4 (1.22 -1.6) ***	0.87 (0.8 -0.94) ***	0.71 (0.57 -0.89) ***	0.56 (0.5 -0.64) ***	2.82 (2.67 -2.97) ***	1.6 (1.13 -2.28) ***	2.18 (1.91 -2.48) ***	1 (0.89 -1.13)	0.63 (0.58 -0.69) ***
5-9	1.72 (1.49 -1.99) ***	0.88 (0.8 -0.96) ***	0.72 (0.55 -0.93) ***	0.73 (0.63 -0.84) ***	2.13 (1.98 -2.29) ***	5.61 (3.8 -8.3) ***	1.37 (1.17 -1.6) ***	1.37 (1.21 -1.56) ***	0.76 (0.68 -0.84) ***
10-14	1.19 (1 -1.41) **	0.99 (0.87 -1.11)	0.6 (0.43 -0.83) ***	0.98 (0.83 -1.17)	1.76 (1.59 -1.96) ***	1.29 (0.75 -2.21)	1.66 (1.38 -2) ***	1.41 (1.21 -1.64) ***	0.75 (0.66 -0.86) ***
≥15	0.46 (0.37 -0.57) ***	0.49 (0.42 -0.58) ***	0.71 (0.48 -1.06)	1.29 (1.05 -1.58) ***	0.53 (0.45 -0.63) ***	2.42 (0.98 -5.97)	1.18 (0.93 -1.49)	1.28 (1.06 -1.54) ***	0.81 (0.69 -0.95) ***
First primary cancer type (Ref = Neuroblastoma)									
Other solid cancer	2.07 (1.71 -2.52) ***	2.16 (1.87 -2.51) ***	1.2 (0.74 -1.94)	0.38 (0.29 -0.49) ***	0.5 (0.43 -0.58) ***	0.29 (0.13 -0.67) ***	2.53 (2.03 -3.17) ***	1.39 (1.17 -1.67) ***	2.76 (2.37 -3.21) ***
Kidney tumours	1.53 (1.3 -1.79) ***	2.09 (1.87 -2.35) ***	0.92 (0.68 -1.25)	0.89 (0.78 -1.02)	0.81 (0.76 -0.86) ***	0.68 (0.44 -1.07)	1.6 (1.35 -1.9) ***	0.55 (0.47 -0.64) ***	0.99 (0.87 -1.14)
Lymphoma	1.44 (1.21 -1.7) ***	1.42 (1.25 -1.61) ***	1.4 (1.03 -1.9) **	0.63 (0.54 -0.74) ***	0.4 (0.37 -0.44) ***	0.69 (0.39 -1.23)	1.52 (1.26 -1.83) ***	0.7 (0.6 -0.82) ***	1.06 (0.92 -1.21)
Soft tissue sarcomas	0.61 (0.5 -0.74) ***	2.37 (2.1 -2.68) ***	1.94 (1.44 -2.61) ***	0.7 (0.6 -0.82) ***	0.46 (0.42 -0.5) ***	0.3 (0.15 -0.58) ***	1.79 (1.5 -2.15) ***	0.94 (0.81 -1.1) ***	1.52 (1.33 -1.75) ***
Bone sarcomas	1.77 (1.48 -2.12) ***	0.9 (0.76 -1.06)	2.62 (1.88 -3.64) ***	2.59 (2.24 -3) ***	0.05 (0.04 -0.06) ***	0.5 (0.21 -1.22)	1.67 (1.35 -2.06) ***	2.4 (2.08 -2.78) ***	1.24 (1.06 -1.44) ***
Central nervous system tumour	2.38 (2.01 -2.81) ***	1.5 (1.31 -1.72) ***	1.72 (1.26 -2.34) ***	0.69 (0.58 -0.81) ***	0.49 (0.44 -0.55) ***	8.61 (5.68 -13.07) ***	3.85 (3.22 -4.6) ***	2.7 (2.35 -3.11) ***	3.64 (3.21 -4.14) ***
Gonadal tumour	0.19 (0.13 -0.27) ***	2.79 (2.45 -3.19) ***	1.67 (1.17 -2.39) ***	0.56 (0.45 -0.69) ***	2.59 (2.39 -2.8) ***	0.67 (0.34 -1.33)	1.97 (1.6 -2.44) ***	0.65 (0.54 -0.8) ***	1.97 (1.69 -2.29) ***
Thyroid tumour	0.3 (0.16 -0.57) ***	1.45 (1.07 -1.97) **	0 (0 -)	1.96 (1.51 -2.53) ***	0.07 (0.04 -0.13) ***	0.21 (0.03 -1.54)	1.03 (0.58 -1.82)	0.16 (0.08 -0.34) ***	0.53 (0.31 -0.89) **
Retinoblastoma	0.78 (0.61 -1) **	0.97 (0.82 -1.15)	0.98 (0.66 -1.45)	0.44 (0.35 -0.56) ***	5.55 (5.18 -5.95) ***	1.32 (0.78 -2.25)	1.03 (0.81 -1.32)	0.34 (0.27 -0.43) ***	3.67 (3.21 -4.19) ***
Treatment (Ref = No radiation or chemotherapy)									
Chemotherapy	1.93 (1.61 -2.32) ***	1.32 (1.18 -1.47) ***	2.72 (2.01 -3.68) ***	1.47 (1.27 -1.71) ***	25.56 (22.18 -29.45) ***	0.72 (0.5 -1.04)	2.78 (2.32 -3.33) ***	2.91 (2.5 -3.37) ***	1.77 (1.54 -2.02) ***

Radiation	3.69 (3.09 -4.42) ***	1.18 (1.04 -1.33) ***	2.59 (1.83 -3.65) ***	1.49 (1.26 -1.75) ***	6.25 (5.35 -7.3) ***	0.99 (0.67 -1.44)	2.24 (1.85 -2.71) ***	2.65 (2.26 - 3.1) ***	2.24 (1.96 - 2.56) ***
Radiation and Chemotherapy	3.1 (2.61 -3.69) ***	1.95 (1.76 -2.16) ***	3.09 (2.28 -4.19) ***	2.42 (2.09 -2.79) ***	10.77 (9.33 - 12.43) ***	0.17 (0.11 -0.26) ***	2.31 (1.93 -2.77) ***	2.03 (1.75 - 2.36) ***	3.78 (3.34 - 4.28) ***

*** p<0.01, ** p<0.05, † Reference in First primary Cancer "Kidney Tumours"

Supplementary Table 14. Multivariate analysis of the number of bed days by the type of hospitalisation. Continued.

	Pulmonary	Gastrointestinal	Skin	Musculoskeletal	Genitourinary	Congenital Malformations	Symptoms Unclassified	Injury - Poisoning	Other Factors
Intercept	0.17 (0.13 -0.22) ***	1.02 (0.87 -1.21)	0.71 (0.46 -1.09)	2.6 (2.11 -3.21) ***	0.23 (0.19 -0.27) ***	3.65 (2.09 -6.39) ***	0.54 (0.41 -0.7) ***	0.43 (0.35 -0.53) ***	1.03 (0.85 -1.25)
Female (Ref = Male)	2.09 (1.96 -2.23) ***	1.23 (1.16 -1.29) ***	1.01 (0.88 -1.17)	1.21 (1.13 -1.3) ***	0.73 (0.7 -0.76) ***	0.69 (0.57 -0.84) ***	1.32 (1.22 -1.41) ***	2.01 (1.89 -2.13) ***	1.32 (1.25 -1.39) ***
Age in 2006	1.05 (1.04 -1.06) ***	1 (1 -1.01)	1 (0.98 -1.03)	0.97 (0.96 -0.98) ***	0.96 (0.96 -0.97) ***	0.92 (0.89 -0.95) ***	0.98 (0.97 -0.99) ***	1 (0.99 -1.01)	1.01 (1 -1.02) **
Year of Diagnosis (Ref = >1990)									
<1970	0.32 (0.23 -0.44) ***	1.31 (1.03 -1.68) **	1.62 (0.84 -3.14)	2.87 (2.04 -4.02) ***	16.56 (13.65 -20.1) ***	217.92 (73.55 -645.69) ***	2.47 (1.71 -3.57) ***	1.46 (1.08 -1.98) ***	0.66 (0.51 -0.86) ***
1970-1979	0.88 (0.72 -1.07)	1.1 (0.94 -1.3)	1.02 (0.66 -1.57)	1.51 (1.2 -1.89) ***	9.07 (7.94 -10.36) ***	21.56 (10.18 -45.67) ***	3.39 (2.67 -4.3) ***	1.72 (1.42 -2.08) ***	0.94 (0.8 -1.11)
1980-1989	1.5 (1.32 -1.72) ***	1.05 (0.94 -1.16)	1.59 (1.22 -2.07) ***	1.79 (1.55 -2.06) ***	9.54 (8.69 -10.48) ***	10.11 (6.22 -16.44) ***	3.03 (2.6 -3.53) ***	1.81 (1.61 -2.03) ***	0.91 (0.82 -1.01)
2-4	1.4 (1.22 -1.6) ***	0.87 (0.8 -0.94) ***	0.71 (0.57 -0.89) ***	0.56 (0.5 -0.64) ***	2.82 (2.67 -2.97) ***	1.6 (1.13 -2.28) ***	2.18 (1.91 -2.48) ***	1 (0.89 -1.13)	0.63 (0.58 -0.69) ***
5-9	1.72 (1.49 -1.99) ***	0.88 (0.8 -0.96) ***	0.72 (0.55 -0.93) ***	0.73 (0.63 -0.84) ***	2.13 (1.98 -2.29) ***	5.61 (3.8 -8.3) ***	1.37 (1.17 -1.6) ***	1.37 (1.21 -1.56) ***	0.76 (0.68 -0.84) ***
10-14	1.19 (1 -1.41) **	0.99 (0.87 -1.11)	0.6 (0.43 -0.83) ***	0.98 (0.83 -1.17)	1.76 (1.59 -1.96) ***	1.29 (0.75 -2.21)	1.66 (1.38 -2) ***	1.41 (1.21 -1.64) ***	0.75 (0.66 -0.86) ***
≥15	0.46 (0.37 -0.57) ***	0.49 (0.42 -0.58) ***	0.71 (0.48 -1.06)	1.29 (1.05 -1.58) ***	0.53 (0.45 -0.63) ***	2.42 (0.98 -5.97)	1.18 (0.93 -1.49)	1.28 (1.06 -1.54) ***	0.81 (0.69 -0.95) ***
First primary cancer type (Ref = Neuroblastoma)									
Other solid cancer	2.07 (1.71 -2.52) ***	2.16 (1.87 -2.51) ***	1.2 (0.74 -1.94)	0.38 (0.29 -0.49) ***	0.5 (0.43 -0.58) ***	0.29 (0.13 -0.67) ***	2.53 (2.03 -3.17) ***	1.39 (1.17 -1.67) ***	2.76 (2.37 -3.21) ***
Kidney tumours	1.53 (1.3 -1.79) ***	2.09 (1.87 -2.35) ***	0.92 (0.68 -1.25)	0.89 (0.78 -1.02)	0.81 (0.76 -0.86) ***	0.68 (0.44 -1.07)	1.6 (1.35 -1.9) ***	0.55 (0.47 -0.64) ***	0.99 (0.87 -1.14)
Lymphoma	1.44 (1.21 -1.7) ***	1.42 (1.25 -1.61) ***	1.4 (1.03 -1.9) **	0.63 (0.54 -0.74) ***	0.4 (0.37 -0.44) ***	0.69 (0.39 -1.23)	1.52 (1.26 -1.83) ***	0.7 (0.6 -0.82) ***	1.06 (0.92 -1.21)
Soft tissue sarcomas	0.61 (0.5 -0.74) ***	2.37 (2.1 -2.68) ***	1.94 (1.44 -2.61) ***	0.7 (0.6 -0.82) ***	0.46 (0.42 -0.5) ***	0.3 (0.15 -0.58) ***	1.79 (1.5 -2.15) ***	0.94 (0.81 -1.1) ***	1.52 (1.33 -1.75) ***
Bone sarcomas	1.77 (1.48 -2.12) ***	0.9 (0.76 -1.06)	2.62 (1.88 -3.64) ***	2.59 (2.24 -3) ***	0.05 (0.04 -0.06) ***	0.5 (0.21 -1.22)	1.67 (1.35 -2.06) ***	2.4 (2.08 -2.78) ***	1.24 (1.06 -1.44) ***
Central nervous system tumour	2.38 (2.01 -2.81) ***	1.5 (1.31 -1.72) ***	1.72 (1.26 -2.34) ***	0.69 (0.58 -0.81) ***	0.49 (0.44 -0.55) ***	8.61 (5.68 -13.07) ***	3.85 (3.22 -4.6) ***	2.7 (2.35 -3.11) ***	3.64 (3.21 -4.14) ***
Gonadal tumour	0.19 (0.13 -0.27) ***	2.79 (2.45 -3.19) ***	1.67 (1.17 -2.39) ***	0.56 (0.45 -0.69) ***	2.59 (2.39 -2.8) ***	0.67 (0.34 -1.33)	1.97 (1.6 -2.44) ***	0.65 (0.54 -0.8) ***	1.97 (1.69 -2.29) ***
Thyroid tumour	0.3 (0.16 -0.57) ***	1.45 (1.07 -1.97) **	0 (0 -)	1.96 (1.51 -2.53) ***	0.07 (0.04 -0.13) ***	0.21 (0.03 -1.54)	1.03 (0.58 -1.82)	0.16 (0.08 -0.34) ***	0.53 (0.31 -0.89) **
Retinoblastoma	0.78 (0.61 -1) **	0.97 (0.82 -1.15)	0.98 (0.66 -1.45)	0.44 (0.35 -0.56) ***	5.55 (5.18 -5.95) ***	1.32 (0.78 -2.25)	1.03 (0.81 -1.32)	0.34 (0.27 -0.43) ***	3.67 (3.21 -4.19) ***
Treatment (Ref = No radiation or chemotherapy)									
Chemotherapy	1.93 (1.61 -2.32) ***	1.32 (1.18 -1.47) ***	2.72 (2.01 -3.68) ***	1.47 (1.27 -1.71) ***	25.56 (22.18 -29.45) ***	0.72 (0.5 -1.04)	2.78 (2.32 -3.33) ***	2.91 (2.5 -3.37) ***	1.77 (1.54 -2.02) ***

Radiation	3.69 (3.09 -4.42) ***	1.18 (1.04 -1.33) ***	2.59 (1.83 -3.65) ***	1.49 (1.26 -1.75) ***	6.25 (5.35 -7.3) ***	0.99 (0.67 -1.44)	2.24 (1.85 -2.71) ***	2.65 (2.26 - 3.1) ***	2.24 (1.96 - 2.56) ***
Radiation and Chemotherapy	3.1 (2.61 -3.69) ***	1.95 (1.76 -2.16) ***	3.09 (2.28 -4.19) ***	2.42 (2.09 -2.79) ***	10.77 (9.33 - 12.43) ***	0.17 (0.11 -0.26) ***	2.31 (1.93 -2.77) ***	2.03 (1.75 - 2.36) ***	3.78 (3.34 - 4.28) ***

*** p<0.01, ** p<0.05, † Reference in First primary Cancer "Kidney Tumours"

A.3.5 Discussion

Supplementary Table 15. Characteristics of the studies included in the discussion.

Author	Type of CC	Country	N CCSS	Diagnosed	Comparison cohort, N	Hospitalisation follow-up period	Average age at end of follow-up	RHR, AER (x105PY)	Hospitalizations studied
Kirchhoff (2014)	All	USA	1,499	1973-2005	7,219 Comparison cohort based on birth year and sex	1996-2010 (13.5 years)	33,12*	Survivors were hospitalized, on average, 1.62 (SD=3.37) not RHR	All excluding pregnancy and delivery
Kurt (2011)	All	USA	10,366	1970–1986	U.S. population rates using age- and sex-stratified standardized incidence ratios (SIRs)	1992-2005 (13 Years)	Age at 2000 follow-up (years) Mean (SD) 28.6 (7.7)	1.6 times (95% CI: 1.6; 1.7) / AER of 54.9 hospitalizations per 1,000 person-years.	11 organ systems/categories: infectious, neoplasm, cardiovascular, pulmonary, psychological, neurologic, gastrointestinal, genitourinary, endocrine, obstetric, and external
Sieswerda (2016)	All	Netherlands	1,382	1966-1999	26,583 with corresponding year of birth and gender	1995-2005 (10 Years)	Attained age at the end of follow-up 25.3 (5.9–51.3)	The overall RHR and AER were 2.2 (95%CI:1.9–2.5) and 93.3 per 1000 person-years at risk,	All Hospitalization
Streefkerk (2020)	All	Netherlands	5,650	1963-2001	109,605 age- and sex-matched controls	1995-2016 (20 Years)	30,68*	RHR 2.0 (95% CI: 1.9-2.2) AER was 100.18 per 1,000 PY	Hospitalizations for giving birth were excluded
Mueller (2018)	All	USA	3,152	1974–2014	31,520 matched on birth year and sex	1982–2014 Median follow-up after index date was 9.1 years (range 0.1–27.0 years)	22,58*	Any hospitalization rate (HR 2.7, 95% CI 2.4–3.0) x 1,000 PY not AER reported	Pregnancy-related hospitalizations (ICD9 630–679, 760–779) were excluded

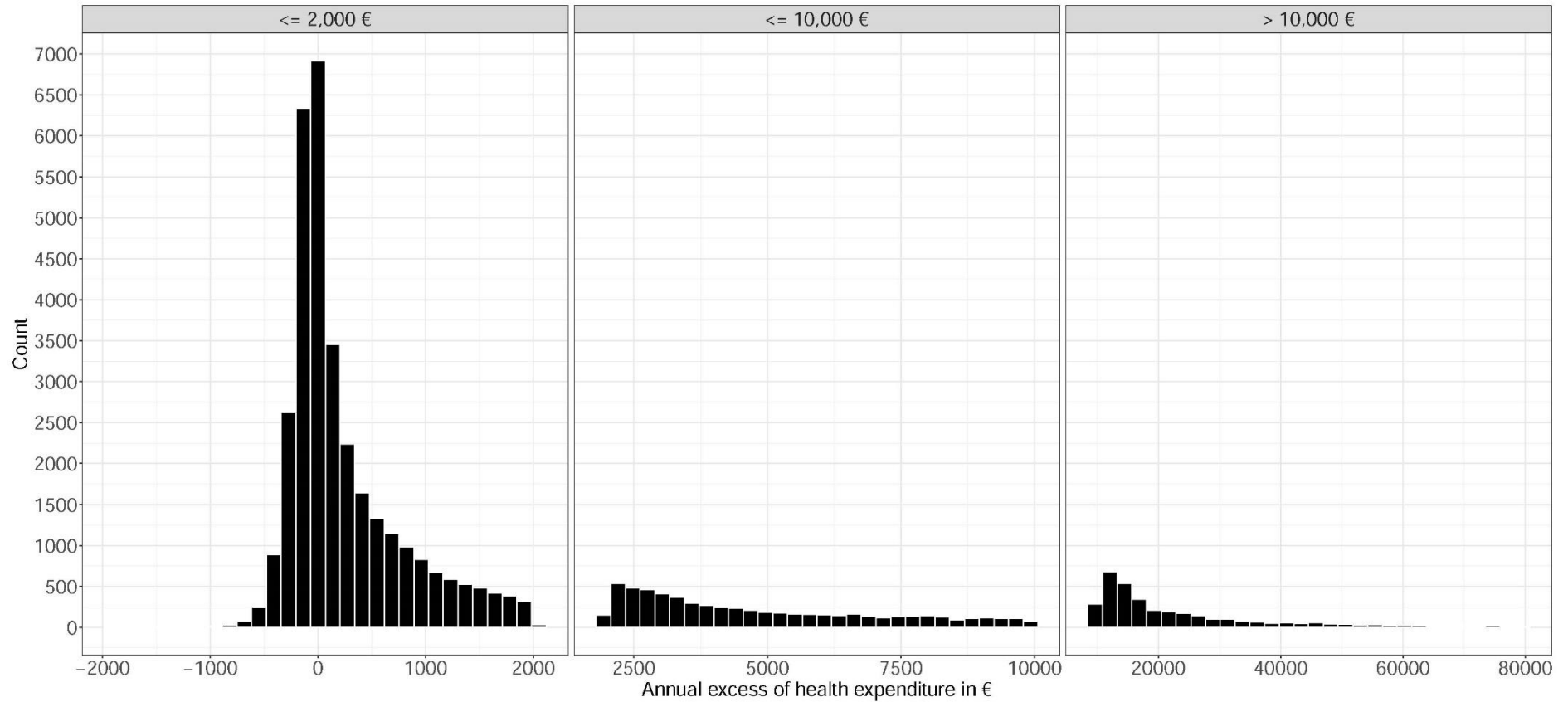
De Fine (2017)	All	Nordic Countries	21,297	1943-2008 in Denmark 1971-2008 in Finland 1955-2008 in Iceland 1958-2008 in Sweden	152,231 matched by age, sex, year, and country	Follow-up was started 5 years after the date of cancer diagnosis or at the beginning of the hospital registers (Denmark, 1977; Finland, 1975; Iceland, 1999; Sweden, from 1968–1987 step-wise inclusion of counties and nationwide since 1987) Follow-up ended on the date of death, the date of emigration, or the end of the study (Iceland: 31 December 2008; Sweden: 31 December 2009; Denmark: 31 October 2010; Finland: 31 December 2012). Mean Follow-up: 16 years; range: 0-42 years	31,45*	RR of 1.94 (95% CI 1.91–1.97). The AER was 3,068 (2,980–3,156) per 100,000 person-years	Not include the ICD sections of ill-defined diseases and the group of injuries and violence in the analysis, Mental disorders, and childbirth and pregnancy complications and congenital malformation or chromosome abnormality (ICD-8 codes 740–759, ICD-10 codes Q00–Q99)
Brewster (2014)	All (0-25 Years)	Scotland	5,229	1981 - 2003	Indirect standardisation for age and sex compared with the general Scottish population	Follow-up was from 5 years after diagnosis to date of emigration, date of death, or end of 2009 (14,8 Years)	No Info	SHR 2.8 (95% CI 2.7–2.9) AER of 6.4 (6.0–6.6) hospital admissions per 100 cancer survivors per year	Disease-specific outcome codes
Font-Gonzalez (2017)	All	Netherlands	1,382	1966 - 1999	26,583 corresponding year of birth and gender	1995 - 2005 (10 years)	Attained age at the end of follow-up 25.3 (19.5–32.1)	The overall RHR and AER for all the four disease groups in CCS compared to the general population were 7.2 (95% CI: 5.5–9.4) and 38 per 1000 person-years at risk, respectively.	Four categories neoplasms, diseases of the circulatory system, endocrine/ nutritional/metabolic diseases and diseases of the eye.
Lorenzi (2011)	All	Canada	1,374	1981-1995	13740 frequency matching was done by gender and birth year	1986 - 2000 Mean follow-up time for survivors was 7 years (maximum 15 years).	No Info	Relative risk of hospital-related late morbidity (4.1 (3.7–4.5))	except pregnancy

* Estimated from reported data

Appendix 4 Supplementary results for Chapter V

A.4.1 Excess healthcare expenditure

Supplementary Figure 5. Histogram of annual excess healthcare expenditures.



Supplementary Table 16. Annual mean of excess healthcare expenditures per patient in euros (% of the total excess) by item according to the type of primary cancer.

	Lymphoma (n = 920)	Kidney tumours (n = 810)	Neuroblastoma (n = 737)	Central nervous system tumour (n = 679)	Soft tissue sarcomas (n = 583)	Bone sarcomas (n = 473)	Retinoblastoma (n = 467)	Gonadal tumour (n = 331)	Other solid cancer (n = 306)	Thyroid tumour (n = 47)
General practitioner visits	66 (1.6)	64 (1.3)	36 (1.4)	93 (1.4)	65 (1.6)	70 (1.6)	28 (1.5)	46 (1.2)	47 (1.7)	107 (2.8)
Specialist visits	188 (4.6)	168 (3.5)	107 (4.1)	128 (1.9)	138 (3.3)	142 (3.2)	79 (4.1)	146 (3.7)	128 (4.6)	276 (7.3)
Physiotherapy visits	95 (2.3)	63 (1.3)	44 (1.7)	230 (3.4)	71 (1.7)	108 (2.4)	26 (1.4)	62 (1.6)	66 (2.4)	75 (2)
Nursing visits	103 (2.5)	52 (1.1)	39 (1.5)	195 (2.8)	71 (1.7)	38 (0.8)	17 (0.9)	26 (0.7)	114 (4.1)	39 (1)
Other health professional visits	21 (0.5)	5 (0.1)	8 (0.3)	63 (0.9)	11 (0.3)	3 (0.1)	2 (0.1)	7 (0.2)	36 (1.3)	3 (0.1)
Pharmacy	601 (14.6)	1408 (29.6)	335 (12.8)	694 (10.1)	593 (14.1)	491 (11)	164 (8.7)	1037 (26.4)	274 (9.9)	1346 (35.7)
Medical devices	216 (5.2)	357 (7.5)	262 (10)	389 (5.7)	295 (7)	986 (22.1)	99 (5.2)	205 (5.2)	118 (4.3)	159 (4.2)
Laboratory tests	91 (2.2)	112 (2.3)	54 (2.1)	72 (1)	71 (1.7)	74 (1.7)	35 (1.8)	80 (2)	60 (2.2)	180 (4.8)
Technical Medical Procedures	132 (3.2)	101 (2.1)	55 (2.1)	88 (1.3)	93 (2.2)	111 (2.5)	46 (2.4)	170 (4.3)	78 (2.8)	105 (2.8)
Transport	155 (3.8)	164 (3.4)	134 (5.1)	349 (5.1)	124 (3)	189 (4.2)	123 (6.5)	103 (2.6)	54 (1.9)	52 (1.4)
Hospitalizations	1521 (36.8)	1420 (29.8)	986 (37.6)	3732 (54.4)	1574 (37.5)	1028 (23.1)	1070 (56.5)	1250 (31.8)	923 (33.4)	956 (25.4)
Disability Benefits	369 (8.9)	424 (8.9)	181 (6.9)	499 (7.3)	566 (13.5)	664 (14.9)	73 (3.9)	377 (9.6)	433 (15.7)	28 (0.7)
Sick Leave	527 (12.8)	373 (7.8)	366 (13.9)	186 (2.7)	477 (11.4)	514 (11.5)	120 (6.3)	394 (10)	364 (13.2)	426 (11.3)
Others	43 (1)	50 (1)	16 (0.6)	142 (2.1)	45 (1.1)	42 (0.9)	15 (0.8)	26 (0.7)	68 (2.5)	12 (0.3)
Total	3962 €	4594 €	2498 €	6712 €	4030 €	4283 €	1798 €	3750 €	2609 €	3511 €

A.4.2 Multivariate analysis

Supplementary Table 17. Predictors of annual excess health care expenditures by the type of cancer.

	Lymphoma (n = 920)	Kidney tumours (n = 810)	Neuroblastoma (n = 738)	Central nervous system tumour (n = 679)	Soft tissue sarcomas (n = 583)	Bone sarcomas (n = 471)	Retinoblastoma (n = 467)	Gonadal tumour (n = 331)	Other solid cancer (n = 307)	Thyroid tumour (n = 47)
Intercept	3457.7 *	11793.89	800.77	2082.17	-1067.6	-2620.97	1032.04	4676.46	-4664.8 **	737.66
Time	358.98 ***	141.91 ***	256.61 ***	319.76 ***	189.5 ***	88.55 *	136.53 ***	234.83 ***	195.69 ***	314.77 ***
Female (Ref = Male)	857.53 *	-1237.04	-316.63	383.3	2775.01 ***	307.23	534.47	-1360.57	-1096.93	-143.26
Age at January 2011	-131.09 *	-233.51	102.11	140.02	-199.61	236.38 **	49.57	-72.07	239.56 **	92.29
French geographical deprivation index (Ref = 1 Quintile)										
2 Quintile	-55.85	-502.21	926.97	-1668.04	-1411.52	1644.27 **	-786.89	1260.05	-1614.48 *	-88.21
3 Quintile	1424.06 **	-2898.98	1948 **	-2277.68	-3044.75 **	-39.68	-429.99	-1049.86	-910.72	3428.59
4 Quintile	317.55	-3001.75	-529.89	-2406.87	-2650 *	245.36	521.28	1399.99	-1632.15	228.49
5 Quintile	897.92	-2226.45	1123.97	-2559.17 *	-1707.89	152.74	-993.69	4896.41 **	-1047.34	4849.69 ***
Age at first cancer	158.02 *	235.94	-5.57	-275.34	298.84 *	-159.97	641.32 ***	147.17	-54.28	-354.48
Year of Diagnosis (Ref = >1990)										
<1970	8016.94 ***	10903.16	435.63	2930.94	15535.76 ***	-6274.01 *	-1714.56	942.28	-5420.08	-2826.92
1970-1979	6162.08 ***	9326.49 *	-965.7	6271.95 *	7537.03 **	-1239.64	2311.34	-675.84	-625.35	1739.46
1980-1989	2839.15 ***	3377.72	1117.83	3235.96	5115.78 ***	-5.83	2545.56 **	444.26	-2454.74 *	836.53
Treatment (Ref = Radiotherapy)										
No radiotherapy or chemotherapy	-5598.64 ***	-5900.58	-3238.37 **	-3282.49	733.14	-1914.39	-3389.84 ***	-578.48	352.56	344.07
Chemotherapy	-2833.56 ***	-6396.97	-3568.22 ***	-2092.72	4407.27 ***	-188.42	-2954.49 ***	-2656.78	2716.05 **	65078.45 ***
Radiotherapy and chemotherapy	-1154	-3146.38	-2060.18	257.3	6047.8 ***	45.36	-1030.2	3698.76	3995.3 ***	

* p<0.05 *** p<0.01

Supplementary Table 18. Predictors of annual excess healthcare expenditures by item.

	General practitioner visits		Specialist visits		Physiotherapy visits		Nursing visits		Other health professionals visits		Pharmacy		Medical device	
Intercept	32.66	0.01 ***	-21.27	0.39	179.52	0 ***	44.63	0.43	44.84	0 ***	1152.59	0.14	426.58	0 ***
Time	-0.07	0.83	5.91	0 ***	5.39	0 ***	13.50	0 ***	1.09	0 ***	26.79	0 ***	16.45	0 ***
Female (Ref = Male)	4.88	0.14	21.18	0 ***	36.69	0 ***	51.39	0 ***	-9.33	0.03 ***	-259.65	0.25	-13.55	0.74
Age at January 2011	1.81	0 ***	5.60	0 ***	-0.09	0.95	-2.23	0.36	0.93	0.15	-29.67	0.38	-7.72	0.21
French geographical deprivation index (Ref = 1 Quintile)														
2 Quintile	8.86	0.06	-10.94	0.27	-14.98	0.22	-6.21	0.78	-10.95	0.07	-246.73	0.44	-35.45	0.54
3 Quintile	9.34	0.06	-26.89	0.01 ***	-14.06	0.28	71.53	0 ***	-14.52	0.02 ***	-281.46	0.4	-9.18	0.88
4 Quintile	-1.61	0.76	-34.27	0 ***	-40.72	0 ***	-36.15	0.16	-11.79	0.08	-206.54	0.56	-109.74	0.09
5 Quintile	18.54	0 ***	-20.40	0.05 ***	-33.60	0.01 ***	-12.55	0.61	2.21	0.73	-394.43	0.25	-133.15	0.03 ***
Year of Diagnosis (Ref = >1990)														
<1970	-25.55	0.13	-92.44	0.01 ***	126.71	0 ***	159.32	0.05 ***	-8.62	0.69	1205.21	0.29	610.57	0 ***
1970-1979	-4.67	0.68	-58.56	0.01 ***	78.85	0.01 ***	194.57	0 ***	5.77	0.69	1098.52	0.14	444.02	0 ***
1980-1989	10.12	0.14	-7.50	0.61	49.32	0.01 ***	70.25	0.04 ***	-3.98	0.65	479.23	0.3	287.66	0 ***
Age at first cancer	-0.95	0.13	-3.60	0.01 ***	-0.12	0.94	10.89	0 ***	-0.41	0.61	35.85	0.39	4.95	0.52
First primary cancer type (Ref = Central nervous system tumour)														
Kidney tumours	-27.95	0 ***	41.76	0 ***	-191.47	0 ***	-122.59	0 ***	-63.26	0 ***	731.83	0.12	-64.13	0.46
Neuroblastoma	-39.89	0 ***	18.25	0.24	-174.33	0 ***	-96.50	0.01 ***	-48.48	0 ***	-218.63	0.66	-71.81	0.43
Lymphoma	-29.43	0 ***	63.69	0 ***	-131.68	0 ***	-113.28	0 ***	-39.15	0 ***	-144.39	0.75	-162.67	0.05 ***
Soft tissue sarcomas	-28.10	0 ***	12.98	0.39	-166.37	0 ***	-140.13	0 ***	-53.19	0 ***	-144.03	0.77	-98.91	0.26
Bone sarcomas	-20.70	0.01 ***	19.57	0.24	-121.81	0 ***	-199.11	0 ***	-63.39	0 ***	-172.21	0.74	615.07	0 ***
Gonadal tumour	-39.80	0 ***	21.92	0.22	-167.55	0 ***	-187.05	0 ***	-55.42	0 ***	458.27	0.43	-150.56	0.15
Thyroid tumour	13.51	0.37	120.85	0 ***	-202.01	0 ***	-226.38	0 ***	-62.16	0 ***	726.73	0.48	-303.06	0.1
Retinoblastoma	-39.17	0 ***	7.44	0.64	-170.39	0 ***	-94.48	0.01 ***	-48.93	0 ***	-327.06	0.53	-181.34	0.05 ***
Other solid cancer	-34.95	0 ***	16.22	0.38	-146.24	0 ***	-95.62	0.03 ***	-24.75	0.03 ***	-331.91	0.58	-192.04	0.08
Treatment (Ref = Radiotherapy)														
No radiotherapy or chemotherapy	-26.27	0 ***	-51.61	0 ***	-52.69	0 ***	-56.51	0.09	-17.66	0.04 ***	-219.01	0.63	-214.12	0.01 ***
Chemotherapy	-19.95	0 ***	-55.21	0 ***	-40.61	0.01 ***	-36.95	0.21	-7.60	0.32	-295.26	0.47	-171.34	0.02 ***
Radiotherapy and chemotherapy	11.08	0.04 ***	-1.30	0.91	-2.69	0.85	1.44	0.96	0.71	0.92	179.01	0.62	-72.18	0.28

Supplementary Table 18. Predictors of annual excess healthcare expenditures by item. Continued

	Laboratory		Technical Medical Procedures		Transport		Hospitalizations		Disability Benefits		Sick Leave		Others	
Intercept	41.94	0.01 ***	-31.11	0.14	136.34	0.04 ***	2991.67	0 ***	-385.79	0.02 ***	-331.09	0 ***	-6.06	0.94
Time	2.36	0 ***	8.19	0 ***	17.00	0 ***	81.60	0 ***	33.31	0 ***	8.86	0.01 ***	7.20	0 ***
Female (Ref = Male)	22.64	0 ***	36.98	0 ***	32.64	0.09	125.90	0.47	34.40	0.47	167.77	0 ***	6.91	0.75
Age at January 2011	0.34	0.62	1.80	0.05 ***	2.44	0.41	-15.89	0.54	21.79	0 ***	8.26	0.06	4.29	0.19
French geographical deprivation index (Ref = 1 Quintile)														
2 Quintile	2.25	0.73	29.69	0 ***	39.63	0.15	-24.34	0.92	30.72	0.65	22.59	0.58	-41.91	0.17
3 Quintile	-3.28	0.63	-11.31	0.2	49.03	0.09	-349.21	0.17	47.25	0.5	14.99	0.73	-44.93	0.16
4 Quintile	-16.46	0.02 ***	-17.39	0.07	35.86	0.24	-353.40	0.19	36.09	0.63	-8.76	0.85	-32.17	0.35
5 Quintile	-18.45	0.01 ***	-13.65	0.13	18.32	0.53	-68.20	0.79	380.22	0 ***	99.03	0.02 ***	-50.77	0.12
Age at first cancer	-0.49	0.56	-2.02	0.07	-1.83	0.61	48.24	0.13	-15.89	0.07	5.61	0.3	-0.45	0.91
Year of Diagnosis (Ref = >1990)														
<1970	41.44	0.07	44.03	0.15	60.97	0.54	2534.15	0 ***	-28.03	0.91	-278.60	0.06	-86.82	0.43
1970-1979	12.50	0.41	11.12	0.58	106.16	0.1	1713.08	0 ***	136.89	0.39	13.12	0.89	21.49	0.77
1980-1989	26.86	0 ***	11.20	0.37	75.62	0.06	1170.15	0 ***	14.82	0.88	96.83	0.11	-20.94	0.64
First primary cancer type (Ref = Central nervous system tumour)														
Lymphoma	24.59	0.01 ***	33.70	0.01 ***	-209.18	0 ***	-2394.02	0 ***	-128.39	0.18	280.76	0 ***	-132.82	0 ***
Kidney tumours	36.77	0 ***	-13.35	0.29	-192.98	0 ***	-2417.32	0 ***	-142.58	0.15	231.92	0 ***	-97.82	0.03 ***
Neuroblastoma	-2.33	0.82	-27.79	0.04 ***	-184.08	0 ***	-2342.31	0 ***	-184.64	0.08	266.83	0 ***	-112.49	0.02 ***
Soft tissue sarcomas	3.94	0.69	-6.74	0.6	-234.52	0 ***	-1965.48	0 ***	54.31	0.6	266.11	0 ***	-128.38	0.01 ***
Bone sarcomas	10.21	0.34	21.87	0.12	-154.07	0 ***	-2878.70	0 ***	225.15	0.04 ***	274.34	0 ***	-136.45	0.01 ***
Retinoblastoma	-15.93	0.13	-19.26	0.16	-150.84	0 ***	-1799.09	0 ***	-116.07	0.29	82.65	0.22	-83.95	0.09
Gonadal tumour	16.84	0.15	78.25	0 ***	-242.68	0 ***	-2519.36	0 ***	-66.82	0.58	176.43	0.02 ***	-144.70	0.01 ***
Other solid cancer	2.68	0.82	6.83	0.67	-263.83	0 ***	-2473.27	0 ***	20.73	0.87	158.61	0.04 ***	-67.58	0.24
Thyroid tumour	98.98	0 ***	-10.56	0.7	-320.73	0 ***	-3403.64	0 ***	-700.49	0 ***	237.71	0.07	-146.59	0.14
Treatment (Ref = Radiotherapy)														
No radiotherapy or chemotherapy	-44.25	0 ***	-20.78	0.09	-94.86	0.02 ***	-1127.53	0 ***	-65.93	0.49	16.57	0.78	-0.50	0.99
Chemotherapy	-36.19	0 ***	-5.95	0.59	-52.68	0.14	-622.97	0.05 ***	-215.12	0.01 ***	10.86	0.84	21.96	0.58
Radiotherapy and chemotherapy	2.36	0.75	36.73	0 ***	8.20	0.8	30.14	0.91	-0.41	1	152.16	0 ***	60.00	0.09

*** p<0.05

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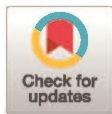
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PUBLICATIONS DURING THE THESIS

RESEARCH ARTICLE

Health care expenditures among long-term survivors of pediatric solid tumors: Results from the French Childhood Cancer Survivor Study (FCCSS) and the French network of cancer registries (FRANCIM)

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Abstract

Background

Childhood cancer survivors (CCS) may require lifelong medical care due to late effects of cancer treatments. Little is known about of their healthcare utilization and expenditures at long-term especially in publicly funded health care system. We aim to estimate and describe the health care expenditures among long-term CCS in France.

Methods

A total of 5319 five-year solid CCS diagnosed before the age of 21 between 1945 and 2000 in France were identified in the French Childhood Cancer Survivors Study cohort (FCCSS) and the French cancer registry. Information about health care expenditure was taken from the French national health data system between 2011 and 2016, and was described according to survivors' characteristics. Generalized linear models were used to determine associations between health care expenditures and survivors' characteristics.

Data Availability Statement: The study data (FCCSS Cohort Data, which contain potentially identifying or sensitive patient information) are data that can be accessed upon request. However, there is no non-author to whom requests for access to the data can be made. The data were obtained and are managed by our team and all contact details are on the cohort website (<https://fccss.fr>). On the other hand, the committee of the French National Institute of Health and Medical Research (French Acronym: INSERM), which approved the study, is a large national public institution, the member of which having no specific link with the cohort and no authorization for taking decision about data sharing. Therefore, is best to leave our team contact, for the data requests that appear on the FCCSS website: Inserm, CESP, Team Cancer and Radiation Gustave Roussy B2M 114 rue Edouard Vaillant 94805 Villejuif CEDEX Phone: 0800 804 024 (toll free) Email: contact.fccss@gustaveroussy.fr.

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Competing interests: The authors have declared that no competing interests exist.

Results

Mean annual amount of healthcare expenditures was € 4,255. Expenditures on hospitalizations and pharmacy represents 60% of total expenditures. Mean annual of healthcare expenditures were higher at increasing age, among women survivors (€ 4,795 vs € 3,814 in men) and in central nervous system (CNS) tumor survivors (€ 7,116 vs € 3,366 in lymphoma and € 3,363 in other solid tumor survivors).

Conclusions

Childhood cancer survivorship is associated with a substantial economic burden in France. We found that female gender and CNS primary cancer were associated with increased healthcare expenditures.

Introduction

Childhood cancer survivorship has improved considerably in the last few decades. Nowadays, more than 80% of pediatric cancer patients reach 5-year survival, leading to a growing number of long term survivors. In Europe, it is estimated that there are between 300,000 and 500,000 former pediatric cancer patients [1].

Nevertheless, most of this progress has been obtained using treatments that can damage healthy tissues. Consequently, childhood cancer survivors (CCS) carry a significant risk of cancer treatments related late effects [2]. Main late effects are secondary neoplasms, cardiac-vascular diseases, growth problems, mental health issues, infertility and organ dysfunction [3]. Therefore, long-term after-cancer care involves lifelong medical visits and tests to prevent and manage these potential life-threatening or disabling late effects [4]. This higher burden of morbidity and surveillance of late effects is likely associated with higher costs to the health care system [5]. Moreover, previous studies have shown that some CCS could have difficulties into educational attainment and are more likely to be unable to work or to miss work days due to health conditions [6–8]. Under those circumstances, a better understanding of the healthcare use and expenditure of CCS is important to evaluate long-term consequences of survivorship.

In France, there are about 50,000 adults who had cancer in their childhood [9]. Healthcare system in France is mainly publicly funded and provides universal coverage to its citizens covering most medical expenses [10] especially for long-term conditions, however, no studies have estimated the global healthcare expenditures among CCS. The French Childhood Cancer Survivor Study (FCCSS) which includes CCS treated before 2001 provides an opportunity to detail the overall healthcare expenditures among very long-term cancer survivors. Nevertheless, FCCSS survivors were treated during their childhood in Centers for the fight against cancer (CLCC) which are specialized hospitals in cancer treatment in France. Therefore, we hypothesize that the FCCSS could include patients with more advanced and/or aggressive cancers, or they may have received more innovative treatments and consequently differ in terms of long-term outcomes and future health expenses from other CCS treated in other hospital settings.

The aims of this paper was to quantify and describe the health care expenditures among very long-term CCS in France. Subsequently, we compared the level of expenditures between FCCSS survivors with those from other settings included in the French cancer registries existing during FCCSS recruitment period.

Material & methods

Study population

We used data from two sources, a multicenter cohort study (FCCSS) and the French Network of cancer registries (FRANCIM).

The FCCSS is a retrospective cohort of 7,670 five-year CCS diagnosed for solid cancer or lymphoma (all malignancies except leukemia), before the age of 21 years between 1945 and 2000. Detailed information on the methods for data collection and validation has been already described [11, 12].

FRANCIM includes all the population-based registries of cancer in France. This network records all newly diagnosed and confirmed cancer cases since 1975 in diverse areas of France [13, 14]. The population covered by the FRANCIM's database represents 22% of the French population [15]. Therefore, the FCCSS survivors who were included also in FRANCIM were considered as FCCSS patients. Leukemia survivors from FRANCIM were excluded for better comparability with the FCCSS which did not include leukemia.

From both data bases, we selected all five-year solid CCS diagnosed before January 2001 who were alive in January 2011 and who were linked to the National Health Data System (*Système National des Données de Santé*) (SNDS). Since no social security number is collected in the study, patients are identified within the SNDS by probabilistic matching with the full involvement of different French healthcare-related organizations: Caisse nationale de l'assurance vieillesse des travailleurs salariés (CNAVTS) is the third party for social security number reconstruction and Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS) is the trust third party for SNDS health data gathering based on a non-identifiable number derived from the retrieved social security number. The highly specific identification data that are provided to CNAMTS by the National Institute of Health and Medical Research (INSERM) are listed as below: family and first name, sex, date and place of birth and, unique arbitrary number. CNAMTS was in charge of both communication with CNAVTS and SNDS data extraction. The percentage of survivors linked to SNDS data after this procedure was 55.6% (n = 3786) for FCCSS and 71.9% (n = 2031) for FRANCIM survivors. In the present study, French national security number is not held by INSERM at any time.

Survivors were followed throughout the SNDS until December 2016 or death. We excluded survivors who lived outside metropolitan France during follow-up due to the difference in the health insurance system, characteristics of the population and funding of care in French overseas territories [16].

The study was approved by the French Data Protection Authority (CNIL) (Authorization n°902287) and by the ethics committee of the INSERM. Patient informed consent was not required for this study because we obtained a specific act in law from the French "Conseil d'Etat", the highest court in France (Order 2014-96 of 2014 February 3), that approved the cession of the SNDS data for all patients included in the FCCSS and FRANCIM.

Data sources

The SNDS is the health care claims dataset in France, which contains exhaustive individual data used for the billing and reimbursement data of the beneficiaries of the various national health insurance schemes which now covers more than 95% of the French population [17, 18].

The SNDS is mainly composed by the outpatient healthcare consumption database (*Données de Consommation Inter-Régimes database*, DCIR) and the private and public hospital database (*Programme de Médicalisation des Systèmes d'Information*, PMSI) which is divided in four categories: Medicine, surgery and obstetrics hospitalizations (MCO), home

hospitalizations (HAD), after-care and rehabilitation (SSR) and psychiatry (PSY). Although MCO and HAD had cost information since 2006, the availability of billing records for PSY and SSR systems began in 2011, thus we established this year as starting date when data was available for all systems.

Information in the SNDS includes some demographic characteristics (age, gender, place of residence); diagnosis of long-term conditions (*affections de longue durée*) defined as a disease in which the severity and/or the chronicity require a long-term costly treatment; as well as dates, nature and reimbursement of outpatient visits, dispensed medication, allied health professional visits, lab tests, medical devices, medical transports, paid sick leave and hospital admissions, including procedures performed within diagnosis-related groups [18].

Primary measures

This study was carried out from the *Assurance Maladie* (AM) [French national health insurance] perspective (payer). Expenditures were estimated considering all the reimbursements made by the AM between January 2011 and December 2016 or date of death. Therefore, reimbursements from private health insurance, especial schemes or the final out-of-pocket were not included.

Our primary outcome variables were the total sums of direct healthcare expenditure for every calendar year for each patient in both cohorts. Direct expenditure was also classified for every year into fourteen categories: General practitioner visits, other specialist visits, physiotherapy, nursing visits, other health professionals visits, pharmacy, medical device, laboratory test, technical medical procedures, transport, hospitalizations, disability benefits, sick leave and others. All expenditures were expressed in real terms using the consumer price index with a 2015 base year provided by the National Institute of Statistics and Economic Studies (INSEE).

Covariates

Other covariates included age, sex, year of diagnosis, age at diagnosis, type of primary cancer (kidney tumor, neuroblastoma, lymphoma, soft tissue sarcoma, bone sarcoma, central nervous system tumor, gonadal tumor, thyroid tumor, retinoblastoma and others), French deprivation index in 2009 which is an area-based multidimensional index that measures socioeconomic differences [19] and where higher scores implies a higher "deprivation" (categorized into quintiles), and death (alive or death at December 2016).

Statistical analysis

Patient's characteristics were described along with the estimation of annual mean expenditure over 2011–2016 period. Categorical variables were expressed as numbers and percentages, and continuous variables as mean \pm SD. Direct total expenditures were described by categories and also according to primary cancer.

Given the population studied, the frequency of persons having no healthcare expenses during the 6 years follow-up period was less than 4% of the total patients within each cohort group, therefore a 2-stage model was not required. Instead, we used a repeated measures generalized linear model (GLM) with a gamma distribution and a log link to estimate per-person annual medical expenditures for all patients accounting the skewness in the distribution. We added 1€ to all expenditures to allow inclusion of individuals with no expenses [20] and used age at diagnosis as categorical variable in the models due to the strong correlation with age at follow-up and year of diagnosis. Neuroblastoma was chosen as the referent for type of primary cancer variable since was one of the larger group of cancer of same histology. We compared

the output of the model adjusted by all covariates (Model I), with models excluding variable of death (Model II) and patients who died (Model III).

Finally, we performed several analysis by considering separately each type of expenditure and each type of cancer along with different interactions between cohort (FCCSS or French cancer registries) and type of cancer. Statistical significance was determined using $p < 0.05$. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

Survivors' characteristics and total health care expenditure

A total of 5,319 CCS were included in the study, among which 67.5% belong to the FCCSS (Table 1). Almost half of the patients were women and were diagnosed after 1990 (44.9% and 46.6% respectively). More than 50% of the patients were over 30 years old at the beginning of follow-up. The most common primary cancer was lymphoma (20.1%) followed by central nervous system (CNS) tumor (14.2%). Between 2011 and 2016, around 3% of the total patients had died. Details of patient characteristics by cohort are shown in the S1 and S2 Tables.

Total direct healthcare expenditure for the 5,319 patients between 2011 and 2016 were € 134,523,643. Annual mean of health care expenditures of survivors was € 4,255. However, this variable was positive skewed due to a few very high values among survivors. In detail, 50% of patients had an annual mean of healthcare expenditures lower than € 1,000 and almost 10% was above € 10,000 (S1 Fig).

On average, annual health care expenditures was higher in women than men (€ 4,795 and € 3,814), survivors diagnosed before 1980 (€ 6,970) who likely correspond with survivors between 41–50 years old (€ 7,676), among diagnosed with CNS tumor (€ 7,116), and in FCCSS (€ 4,556 vs € 3,663 in FRANCIM) (Table 1). It is noteworthy that the 167 survivors who died between 2011 and 2016, had an annual mean of expenditures of € 25,611 and accounted for 13.4% of the total expenditures.

Healthcare utilization

Health care expenditures by items are reported in Table 2. The leading expenditure item was hospitalizations which represents 45% of total expenses and were experienced by 65% of survivors during the study period. The number of hospitalizations was higher in women than in men (73% vs 59%) (S3 Table). The annual mean for hospitalization expenses was € 1,919. Pharmacy was also an important expenditure item representing 16% of total healthcare expenditure with an annual mean of € 676 per patient (€ 719 in men vs 622 in women).

Around half of survivors received sick leave during the 6-year follow-up and their annual mean per patient was € 410 but notably was almost the double for women than for men (€ 557 vs 289) (S3 Table). On the contrary, only 6.5% of patients had expenditures related to disability benefits but their cost reached almost € 8 million which is more than 5% of the total expenses. The distribution of health care expenditure by items was quite similar in both cohorts (S4 Table).

Health care expenditure by type of primary cancer

Details on expenditures by each type of primary cancer are shown in Table 3. Survivors from CNS tumors had the highest annual mean of hospitalizations expenses (€ 4,142), while kidney tumor survivors had the highest annual mean of pharmacy (€ 1,578) compared with the other types of cancer. Disability benefits annual mean were higher among bone sarcoma survivors (€ 479) while sick leave were major for thyroid tumor survivors (€ 708).

Table 1. Survivors characteristics and health care expenditures.

	N° Patients (%)	PY	Annual Health care expenditures	
			Mean (SD)	Median (IQR)
Total	5319	31533.6	4255 (18790)	494 (105–2151)
Sex				
Man	2929 (55.1)	17351.9	3814 (19289)	338 (64–1554)
Women	2390 (44.9)	14181.7	4795 (18147)	721 (198–3290)
Year of childhood cancer diagnosis				
<1980	988 (18.6)	5760.3	6970 (28210)	995 (242–4552)
1980–1989	1852 (34.8)	10974.5	4731 (20024)	607 (149–2749)
> = 1990	2479 (46.6)	14798.8	2841 (11813)	326 (52–1334)
Age at childhood cancer				
0–1	937 (17.6)	5575.0	2905 (9828)	257 (15–1337)
2–4	1034 (19.4)	6140.2	4926 (26253)	413 (69–2003)
5–9	1088 (20.5)	6433.3	4420 (14300)	552 (126–2743)
10–14	1130 (21.2)	6685.2	5072 (24480)	640 (170–2686)
≥15	1130 (21.2)	6699.8	3790 (12352)	600 (179–2135)
Age at January 2011 (Start date)				
<20	550 (10.3)	3291.9	1475 (8143)	0 (0–309)
20–30	1979 (37.2)	11812.8	3561 (13189)	443 (113–1891)
31–40	1878 (35.3)	11142.6	4303 (20597)	592 (157–2312)
41–50	753 (14.2)	4355.4	7676 (29734)	1072 (265–5056)
> = 51	159 (3)	930.9	6233 (14164)	1378 (398–5272)
French geographical deprivation index**				
1 Quintile	1063 (20)	6312.9	4569 (24995)	459 (92–1952)
2 Quintile	1061 (19.9)	6293.3	3688 (11473)	507 (118–2020)
3 Quintile	1066 (20)	6322.3	4034 (16209)	471 (103–1920)
4 Quintile	1064 (20)	6320.5	4699 (23783)	507 (97–2374)
5 Quintile	1065 (20)	6284.6	4283 (13374)	539 (119–2529)
First primary cancer type				
Kidney tumors	668 (12.6)	3942.0	5021 (30330)	383 (78–1776)
Neuroblastoma	574 (10.8)	3434.2	2952 (12224)	285 (37–1301)
Lymphoma	1071 (20.1)	6350.7	3366 (10662)	442 (106–1770)
Soft tissue sarcomas	523 (9.8)	3117.3	4007 (14074)	471 (108–2219)
Bone sarcomas	445 (8.4)	2636.7	5207 (14193)	827 (188–4303)
Central nervous system tumor	756 (14.2)	4427.7	7116 (29617)	1130 (256–4925)
Gonadal tumor	389 (7.3)	2322.3	3575 (15215)	392 (93–1401)
Thyroid tumor	109 (2)	650.7	3202 (7882)	785 (348–2210)
Retinoblastoma	305 (5.7)	1815.5	2852 (9698)	235 (0–1161)
Other solid cancer	479 (9)	2836.5	3363 (12231)	495 (143–1797)
Cohort				
FCCSS	3589 (67.5)	21247.6	4556 (18830)	507 (97–2297)
French cancer registry	1730 (32.5)	10286.0	3633 (18692)	476 (122–1890)
Status at December 2016 (Ending date)				
Alive	5152 (96.9)	30912.0	3770 (17677)	473 (101–2003)
Death	167 (3.1)	621.6	25611 (40950)	10208 (1437–34703)

PY: Person-years of follow-up, SD: Standard deviation, IQR: Inter Quartile Range.

** : Ecological Index measuring the deprivation, and based on the median household income, the percentage high school graduates in the population aged 15 years and older, the percentage blue-collar workers in the active population, and the unemployment rate [19].

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Table 2. Health care expenditures by items.

	N° Patients (%)	N° Claims	Total Expenditures in Millions € (%)	Annual mean Expenditure Per-Patient in €* (SD)
General practitioner visits	5,055 (95)	144,107	3.1 (2.3)	97 (133)
Other specialists visits	4,935 (92.8)	161,998	5.4 (4)	170 (439)
Physiotherapy visits	2,195 (41.3)	123,828	2.1 (1.6)	67 (319)
Nursing visits	3,519 (66.2)	118,548	1.7 (1.3)	55 (650)
Other health professionals visits †	597 (11.2)	12,548	0.4 (0.3)	12 (135)
Pharmacy	5,046 (94.9)	502,872	21.4 (15.9)	676 (9,736)
Medical device	4,223 (79.4)	52,479	8.2 (6.1)	260 (1,800)
Laboratory test	4,597 (86.4)	101,246	2.5 (1.9)	80 (302)
Technical medical procedures ‡	4,700 (88.4)	48,583	2.6 (1.9)	83 (287)
Transport	1,743 (32.8)	24,604	4.4 (3.3)	140 (979)
Hospitalizations	3,450 (64.9)	35,001	60.7 (45.1)	1,919 (13,730)
Disability Benefits §	345 (6.5)	13,863	7.9 (5.9)	251 (1,538)
Sick Leave	2,731 (51.3)	41,722	13.0 (9.6)	410 (1,623)
Others	571 (10.7)	3,442	1.2 (0.9)	37 (1,039)
Total	5,319	1,384,841	134.5	4,255 (18,790)

* Annual mean expenditure per-patient in € were calculated for the entire population (= 5,319). † Other medical professional visits included expenditures related to visits to podiatrist, optometrists, speech therapist, and others ‡ Technical medical procedures includes expenditures mainly related to medical imaging techniques. § Disability benefits includes all welfare payments or pensions made by the French Government to assistance people with disabilities.

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Table 3. Annual mean and percentage* (%) of healthcare expenditures items by type of primary cancer.

	Kidney tumors (n = 668)	Neuroblastoma (n = 574)	Lymphoma (n = 1071)	Soft tissue sarcomas (n = 523)	Bone sarcomas (n = 445)	Central nervous system tumor (n = 756)	Gonadal tumor (n = 389)	Thyroid tumor (n = 109)	Retinoblastoma (n = 305)	Other solid cancer (n = 479)
General practitioner visits	84 (1.7)	70 (2.4)	96 (2.8)	94 (2.4)	116 (2.2)	130 (1.8)	81 (2.3)	128 (4)	72 (2.5)	102 (3)
Other specialist visits	172 (3.4)	134 (4.5)	185 (5.5)	162 (4.1)	179 (3.4)	181 (2.5)	160 (4.5)	250 (7.8)	126 (4.4)	182 (5.4)
Physiotherapy	37 (0.7)	35 (1.2)	49 (1.5)	55 (1.4)	90 (1.7)	182 (2.6)	37 (1)	40 (1.2)	21 (0.7)	59 (1.8)
Nursing visits	39 (0.8)	57 (1.9)	35 (1)	55 (1.4)	28 (0.5)	144 (2)	29 (0.8)	22 (0.7)	25 (0.9)	56 (1.7)
Other health professionals visits	5 (0.1)	8 (0.3)	7 (0.2)	9 (0.2)	4 (0.1)	39 (0.5)	4 (0.1)	15 (0.5)	1 (0)	16 (0.5)
Pharmacy	1578 (31.4)	350 (11.8)	498 (14.8)	469 (11.7)	564 (10.8)	864 (12.1)	777 (21.7)	944 (29.5)	220 (7.7)	397 (11.8)
Medical device	288 (5.7)	201 (6.8)	131 (3.9)	275 (6.9)	956 (18.4)	295 (4.2)	80 (2.2)	56 (1.7)	124 (4.3)	138 (4.1)
Laboratory test	99 (2)	63 (2.1)	85 (2.5)	67 (1.7)	80 (1.5)	87 (1.2)	74 (2.1)	130 (4)	49 (1.7)	81 (2.4)
Technical Medical Procedures	74 (1.5)	54 (1.8)	81 (2.4)	90 (2.3)	104 (2)	93 (1.3)	101 (2.8)	110 (3.4)	57 (2)	81 (2.4)
Transport	159 (3.2)	107 (3.6)	88 (2.6)	107 (2.7)	183 (3.5)	286 (4)	94 (2.6)	35 (1.1)	160 (5.6)	85 (2.5)
Hospitalizations	1827 (36.4)	1401 (47.5)	1345 (40)	1831 (45.7)	1863 (35.8)	4142 (58.2)	1500 (42)	658 (20.6)	1731 (60.7)	1384 (41.2)
Disability Benefits	245 (4.9)	152 (5.1)	276 (8.2)	287 (7.2)	479 (9.2)	303 (4.3)	205 (5.7)	91 (2.9)	69 (2.4)	176 (5.2)
Sick Leave	380 (7.6)	309 (10.5)	460 (13.7)	482 (12)	532 (10.2)	266 (3.7)	412 (11.5)	708 (22.1)	182 (6.4)	565 (16.8)
Others	34 (0.7)	12 (0.4)	30 (0.9)	23 (0.6)	30 (0.6)	103 (1.4)	19 (0.5)	15 (0.5)	15 (0.5)	39 (1.2)
Total	5 021 €	2 952 €	3 366 €	4 007 €	5 207 €	7 116 €	3 575 €	3 202 €	2 852 €	363 €

* Percentage (%) of each expenditure items were calculated for each primary cancer population.

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Multivariate analysis of survivor's characteristics impact on healthcare expenditures

Table 4 shows the estimations of the GLM model using gamma distributions after adjusting by patients' characteristics. Total healthcare expenditures were higher at increasing age (Beta: 0.04, $p < .0001$), in women (Beta: 0.30, $p < .0001$), in patients treated for CNS tumor (Beta: 0.70, as compared to neuroblastoma, $p < .0001$), in patients treated between aged 2 and 4 (Beta: 0.36, as compared to age 0–1, $p = 0.05$) and among survivors who died during 2011 and 2016 (Beta: 1.85, $p < .0001$). Annual healthcare expenditures of survivors from FCCSS were not significantly higher than survivors' expenditures from FRANCIM (Beta: 0.12, $p = 0.23$). These results did not vary by excluding variable "death" from the model or excluding deceased survivors from the study population (Model II and III, respectively).

Fig 1 shows the adjusted estimates for the annual mean of healthcare expenditures from the gamma model by type of primary cancer. Survivors with neuroblastoma, lymphoma, soft tissue sarcoma, gonadal, thyroid tumor and other solid tumors had similar annual mean of health care expenditures between 3,000 and 3,500 euros whereas, survivors with kidney tumor, bone sarcoma and retinoblastoma had a similar mean of expenditures around 4,000 and 4,500 euros per year.

Finally, we investigated each item of the healthcare expenditure separately and showed that women had significantly higher adjusted expenditures than men, for all items, excepted for

Table 4. Multivariate analysis*.

	Total Patients (n = 5,319)				Patients Alive (n = 5,152)	
	Model I		Model II		Model III	
	Beta	Pr > Z	Beta	Pr > Z	Beta	Pr > Z
Intercept	11.54	0.69	1.26	0.96	21.67	0.45
Women	0.30	< .0001	0.27	< .0001	0.31	< .0001
Age	0.04	< .0001	0.06	< .0001	0.04	< .0001
Year of Diagnosis	0.00	0.85	0.00	0.86	-0.01	0.59
Age at first cancer (Ref = 0–1)						
2–4	0.36	0.05	0.33	0.06	0.37	0.05
5–9	0.08	0.64	0.07	0.69	0.10	0.56
10–14	0.16	0.50	0.08	0.72	0.20	0.38
≥15	-0.03	0.92	-0.16	0.57	0.04	0.90
French Index Deprivation	0.02	0.47	0.04	0.27	0.03	0.40
First primary cancer type (Ref = Neuroblastoma)						
Kidney tumor	0.19	0.46	0.32	0.17	0.20	0.46
Lymphoma	-0.12	0.54	0.03	0.86	-0.13	0.50
Soft tissue sarcoma	-0.03	0.87	0.07	0.71	-0.04	0.83
Bone sarcoma	0.30	0.14	0.41	0.04	0.30	0.14
Central nervous system tumor	0.70	< .0001	0.86	< .0001	0.72	< .0001
Gonadal tumor	0.08	0.77	0.08	0.74	0.09	0.74
Thyroid tumor	0.01	0.98	0.01	0.98	0.02	0.95
Retinoblastoma	0.05	0.79	0.32	0.13	0.02	0.92
Other solid cancer	-0.05	0.81	0.11	0.59	-0.05	0.80
FCCSS Survivors	0.12	0.23	0.14	0.16	0.12	0.22
Death	1.85	< .0001

* GLM model using gamma distributions. Model I were adjusted using all variables. Model II excluded "death" variable. Model III excluded dead patients.

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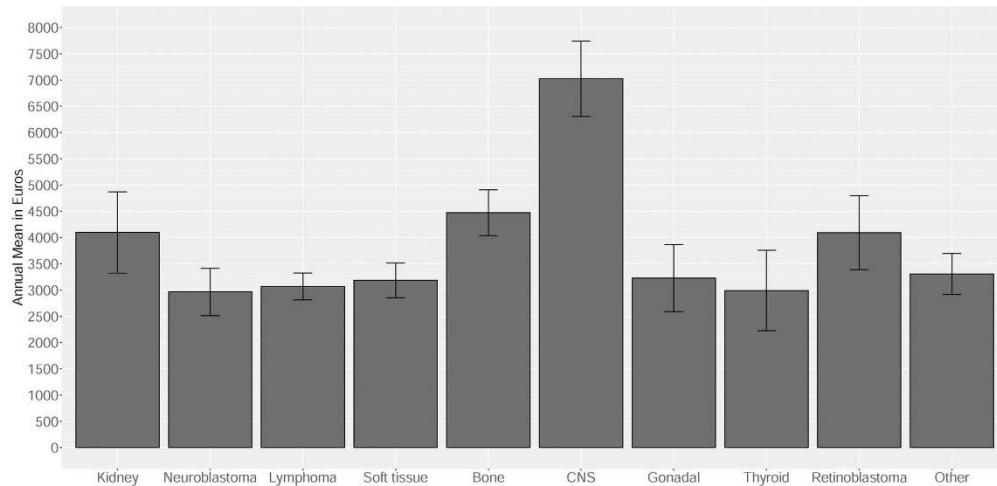


Fig 1. Adjusted* annual health care expenditures by type of primary cancer. * Adjusted by age, sex, year of diagnosis, age at diagnosis, French index deprivation, cohort and type of primary cancer. Type of primary cancer: Kidney tumor, neuroblastoma, lymphoma, soft tissue sarcoma, bone sarcoma, central nervous system tumor (CNS), gonadal tumor, thyroid tumor, retinoblastoma and other solid cancer.

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disability benefits, other health professionals visits, pharmacy, and medical device (S5 Table). Men survivors from FCCSS had higher adjusted expenses than the ones from FRANCIM, this difference was not observed in women (interaction $p = <0.001$) (S2 Fig). Lastly, no global interaction was shown between the type of primary cancer and the origin of patients, FCCSS or FRANCIM (S3 Fig).

Discussion

To our knowledge, this is the first detailed study of the economic burden of childhood cancer survivors in France. We found that the annual mean of healthcare expenditures among CCS were € 4,255, which are composed mainly by expenditures on hospitalizations and pharmacy. Additionally, we showed that women had higher expenditures than men, and that CNS tumor survivors had the highest expenditures. Although, FCCSS survivors had higher expenditures than those from FRANCIM, this difference was no longer significant when adjusting on childhood cancer type and on demographics.

CCS have a high rate of illness due to chronic health conditions [21] and require significantly more healthcare resources than the general population [5]. Previous studies have shown that their hospitalization rates are almost twofold increase and their stay was 35% longer than for patients without a cancer history [22]. Consequently, their medical needs translate into substantial healthcare expenditures. In United States, CCS were more likely to have out-of-pocket medical costs [23], and up to 33% of them were unable to see a doctor or go to the hospital due to financial issues [24].

Annual medical expenditures in adolescent or young adult cancer survivors (age 15–35) has been estimated to \$7,417 [25], while annual productivity loss among adult survivors of childhood (<14 years at diagnosis) cancer was estimated to \$8,169 [8]. In Norway, survivors of cancer at young age have by a four-to fivefold increased risk of not being employed and receive

governmental financial assistance than general population [26]. However, it is important to keep in mind that since the nineties, the rate of iatrogenic events decreases because of the reduction in the use of radiation therapy, and more recently, it could be anticipated that this risk will continue to decrease, in particular because of the emergency of proton-therapy [27].

We also highlighted that a few number of CCS especially survivors who die during the follow up period, were the main expenditure drivers. Most of these deaths have been found related to childhood cancer recurrence during the first two decades and to treatment-related sequelae including cardiovascular diseases and second malignant neoplasms, afterward [28]. The mean expenditures during the last year of life in some types of cancer have been estimated up to 43,000 euros in France [29, 30] which correlates well with our results.

Our findings showing that women survivors have a higher annual mean both in total healthcare expenditures and in several specific expenditures items are in agreement with several studies that have shown that hospitalizations occurred more often among females survivors [31, 32], mostly due to endocrine, metabolic and nutritional disorders and subsequent neoplasms [33]. Additionally all the expenditures associated with pregnancies and perinatal conditions were included in the health expenditures in our analysis. Moreover, women survivors have higher rates of miscarriage or preterm birth than the general population, including risks to both the mother and the fetus [34], which could at least partly explain the difference in the healthcare utilization compared with men survivors.

As expected, expenditures were also higher in CNS tumor survivors. A previous study showed that the cumulative burden of chronic health conditions at age 50 was higher in CCS with CNS tumor than in CCS with any other cancer [35]. This, together with the evidence that survivors from CNS tumor have at least one disability condition [36], were less likely to progress in educational attainment [37] and to have a higher risk of unemployment and reduced incomes compared with the cancer-free population [26, 38], explained their excess of healthcare expenditures. Additionally, progressive disease or relapses more than 5 years after diagnosis of a brain tumor in children is common, particularly, in slowly evolving low grade tumors [39].

Despite the fact that FCCSS survivors were treated in specialized centers to treat cancer, and thus could have been more adverse cases or received a more intense treatment, no significant difference in expenses were found at long term when adjusting on demographical factors and type of childhood cancer to others CCS in France. Although, survivors from FCCSS were younger at time of diagnosis and were recruited in early years than survivors from French cancer registries, they weren't particularly older during follow-up period.

An advantage of our study is to have worked on a large sample of long term survivors. Also, we used a national administrative database which allowed accounting for comprehensive health care expenditures during six years using two sources of long-term CCS in France. Another strength is the inclusion period starting in 1945, which allows us to study variations in cost across the age spectrum.

However, our study is subject to some limitations. First of all, data for a cancer-free control group were not available, which limited our results to the CCS population. Secondly, FRANCIM is a network of population-based registries which does not have national coverage. Thirdly, we were unable to address the association between cancer treatments received by survivors and health expenditures, due to the lack of therapeutic information in survivors from FRANCIM. All in all, our findings provide a first estimation on annual expenditures and the economic burden of CCS in France by type of childhood cancer, and demographical characteristics of survivors. Additionally, transferability to other contexts may be limited to the France territory.

Conclusion

We have estimated and described the magnitude of health expenditures related to consequences in adulthood of having had cancer treated in childhood. These high expenditures in relation to the age of survivors are related to the more frequent multimorbidity than in the general population. These results lead us to recommend that special attention be paid to this population, particularly in terms of prevention of complications and early medical follow-up. Future research should focus on addressing in deep the relationship between cancer treatment and future healthcare expenditures to establish long-term cost-effectiveness of childhood cancer treatment.

Supporting information

S1 Table. Participating French administrative areas in FRANCIM.
(DOCX)

S2 Table. Survivor's characteristics by cohort.
(DOCX)

S3 Table. Health care expenditures by sex.
(DOCX)

S4 Table. Health care expenditures by cohort.
(DOCX)

S5 Table. Multivariate analysis for each type of expenditure.
(DOCX)

S6 Table. Multivariate analysis for total health care expenditure by each type of cancer.
(DOCX)

S1 Fig. Histogram of the survivors mean of healthcare expenditures.
(TIF)

S2 Fig. Adjusted annual health care expenditures by sex and cohort.
(TIF)

S3 Fig. Adjusted annual health care expenditures by type of primary cancer and cohort.
(TIF)

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OPEN

Long-term hospitalisations in survivors of paediatric solid tumours in France

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The late effects of treatments for childhood cancers may lead to severe and multiple health conditions requiring hospitalisation. We aimed to estimate the hospitalisation rate among childhood cancer survivors (CCS) in France, to compare them with the general population and to investigate the associated factors. We matched total of 5439 5-year solid CCS diagnosed before the age of 21 between 1945 and 2000 by sex, birth year and region of residence to 386,073 individuals of the French general population. After linkage with the national hospital discharge database, we estimated the relative hospitalisation rate (RHR), the absolute excess risks (AERs) and the relative bed-day ratio (RBDR) during 2006–2018. We used generalised linear models to estimate associations between hospitalisation and survivor characteristics. Overall, the RHR was 2.49 (95% confidence interval [CI] 2.46–2.52) and the RBDR was 3.49 (95% CI 3.46–3.51). We found that neoplasm-related hospitalisations had the highest AER (105.8 per 1000 person-years), followed by genitourinary system diseases (34.4 per 1000 person-years) and cardiovascular diseases (19.2 per 1000 person-years). In adjusted analysis, CCS treated with chemotherapy (risk ratio [RR] 1.62, 95% CI 1.53–1.70), radiotherapy (RR 2.11, 95% CI 1.99–2.24) or both (RR 2.59, 95% CI 2.46–2.73) had a higher risk of hospitalisation than the ones who had not received any of these treatments. CCS treated during the past decades by chemotherapy and/or radiotherapy now had a higher hospitalisation risk for all main categories of diagnosis than the general population. Prevention strategies and medical surveillance programmes may promote a long-term decrease in the hospitalisation rate among CSS.

Advances in cancer treatment, such as improvements in chemotherapy regimens, radiation techniques and surgery, have allowed achieving 5-year survival rates of more than 80% in patients with paediatric cancer. However, late effects from cancer therapies continue to be a challenge. It is estimated that two thirds of childhood cancer survivors (CCS) will experience at least one treatment-related adverse event and 40% will experience at least one severe or life-threatening or disabling event several years after the cancer diagnosis^{1,2}. Potential life-threatening or disabling late effects include second neoplasms, cardiovascular diseases, growth problems

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and mental health issues³. This increased morbidity may lead to the development of complex health conditions requiring hospitalisation⁴.

Some researchers have evaluated the long-term risk of hospitalisation among CCS and have reported an overall increased risk in survivors compared with the general population^{4–9}. In addition, their average length of stay in the hospital was up to 35% longer than patients without a history of cancer¹⁰. A better understanding of the long-term hospitalisation of CCS is thus important to evaluate their health conditions and health care-related costs several years after cure.

In France, there are about 50,000 adult CCS, with a growing number of long-term survivors¹¹. However, no studies have analysed and detailed the hospitalisation rate in long-term CCS. The aim of this paper was to estimate the hospitalisation rate among CCS residing in France compared those of the French general population. We have also described the hospitalisation-related clinical diagnoses and have investigated cancer-related factors associated with an increased probability of hospitalisation.

Materials and methods

Study population. The French Childhood Cancer Survivor Study (FCCSS) is a retrospective cohort of 7670 5-year CCS diagnosed for solid cancer or lymphoma (all malignancies except leukaemia) before the age of 21 years between 1945 and 2000 in five cancer centres in France. Cancer diagnoses were classified according to ICCC-3, with the exception of thyroid cancer, which was included in a separate group due to the specificity of iodine treatment and its consequences. Detailed information on the methods for data collection and patients has been already described in several articles^{12,13}. To study the FCCSS hospitalisation records, we selected survivors who were alive in January 2006, living in metropolitan France and who were linked to the National Health Data System (French acronym: SNDS). Of the 7670 5-years survivors from the FCCSS, 6,818 were still alive on 1 January 2006.

Data sources. The SNDS is the health care claims dataset in France; it covers around 99% of the population¹⁴. It contains exhaustive data (beginning in 2006) on billing and reimbursement of beneficiaries, including private and public hospital data collected in the national hospital discharge database (French acronym: PMSI).

The PMSI is divided into four categories corresponding to hospitalisation in conventional hospital units (short stays), homecare units, rehabilitation and psychiatry institutions. It includes some demographic characteristics of patients (age, gender, place of residence) as well as clinical information of the hospitalisations such as the in-patient bed-days, primary and secondary diagnoses according to the 10th revision of the International Classification of Diseases (ICD-10), procedures performed, medications administered and the dates of death and cost information under the diagnosis-related group system¹⁵.

Linkage and access of SNDS data of FCCSS cohort was provided by the national health insurance fund (French acronym: CNAM) by probabilistic matching using the survivor's family and first names, sex, date and place of birth and unique arbitrary number. The percentage of survivors linked to SNDS data after this procedure was 81.9% ($n = 5583/6818$), with data availability from 2006 to 2018.

Reference sample. We obtained a reference sample from the General Sample of Beneficiaries (French acronym: EGB). The EGB is a 1/97th anonymised random permanent sample of all population included in the SNDS ($n \approx 830,000$ in 2021) which has been shown to be representative of the French general population¹⁶. Health care claims including hospitalisation records (PMSI) are available in the EGB; however, information regarding hospitalisation in rehabilitation and psychiatric institutions has not yet been supplied. The reference sample was selected matched by sex, year of birth and the region (French administrative area) of residence and randomly assigned to each FCCSS survivors with the same characteristics.

Hospitalisation measures. Using the PMSI, we obtained hospitalisation records in conventional hospital units from January 2006 to December 2018 or death—whichever came first—for each CCS and individual of the reference population. Our endpoints of interest were (1) the total number of hospitalisations and (2) the total number of bed-days spent in hospital, which is the number of days in which the patient stays overnight in a hospital, excluding day hospital visits. We grouped hospitalisations according to the primary diagnosis into the 19 main groups of the ICD-10, excluding the following categories: pregnancy and childbirth (O00–O99), certain conditions originating in the perinatal period (P00–P96), external causes of morbidity and mortality (V01–Y98) and codes for special purposes (U00–U99), in order to focus on hospitalisation potentially linked to childhood cancer sequels.

Ethics approval. The study was approved by the French Data Protection Authority (French acronym: CNIL) (Authorization n°902287) and by the ethics committee of the French National Institute of Health and Medical Research (French acronym: INSERM). Informed consent was obtained for patients who could be contacted ($n = 3312$), and posters containing information about the study and how to decline participation were displayed in the French paediatric oncology departments. Finally, we obtained a specific act in law from the French 'Conseil d'Etat', the highest court in France (Order 2014-96 of 2014 February 3), that approved the cession of the SNDS data for all patients included in the FCCSS with or without informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis. The hospitalisation and bed-day rates were calculated for both the FCCSS and reference populations as the total number of hospitalisations or bed-days divided by the number of person-years

(PY) at risk and expressed as the rate per 1000 PY. Time during hospitalisation was not counted as time at risk when calculating the hospitalisation rate. To compare the FCCSS hospitalisation rate to the reference population, we calculated: (1) the absolute excess risk (AER) as the difference between the hospitalisation or bed-day rate of the FCCSS and reference populations expressed per 1000 PY, and (2) the relative hospitalisation rate (RHR) and the relative bed-day ratio (RBDR) with their corresponding 95% confidence intervals (CIs) as the division of the hospitalisation or bed-day rate of the FCCSS and reference populations based on the assumption that the observed number of hospitalisations and bed-days followed a Poisson distribution. We calculated the AER, RHR and RBDR for overall hospitalisations and for each ICD-10 main group.

We used generalised linear models (GLMs) to model the number of hospitalisations and bed-days. We used the expected number of hospitalisations or bed-days as an offset to study the risk for FCCSS survivors relative to that for the reference population. We adjusted the models for sex, year of cancer diagnosis, age at cancer diagnosis, age in 2006, type of primary cancer, age and cancer treatment(s) received (i.e. chemotherapy, radiotherapy, and/or surgery). We chose neuroblastoma as the reference primary cancer variable because it is one of the larger groups of cancer with the same histology. We have reported risk estimates as risk ratios (RRs) and 95% CIs. Finally, we executed separate models for each ICD main group to evaluate risk factors for the different types of hospitalisations. We performed statistical analyses by using SAS 9.4 software (SAS Institute, Cary, NC, USA), considering $p < 0.05$ to be significant.

Results

We included 5439 FCCSS survivors and 386,073 reference persons. Each CCS was assigned an average of 71 (SD: 73.9) unique reference persons. Between 1 January 2006 and 31 December 2018, 3756 CCS (69%) and 208,217 reference persons (54%) had had at least one hospitalisation. By the end of the follow-up, 383 (7%) FCCSS survivors and 38,458 (10%) reference persons had died. About 28% of FCCSS patients were less than 20 years old at the start of the SNDS follow-up in 2006, 10% being 40 years old or more (Table 1). The average delay between childhood cancer treatment and 2006 was 19.9 years (SD: 9.9, interquartile range 12–26).

Total number of hospitalisations and bed-days. The following results are presented in Table 2. We identified 27,598 hospitalisations in FCCSS survivors, which accounted for 74,814 in-patient bed-days. For the FCCSS survivors, the hospitalisation rate was 401.2 per 1000 PY while the bed-day rate was 1084.4 per 1000 PY. In the matched reference population, the hospitalisation rate was 161.3 per 1000 PY and the bed-day rate was 311.1 per 1000 PY. Hence, the AER of hospitalisation was 239.9 per 1000 PY and the AER of in-patient bed-days was 773.2 per 1000 PY for FCCSS survivors. The RHR was 2.49 (95% CI 2.46–2.52, $p < 0.001$), meaning that FCCSS survivors were hospitalised more than twice as often as the matched reference population. Additionally, they had more than three times as many in-patient bed-days as the reference population (RBDR 3.49, 95% CI 3.46–3.51, $p < 0.001$). When excluding hospitalisation for neoplasms, which could be linked to long-term relapses of childhood cancer and secondary neoplasms, these numbers were, respectively, RHR = 2.12 (95% CI 2.08–2.15) and RBDR = 3.36 (95% CI 3.33–3.38).

Hospitalisations and bed-days by the main diagnostic groups. FCCSS survivors were more frequently hospitalised and had more in-patient bed-days than the matched reference population for all diagnostic groups. Neoplasm-related hospitalisation had the highest AER (105.8 per 1000 PY), followed by genitourinary system diseases (34.4 per 1000 PY), factors influencing health status and contact with health services (other factors) (26.6 per 1000 PY) and circulatory system diseases (19.2 per 1000 PY). There were the fewest hospitalisations for mental and behavioural disorders and auditory issues (AER = 0.6 and 0.7 per 1000 PY, respectively) (Table 2). Details of the main diagnoses of the hospitalisations are reported in Supplementary Table 1.

As a general matter, hospitalisations were not only more frequent in FCCSS survivors than in matched reference population, but their stays were longer for each diagnostic group. The AER of bed-days was higher than the AER of hospitalisation in all main diagnostic groups. In addition, the RBDR was higher than the RHR for all diagnostic groups except endocrine and haematological diseases (Fig. 1, Table 2). This phenomenon was particularly pronounced for hospitalisation related to nervous system and genitourinary system pathologies, leading to over five times as many in-patient bed-days in FCCSS survivors as the reference population (RBDR 5.74, 95% CI 5.57–5.91 and RBDR 5.50, 95% CI 5.40–5.60, respectively).

Hospitalisations and bed-days and the survivors' characteristics. Figure 2 shows that the hospitalisation rate was significantly higher in all types of primary cancer compared with the reference population, except in survivors of thyroid tumours (RHR 0.81, 95% CI 0.69–0.95) (Table 1). Central nervous system (CNS) tumour survivors had the highest RHR (3.56, 95% CI 3.45–3.67) and the highest RBDR (6.29, 95% CI 6.20–6.39) (Table 1). In detail, CNS tumour survivors were most likely to be hospitalised for congenital malformations (RHR 14.34, 95% CI 11.22–18.06), diseases of the nervous system (RHR 10.48, 95% CI 9.44–11.61) and endocrine-related diseases (RHR 10.45, 95% CI 9.29–11.7), with a very high in-patient bed-day rate for the first groups of pathologies (RBDR 33.88, 95% CI 30.27–37.81 and RBDR 32.19, 95% CI 31.02–33.39, respectively), but not for hospitalisation for endocrine diseases (Supplementary Table 1).

In a multivariate analysis, compared with neuroblastoma, thyroid tumour survivors were at lower risk of both hospitalisation and in-patient bed-days (RR 0.66, 95% CI 0.56–0.78 and RR 0.73, 95% CI 0.66–0.80, respectively), while CNS tumour survivors (RR 1.29, 95% CI 1.22–1.36), kidney tumour survivors (RR 1.09, 95% CI 1.04–1.14) and other primary cancer survivors (RR 1.39, 95% CI 1.30–1.48) were at higher risk (Table 3). The in-patient bed-day risk was higher among survivors of CNS tumours, gonadal tumours and retinoblastoma (Table 3).

	Total Patients (%)	Patients Hospitalized (%)	N° Hospitalizations	Hospitalization rate in FCCSS (per 1000 PY)	Hospitalization rate in EGB (per 1,000 PY)	AER per 1,000 PY	RHR (95% CI)	N° Bed-days	Bed-days rate in FCCS (per 1000 PY)	Bed-days rate in EGB (per 1,000 PY)	AER per 1000 PY	RBDR (95% CI)
All	5439	3756	27,598	401.2	161.3	240.0	2.49 (2.46–2.52)	74,814	1084.4	311.1	773.3	3.49 (3.46–3.51)
Sex												
Man	2970 (54.6)	1982 (52.8)	13,646	363.5	145.4	218.1	2.5 (2.46–2.54)	35,870	952.9	313.6	639.3	3.04 (3.01–3.07)
Women	2469 (45.4)	1774 (47.2)	13,952	446.6	177.4	269.2	2.52 (2.48–2.56)	38,944	1242.3	308.6	933.7	4.03 (3.99–4.07)
Age at January 2006 (Start date)												
<20	1535 (28.2)	783 (20.8)	4012	202.0	85.9	116.1	2.35 (2.28–2.43)	7755	390.0	136.3	253.7	2.86 (2.8–2.93)
20–30	2066 (38)	1488 (39.6)	10,665	407.1	111.4	295.7	3.66 (3.59–3.73)	27,159	1033.7	182.7	851.0	5.66 (5.59–5.73)
31–40	1311 (24.1)	1038 (27.6)	8125	496.0	165.8	330.2	2.99 (2.93–3.06)	23,168	1408.9	304.5	1104.4	4.63 (4.57–4.69)
>=41	527 (9.7)	447 (11.9)	4796	756.5	287.0	469.5	2.64 (2.56–2.71)	16,732	2620.3	630.7	1989.6	4.15 (4.09–4.22)
Status at December 2018 (Ending date)												
Alive	5056 (93)	3389 (90.2)	19,606	298.9	163.7	135.2	1.83 (1.8–1.85)	44,789	681.5	310.8	370.7	2.19 (2.17–2.21)
Death	383 (7)	367 (9.8)	7992	2509.9	139.4	2370.5	18 (17.61–18.4)	30,025	9192.1	314.3	8877.8	29.25 (28.92–29.58)
Year of diagnosis												
<1970	351 (6.5)	300 (8)	2925	688.3	300.9	387.4	2.29 (2.21–2.37)	10,688	2498.0	677.7	1820.3	3.69 (3.62–3.76)
1970–1979	980 (18)	783 (20.8)	7387	611.4	197.1	414.3	3.1 (3.03–3.17)	19,820	1633.2	375.3	1257.9	4.35 (4.29–4.41)
1980–1989	1809 (33.3)	1335 (35.5)	9905	433.3	129.5	303.8	3.34 (3.28–3.41)	29,690	1294.1	227.8	1066.3	5.68 (5.62–5.75)
>=1990	2299 (42.3)	1338 (35.6)	7381	249.4	93.0	156.4	2.68 (2.62–2.74)	14,616	493.2	150.3	342.9	3.28 (3.23–3.33)
Age at first cancer												
0–1	1288 (23.7)	770 (20.5)	5687	345.1	126.1	219.0	2.74 (2.67–2.81)	12,031	728.7	227.3	501.4	3.21 (3.15–3.26)
2–4	1276 (23.5)	857 (22.8)	5864	362.9	146.6	216.3	2.48 (2.41–2.54)	18,753	1156.7	268.3	888.4	4.31 (4.25–4.37)
5–9	1207 (22.2)	868 (23.1)	6617	437.5	164.5	273.0	2.66 (2.6–2.73)	19,619	1292.5	326.9	965.6	3.95 (3.9–4.01)
10–14	1108 (20.4)	839 (22.3)	6839	492.1	193.7	298.4	2.54 (2.48–2.6)	18,031	1292.9	397.4	895.5	3.25 (3.21–3.3)
≥15	560 (10.3)	422 (11.2)	2591	363.5	199.3	164.2	1.82 (1.75–1.9)	6380	893.0	384.3	508.7	2.32 (2.27–2.38)
First primary cancer type												
Other solid cancer	312 (5.7)	222 (5.9)	1622	414.1	152.8	261.3	2.71 (2.58–2.84)	3645	928.2	285.9	642.3	3.25 (3.14–3.35)
Kidney tumors	825 (15.2)	551 (14.7)	4712	453.1	172.1	281.0	2.63 (2.56–2.71)	12,249	1174.0	335.7	838.3	3.5 (3.44–3.56)
Neuroblastoma	746 (13.7)	466 (12.4)	3124	327.1	126.7	200.4	2.58 (2.49–2.67)	6727	703.1	219.9	483.2	3.2 (3.12–3.27)
Continued												

	Total Patients (%)	Patients Hospitalized (%)	N° Hospitalizations	Hospitalization rate in FCCSS (per 1000 PY)	Hospitalization rate in EGB (per 1,000 PY)	AER per 1,000 PY	RHR (95% CI)	N° Bed-days	Bed-days rate in FCCS (per 1000 PY)	Bed-days rate in EGB (per 1,000 PY)	AER per 1000 PY	RBDR (95% CI)
Lymphoma	931 (17.1)	669 (17.8)	4990	421.7	178.6	243.1	2.36 (2.3–2.43)	12,512	1054.3	363.2	691.1	2.9 (2.85–2.95)
Soft tissue sarcomas	591 (10.9)	417 (11.1)	3098	410.7	184.1	226.6	2.23 (2.15–2.31)	7680	1015.3	360.3	655.0	2.82 (2.76–2.88)
Bone sarcomas	476 (8.8)	368 (9.8)	2428	400.9	187.0	213.9	2.14 (2.06–2.23)	6129	1009.2	371.8	637.4	2.71 (2.65–2.78)
Central nervous system tumor	708 (13)	567 (15.1)	4314	502.1	141.0	361.1	3.56 (3.45–3.67)	15,558	1801.7	286.3	1515.4	6.29 (6.2–6.39)
Gonadal/Germ cell tumours	334 (6.1)	231 (6.2)	1441	337.2	182.7	154.5	1.85 (1.75–1.94)	4731	1103.7	352.2	751.5	3.13 (3.04–3.22)
Thyroid tumor	48 (0.9)	33 (0.9)	150	247.0	303.8	-56.8	0.81 (0.69–0.95)	424	696.8	595.4	101.4	1.17 (1.06–1.29)
Retinoblastoma	468 (8.6)	232 (6.2)	1719	285.8	105.0	180.8	2.72 (2.59–2.85)	5159	855.8	165.7	690.1	5.17 (5.03–5.31)
Treatment received												
No radiotherapy or chemotherapy	720 (13.2)	394 (10.5)	1789	192.6	152.0	40.6	1.27 (1.21–1.33)	3105	333.9	280.8	53.1	1.19 (1.15–1.23)
Radiotherapy	696 (12.8)	549 (14.6)	4670	549.3	233.6	315.7	2.35 (2.28–2.42)	15,418	1804.4	500.9	1303.5	3.60 (3.55–3.66)
Chemotherapy	1990 (36.6)	1236 (32.9)	7275	284.5	125.8	158.7	2.26 (2.21–2.31)	19,361	755.6	226.9	528.7	3.33 (3.28–3.38)
Radiotherapy and Chemotherapy	2033 (37.4)	1577 (42)	13,864	545.3	158.3	387.0	3.45 (3.39–3.5)	36,930	1446.8	297.7	1149.1	4.86 (4.81–4.91)

Table 1. Survivor characteristics and hospitalisation and bed-day rates. FCCSS, French Childhood Cancer Survivor Study; EGB, general sample of beneficiaries; AER, absolute access risk; PY, person-year; RHR, relative hospitalization ratio; RBDR, relative bed-days ratios.

FCCSS women were slightly more frequently hospitalised and accumulated more bed-days than men (Table 1). In an adjusted analysis, compared with the reference population, FCCSS women had a lower relative hospitalisation risk (RR 0.97, 95% CI 0.95–0.99) than FCCSS men; however, they had a higher in-patient relative bed-day risk (RR 1.29, 95% CI 1.27–1.31) (Table 3).

In a univariate analysis, there was no clear variation in the RHR according to the calendar period and the age at childhood cancer diagnosis, nor with the age at the start of the SNDS follow-up (2006) (Table 1). Compared with the reference population, the hospitalisation rate in the FCCSS survivors increased with age. This phenomenon was denoted by the higher AER with increasing age at the start of the SNDS follow-up. There were similar results for in-patient bed-days (Table 1). In a multivariate analysis, the variations in the adjusted RHR according to age at childhood cancer diagnosis were very low, and the variations in adjusted RBDR were low, whereas the RHR and RBDR significantly decreased as the age at the start of the SNDS follow-up increased. These changes were greater in patients treated between 1970 and 1990 than in the ones treated before that time (Table 3).

When investigating the role of age in each hospitalisation category for the RHR (Supplementary Table 2) and the RBDR (Supplementary Table 3) in a multivariate analysis, there were no clear variations, except for an increase with age at childhood cancer for hospitalisation for auditory diseases and a decrease for hospitalisation for genitourinary diseases.

Role of treatments. Survivors who had been treated with surgery or who had not received treatment had a small increase in the hospitalisation rate (RHR 1.27, 95% CI 1.21–1.33) (Table 1). However, the hospitalisation and bed-day risks increased in survivors who had been treated with chemotherapy (RR 1.62, 95% CI 1.53–1.70 and RR 2.63, 95% CI 2.53–2.74, respectively), radiotherapy (RR 2.11, 95% CI 1.98–2.22 and RR 2.72, 95% CI 2.61–2.83, respectively) or both (RR 2.60, 95% CI 2.46–2.73 and RR 3.72, 95% CI 3.58–3.86, respectively) compared with survivors who had not received these treatments (Table 3). Chemotherapy was also associated with a significant increase in hospitalisation related to neoplasms, endocrine disorders and cardiovascular diseases; this increase was enhanced by radiotherapy (Supplementary Table 3). Chemotherapy was the most important

	Hospitalizations							Bed-days in the hospital						
	N° Hospitalizations in FCCSS	Hospitalization rate in FCCSS (per 1000 PY)	N° Hospitalizations in EGB	Hospitalization rate in EGB (per 1000 PY)	AER per 1000 PY	RHR	(95% CI)	N° Bed-Days in FCCSS	Bed-Days rate in FCCSS (per 1000 PY)	N° Bed-Days in EGB	Bed-Days rate in EGB (per 1000 PY)	AER per 1000 PY	RBDR	(95% CI)
Total	27,598	401.2	805,758	161.3	240.0	2.49	(2.46–2.52)	74,814	1084.4	1,555,993	311.1	773.3	3.49	(3.46–3.51)
Infections	245	3.6	7585	1.5	2.0	2.35	(2.06–2.66)	1512	21.9	35,350	7.1	14.8	3.10	(2.95–3.26)
Neoplasms	10,100	146.8	205,097	41.0	105.8	3.58	(3.51–3.65)	16,156	234.2	289,619	57.9	176.3	4.04	(3.98–4.11)
Haematological	237	3.4	5233	1.0	2.4	3.29	(2.88–3.74)	858	12.4	19,169	3.8	8.6	3.24	(3.03–3.47)
Endocrine	830	12.1	17,153	3.4	8.6	3.51	(3.28–3.76)	2185	31.7	67,426	13.5	18.2	2.35	(2.25–2.45)
Mental	300	4.4	18,899	3.8	0.6	1.15	(1.03–1.29)	782	11.3	48,923	9.8	1.6	1.16	(1.08–1.24)
Neurological	803	11.7	23,414	4.7	7.0	2.49	(2.32–2.67)	4433	64.3	55,985	11.2	53.1	5.74	(5.57–5.91)
Ocular	326	4.7	13,992	2.8	1.9	1.69	(1.51–1.89)	453	6.6	8277	1.7	4.9	3.97	(3.61–4.35)
Auditory	109	1.6	4311	0.9	0.7	1.84	(1.51–2.22)	236	3.4	6865	1.4	2.0	2.49	(2.18–2.83)
Cardiovascular	1900	27.6	42,035	8.4	19.2	3.28	(3.14–3.43)	9065	131.4	139,661	27.9	103.5	4.70	(4.61–4.8)
Pulmonary	601	8.7	20,994	4.2	4.5	2.08	(1.92–2.25)	4155	60.2	84,894	17.0	43.2	3.55	(3.44–3.66)
Gastrointestinal	2113	30.7	116,056	23.2	7.5	1.32	(1.27–1.38)	5901	85.5	171,616	34.3	51.2	2.49	(2.43–2.56)
Skin	393	5.7	14,316	2.9	2.8	1.99	(1.8–2.2)	872	12.6	25,460	5.1	7.5	2.48	(2.32–2.65)
Musculoskeletal	881	12.8	54,634	10.9	1.9	1.17	(1.1–1.25)	3317	48.1	137,421	27.5	20.6	1.75	(1.69–1.81)
Genitourinary	3462	50.3	79,401	15.9	34.4	3.17	(3.06–3.27)	11,259	163.2	148,360	29.7	133.5	5.50	(5.4–5.6)
Congenital Malformations	153	2.2	3514	0.7	1.5	3.16	(2.68–3.71)	498	7.2	7390	1.5	5.7	4.88	(4.47–5.33)
Symptoms Unclassified	1160	16.9	42,017	8.4	8.5	2.01	(1.89–2.12)	3108	45.0	60,888	12.2	32.9	3.70	(3.57–3.83)
Injury—Poisoning	1003	14.6	53,385	10.7	3.9	1.36	(1.28–1.45)	4344	63.0	136,490	27.3	35.7	2.31	(2.24–2.38)
Other Factors	2982	43.4	83,722	16.8	26.6	2.59	(2.5–2.68)	5680	82.3	112,199	22.4	59.9	3.67	(3.57–3.77)
Total Excluding Neoplasms	17,498	254.4	600,661	120.2	134.2	2.12	(2.08–2.15)	58,658	850.2	1,266,374	253.2	597.0	3.36	(3.33–3.38)

Table 2. Hospitalisations and bed-days in the French Childhood Cancer Survivor Study (FCCSS) survivors and the reference sample according to the 10th revision of the International Classification of Diseases. FCCSS, French Childhood Cancer Survivor Study; EGB, general sample of beneficiaries; AER, absolute access risk; PY, person-year; RHR, relative hospitalization ratio; RBDR, relative bed-days ratios.

risk factor for hospitalisation related to genitourinary system diseases (RHR 6.53, 95% CI 5.34–7.99) and blood disorders (RR 3.59, 95% CI 1.69–7.66) while radiotherapy was the most important determinant for hospitalisation due to nervous system diseases (RR 1.81, 95% CI 1.34–2.44) (Supplementary Table 3). There were similar results concerning childhood cancer treatments for the bed-day rate in the different hospitalisation groups (Supplementary Table 4).

Discussion

In a cohort of 5439 5-year solid CCS, we found that individuals treated for childhood cancer in 1940–2000 in France were recently hospitalised more than twice as often as the general population during a 13-year follow-up (2006–2018). This increase in the hospitalisation rate occurred among cancer survivors who had been treated

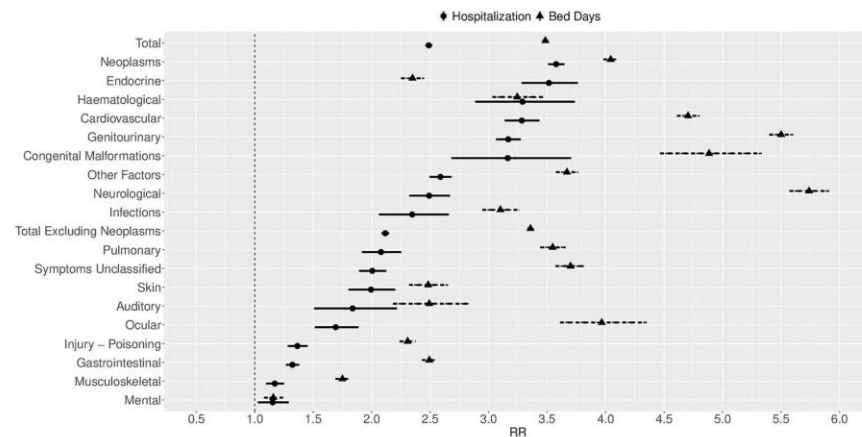


Figure 1. The relative hospitalisation ratio and the relative bed-day ratio according to the 10th revision of the International Classification of Diseases.

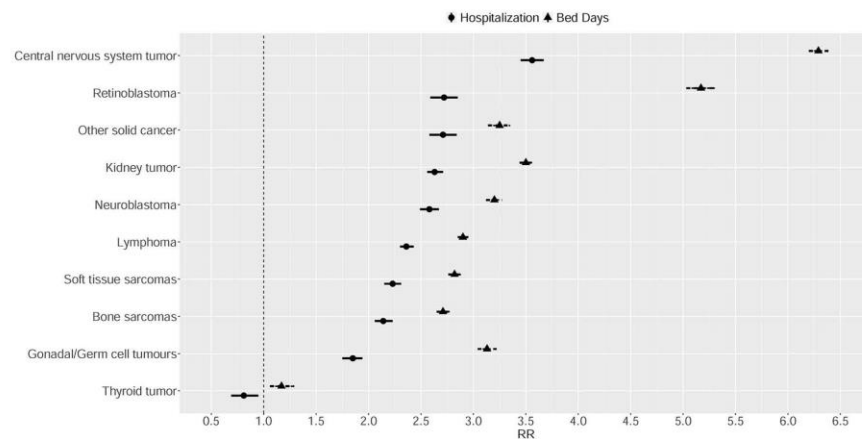


Figure 2. The relative hospitalisation ratio and the relative bed-day ratio by the type of primary cancer.

with chemotherapy and/or radiotherapy. The hospitalisation rate was elevated for all ICD-10 groups of hospitalisation-related pathologies, although the RHR was the highest for hospitalisation related to neoplasms, endocrine conditions and circulatory system diseases.

Our results are consistent with similar studies performed in the USA, Canada, the Nordic countries and the Netherlands in which CCS experienced a higher hospitalisation rate compared with the general population of their countries⁴⁻⁹. In Europe, the RHR was generally higher: about two times higher in the Netherlands⁶ and the Nordic countries⁹, with a bed-day ratio of 5 in the Nordic countries, and an RHR of about 2.8 and a bed-day ratio of 3.7 in Scotland¹⁷, findings similar to our results. On the other hand, there was a lower hospitalisation rate in a small Utah cohort and in the large US Childhood Cancer Survivor Study (CCSS)^{4,5}, probably because most of the children in those studies had been treated before the end of the 1970s. That time corresponds to the beginning of generalised use of combined chemotherapy¹⁸, which was more toxic than the previous single-agent chemotherapy.

Previous studies have shown that survivors are more at risk of hospitalisation due to neoplasms, recurrences and/or subsequent^{4,7,9,17,19}. These results are similar to our findings in which both the AER and RHR were the highest in CCS. In two studies from North America, survivors were hospitalised more often because of blood disorders^{4,19}. However, our results indicate that although blood disorders had a higher RHR, this category had a very low hospitalisation rate and AER. This outcome could be partially explained by the fact that our cohort did not include leukaemia survivors. One study from the UK reported that CCS had a four-fold risk of being

	Number of hospitalizations	Number of bed-days
	RR (95% CI)	RR (95% CI)
Intercept	1.79 (1.66–1.93)***	0.93 (0.89–0.98)***
Women (Ref= Men)	0.97 (0.95–0.99)***	1.29 (1.27–1.31)***
Age in 2006	0.99 (0.99–0.99)***	0.99 (0.98–0.99)***
Age at first cancer (Ref=0–1)		
2–4	0.89 (0.86–0.93)***	1.38 (1.35–1.41)***
5–9	0.99 (0.94–1.03)	1.33 (1.29–1.37)***
10–14	1.04 (0.99–1.11)	1.23 (1.19–1.28)***
≥15	0.83 (0.77–0.9)***	1 (0.96–1.05)
Year of diagnosis (Ref= > 1990)		
< 1970	1.05 (0.93–1.19)	1.86 (1.73–2)***
1970–1979	1.32 (1.22–1.43)***	1.82 (1.74–1.9)***
1980–1989	1.34 (1.27–1.41)***	2.07 (2.01–2.13)***
First primary cancer type (Ref= Neuroblastoma)		
Other solid cancer	1.39 (1.3–1.48)***	1.4 (1.34–1.47)***
Kidney tumors	1.09 (1.04–1.14)***	0.98 (0.95–1.01)
Lymphoma	0.99 (0.94–1.04)	0.98 (0.95–1.01)
Soft tissue sarcomas	0.97 (0.92–1.03)	0.95 (0.91–0.98)***
Bone sarcomas	1.01 (0.95–1.08)	1.03 (0.99–1.07)
Central nervous system tumor	1.29 (1.22–1.36)***	1.97 (1.9–2.03)***
Gonadal/Germ cell tumours	1.02 (0.96–1.1)	1.39 (1.34–1.45)***
Thyroid tumor	0.66 (0.56–0.78)***	0.73 (0.66–0.8)***
Retinoblastoma	0.98 (0.92–1.04)	1.59 (1.54–1.65)***
Treatment (Ref=No radiotherapy or chemotherapy)		
Chemotherapy	1.62 (1.53–1.70)***	2.63 (2.53–2.74)***
Radiotherapy	2.10 (1.98–2.22)***	2.72 (2.61–2.83)***
Radiotherapy and Chemotherapy	2.60 (2.46–2.73)***	3.72 (3.58–3.86)***

Table 3. Multivariate analysis of the total number of hospitalizations and bed-days. RR, risk ratio; CI, confidence interval. *** $p < 0.01$, ** $p < 0.05$.

hospitalised for cardiovascular disease compared to that expected from people of same age, sex and calendar year stratum²⁰. Another study from the Netherlands⁷ showed a higher RHR but the lowest AER for endocrine conditions. These results are consistent with our findings but inconsistent with findings from the Nordic countries, where there was excessive hospitalisation mainly due to nervous system diseases⁹.

Researchers have reported a significantly higher hospitalisation rate in survivors of Hodgkin's lymphoma⁵, CNS tumours¹⁹ and bone tumours^{4,7} compared with other primary cancer types. However, our results showed few variations in the RHR according to the primary cancer type, except for thyroid and CNS tumours. A high hospitalisation rate for nervous system diseases and congenital malformations have been also reported in CNS tumour survivors¹⁷, but the reclassification of neurofibromatosis from a tumour of uncertain behaviour in ICD-9 to congenital malformation in ICD-10 partially explains this excessive hospitalisation. On the contrary, in one study renal tumour survivors were not at additional risk of hospitalisation⁴, and in another one they had among the lowest hospitalisation rate⁵, which disagrees with our findings. However, this could be explained by the fact that we accounted for day hospital admissions, which include dialysis. In fact, our results show that their excessive hospitalisation comes from genitourinary system diseases.

Among FCCSS survivors, women experienced slightly higher hospitalisation and bed-day rates than men (respectively, 446.6 versus 363.5 per 1000 PY and 1242.3 versus 952.9 per 1000 PY, respectively). Compared with the reference population, women and men had a similar RHR and a higher AER for hospitalisation and bed-days, and women had a higher RBDR. These results are similar to a population-based cohort performed in Utah⁴, but not to another population-based cohort study performed in another US state, in which both the RHR and AER were higher for women⁸. Our findings are also different from the U.S. CCSS, in which women had a much lower RHR and AER than men⁵. In the Netherlands, two studies evidenced a higher hospitalisation rate but a lower RHR in women than in men^{6,7}, whereas in the Scotland¹⁷ the standardised bed days ratio was almost the same in women and men.

Our findings are consistent with those of earlier studies in the Netherlands in which survivors initially treated with radiotherapy had a particularly increased hospitalisation rate for neoplasms, endocrine diseases and circulatory system diseases^{7,21}. Another study in British Columbia, Canada, reported that hospital-related morbidity was elevated for all combinations of primary treatment and was highest for those who had received radiation, chemotherapy and surgery¹⁹. Our findings identified chemotherapy as a factor associated with hospitalisation especially for genitourinary system diseases, where cisplatin or ifosfamide have been established as treatment-related causes of chronic renal damage in CCS²².

Unexpectedly, we did not observe a variation in the RHR and RBDR according to the age at childhood cancer onset²¹. Our results about the variations in RHR and RBDR according to year of childhood cancer diagnosis and the age at the start of SNDS follow-up have to be interpreted with caution because these two variables are linked—that is, survivors treated in later years are likely to be older at the start of the follow-up. As a general matter, the differences in results among studies are hardly explained by variations in demographic and clinical characteristics. A more thorough investigation would require performing a meta-analysis. Our results should be interpreted with caution because the SNDS data are only available for 2006–2018, a period of time after the FCCSS recruitment period (1945–2000). Thus, a selection bias could occur in older patients at the time of the SNDS follow-up. For example, patients treated before 1970 who survived until 2006 are not representative of all patients treated before 1970 and correspond to a different distribution of the treatment types.

To our knowledge, this is the first detailed study of the hospitalisation of long-term CCS compared with the general population in France. We used a national administrative database, which provided comprehensive information on hospitalisations over 13 years in both CCS and their reference population. An advantage of our study is that we have accounted for hospitalisation in day hospital units. Admissions to day hospital units are mainly for chemotherapy, radiotherapy and extracorporeal dialysis. By considering in-patient bed-days, we could focus on more severe hospitalisation that required more medical care.

Our study is subject to some limitations. First, we were not able to identify hospitalisations related to relapse or metastasis of childhood cancer to the ones related to secondary neoplasms. Second, we considered only hospitalisation in conventional hospital units because information regarding rehabilitation and psychiatric institution hospitalisation was not available in the EGB sample, which constitutes our reference. Thus, we have underestimated the hospitalisation rate, especially mental-related hospitalisation. Nevertheless, the conventional hospital units treat more than 90% of all patients hospitalised in France²³. Moreover, given that the EGB includes a population that does not receive health care and the data are stored for a period of 20 years¹⁵, the EGB allows researchers to carry out longitudinal studies of hospitalisations²⁴. Third, we could not address the association between specific types of hospitalisations with specific modalities of therapy (e.g. chemotherapy and radiation doses) because this requires special considerations. We will perform these investigations in separate publications. Lastly, the FCCSS included only patients from five non-profit private cancer treatment centres in France, which are not representative of all French childhood cancer treatment centres. Nevertheless, we have found that this did not impact the long-term survivor's medical expenditure²⁵.

In summary, we have shown that the hospitalisation and in-patient bed-day rates among CCS in France were more than twice higher than in the general population. The association of cancer treatment with the different types of hospitalisations suggests special attention should be paid to prevent long-term complications in all organ systems, especially among CCS treated with combined therapies.

Data availability

The datasets generated and/or analysed during the current study are not publicly available because they contain potentially identifying patient information. However, the datasets are available from the corresponding author upon reasonable request.

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Author contributions

F.D.V. and N.P.F. conceived and designed the study. F.D.V. had full access to all the data in the study and take responsibility for its integrity. D.B.Q. carried out the data preparation. D.B.Q. and F.D.V. carried out the statistical analyses. D.B.Q. drafted the manuscript. All authors analyzed and interpreted the data, and contributed to drafting of the manuscript by providing input and guidance over numerous manuscript drafts.

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Competing interests

The authors declare no competing interests.

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1 **Excess healthcare expenditure in adults treated for solid cancer in childhood: A cohort study**
2 **in France.**

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1 **Excess healthcare expenditure in adults treated for solid cancer in childhood: A cohort**
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3
4 **study in France.**

5
6 **Abstract**
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10 **Background:** Due to late effects, childhood cancer survivors (CCS) are more likely to have
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12 multiple chronic conditions than the general population. However, little is known about the
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14 economic burden of care of CCS in the long term.
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18 **Objectives:** To estimate excess healthcare expenditure for long-term CCS in France compared
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20 to the general population and to investigate the associated factors.
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24 **Methods:** We included 5353 5-year solid CCS diagnosed before the age of 21 years before
25
26 2000 from the French CCS cohort and obtained a random reference sample from the general
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28 population for each CCS, matched on age, gender and region of residence. We used the French
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30 national health data system to estimate annual healthcare expenditure between 2011 and 2018
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32 for CCS and the reference sample and computed the excess as the net difference between CCS
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34 expenditure and the median expenditure of the reference sample. We used repeated-measures
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36 generalized linear models to estimate associations between excess healthcare expenditure and
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38 CCS characteristics.
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44 **Results:** Annual mean (95% CI) excess healthcare expenditure was €3,920 (3539 ; 4301),
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46 mainly for hospitalization (39.6%) and pharmacy expenses (17%). Higher excess was
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48 significantly associated with having been treated before the 1990s and having survived a central
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50 nervous system tumor, whereas lower excess was associated with CCS who had not received
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52 treatment with radiotherapy.
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22 **Conclusions:** Of the variables that influence excess healthcare expenditure, a lever for action
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3 23 is the type of treatment administered. Future research should focus on addressing the long-term
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5 24 cost-effectiveness of new approaches, especially those related to radiotherapy.
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25 **Introduction**

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26 Childhood cancer survival has improved substantially in recent decades due to advances in
27 treatment. More than 80% of pediatric cancer patients reach 5-year survival in most high-
28 income countries [1]. This improvement in survival means that 1 in 1000 individuals in the
29 general population is a childhood cancer survivor (CCS) [2]. In Europe, it is estimated that there
30 are 300,000–500,000 CCS patients [2] and it is expected that this population will continue to
31 grow, given that the incidence of childhood cancer has increased slightly in recent decades [3].
32 However, CCS carry an important risk of suffering late effects induced by disease and cancer
33 treatment that can affect, to varying degrees, almost any organ or body system [4]. Somatic and
34 mental late effects include second neoplasms, cardiovascular disease, infertility, growth
35 problems, depression, learning deficits and many more [5]. It is estimated that two-thirds of
36 CCS will experience at least one treatment-related adverse event and by the age of 50 years a
37 survivor will have experienced, on average, 17 chronic health conditions of any grade, 4–7 of
38 which would be classified as severe disabling, life-threatening or fatal [6].
39 In addition, the economic and social consequences in adulthood are potentially significant,
40 varying from country to country. CCS may be at risk of lower educational attainment and this
41 is sustained across different countries [7]. A Swiss study showed that survivors of various
42 diagnostic groups had lower incomes than siblings (after adjusting for sociodemographic
43 characteristics, education and working hours) [8]. Based on the National Health Interview
44 Survey (USA), Guy et al. highlighted that surviving cancer in childhood was associated with
45 productivity loss from health-related unemployment, missed workdays and missed household
46 productivity [9]. Finally, a meta-analysis of 27 studies worldwide found that CCS were at
47 considerable risk of unemployment in adulthood [10]. All these consequences increase the use

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of social security benefits, such as those for unemployment, sickness, disability or permanent
invalidity [11, 12].

The higher burden of morbidity and adverse socioeconomic outcomes for long-term CCS is
likely associated with higher costs to the healthcare system [13]. A few studies in the USA have
looked at the financial burden for healthcare among CCS and reported that they were more
likely to have out-of-pocket medical costs of $\geq 10\%$ of annual income [14], as well as having to
borrow money, skip medical care or not fill a prescription because of costs compared to their
siblings [15, 16]. However, studies on the long-term economic effect of CCS in the publicly
funded healthcare system are lacking.

In France, the healthcare system is mainly publicly funded and provides universal health
coverage to its citizens that covers most medical expenses [17], especially for long-term
conditions such as cancer, regardless of medical history or personal income. In a previous work,
we found that the annual mean of healthcare expenditure for adult CCS was more than €4,200
[18]. However, we were not able to compare their expenditure with that of the general
population or estimate the cancer-attributable (excess) cost of care in the long term. This
information is useful to understand the long-term consequences of survivorship, to improve
follow-up programs of CCS, to evaluate the long-term cost-effectiveness of cancer treatment
and to plan budgets.

The objectives of this study were to estimate excess healthcare expenditure for long-term CCS
in France compared to the general population, matched on gender, age and region of residence,
and to investigate the associated factors leading to the excess.

69 **Methods**

70 **Study population**

71 The French Childhood Cancer Survivor Study (FCCSS) is a retrospectively set up cohort of
72 7670 5-year CCS diagnosed with solid cancer or lymphoma (all malignancies except leukemia)
73 before the age of 21 years between 1945 and 2000 in five cancer centers in France that is
74 prospectively followed. Detailed information on the methods for data collection and patients
75 has been described previously in several articles [19, 20]. For this study, we selected all CCS
76 from the FCCSS who were alive in January 2011, living in metropolitan France and were linked
77 to the National Health Data System (French acronym: SNDS).

78 **Data sources**

79 The SNDS is the healthcare claims dataset in France containing all the reimbursements made
80 by the National Health Insurance Fund (French acronym: CNAM), which covers around 99%
81 of the population [21]. The SNDS contains exhaustive individual data since 1 January 2006 and
82 mainly comprises the outpatient healthcare consumption database (French acronym: DCIR) and
83 the private and public hospital data collected in the national hospital discharge database (French
84 acronym: PMSI), which is divided into four categories corresponding to hospitalizations in
85 conventional hospital units (short-stays), homecare units, rehabilitation and psychiatry
86 institutions.

87 The SNDS includes some demographic characteristics of the patients (age, gender, place of
88 residence), information on eligibility for the government's supplementary healthcare assistance
89 programs and diagnosis of long-term conditions (French acronym: ALD) that are fully
90 reimbursed, together with information on dates, nature and reimbursement of outpatient visits,
91 dispensed medication, allied health professional visits, laboratory tests, medical devices,
92 medical transport, paid sick leave, hospital admissions that are reimbursed using the diagnosis-

93 related groups and information on patients' death, including the cause. The SNDS is one of the
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2 94 world's largest continuous homogeneous claims database [22].
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6 95 Linkage and access to SNDS data of the FCCSS cohort was provided by the CNAM via
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8 96 probabilistic matching using the survivor's family and first names, gender, date and place of
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11 97 birth and unique arbitrary number. Of the 7670 5-year CCS patients from the FCCSS, 6818
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13 98 were still alive at 1 January 2006 (SNDS start date). Therefore, the percentage of CCS patients
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15 99 linked to SNDS data after this procedure was 81.9% ($n = 5583/6818$), with data availability
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18 100 from 2006 to 2018.
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20 101 **Ethics approval**

22 102 The study was approved by the French Data Protection Authority (French acronym: CNIL)
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25 103 (Authorization no. 902287) and by the ethics committee of the French National Institute of
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28 104 Health and Medical Research (French acronym: INSERM). Individual patient informed consent
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31 105 was not required for this study because we obtained a specific act in law from the French
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33 106 "Conseil d'Etat", the highest court in France (Order 2014-96 of 3 February 2014), which
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35 107 approved cession of the SNDS data for all patients included in the FCCSS.
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37 108 **Comparative sample**

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40 109 We obtained a reference sample for the FCCSS from the General Sample of Beneficiaries
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42 110 (French acronym: EGB). The EGB is a 1/97th anonymized random permanent sample of the
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45 111 population included in the SNDS, which has been shown as representative of the French general
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47 112 population [22]. All the healthcare claims and reimbursements included in the SNDS are
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50 113 available in the EGB, except for hospitalizations records from rehabilitation and psychiatry
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52 114 institutions, which are not yet supplied. We selected the reference sample, matching by gender,
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55 115 year of birth and region (French administrative area) of residence, and randomly assigned
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57 116 controls to each FCCSS survivor patient with the same characteristics.
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117 **Estimating excess healthcare expenditure**

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2 118 We conducted this analysis from the perspective of the public payer included in the mandatory
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5 119 reimbursement scheme, the CNAM. Therefore, reimbursements from private health insurance,
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7 120 special schemes or the final out-of-pocket costs were not included. Based on the
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9 121 reimbursement's information, we summed direct healthcare expenditure (including disability
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11 122 benefits and sick leave) for every calendar year for each survivor and controls between January
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13 123 2011 and December 2018, or date of death, whichever came first. We then estimated the annual
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15 124 excess health expenditure as the difference between the survivor's expenditure and the median
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17 125 expenditure of their controls. We used the median instead of the mean because the data on health
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19 126 expenditure were positively skewed, especially in the controls.
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25 127 Our primary outcome variable was the total excess of direct healthcare expenditure for every
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27 128 calendar year for each CCS. We also stratified the excess by items and these were classified,
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29 129 for every year, into 14 categories: general practitioner visits, other specialist visits,
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31 130 physiotherapy, nursing visits, other health professional's visits, pharmacy, medical device,
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33 131 laboratory test, technical medical procedures, transport, hospitalizations, disability benefits,
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35 132 sick leave and others. All expenditures were expressed in real terms using the consumer price
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37 133 index with a 2015 base year provided by the National Institute of Statistics and Economic
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39 134 Studies (French acronym: INSEE).
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45 135 **Statistical analysis**

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47 136 First the CCS characteristics were described, along with estimation of the annual mean excess
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49 137 expenditure over the 2011–2018 period. Categorical variables were expressed as number and
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51 138 percentage and continuous variables as the mean \pm SD and 95% confidence interval (CI). Then,
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53 139 we described excess healthcare expenditure by item and according to type of primary cancer.
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140 We used linear mixed models to assess the association between excess healthcare expenditure
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2 141 and the survivor's characteristics. As the excess expenditure for each survivor was computed
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5 142 with different numbers of controls, the models were weighted according to the number of
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7 143 controls used for each survivor in each year. Models were adjusted for gender, age in 2011,
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10 144 French deprivation index (an area-based multidimensional index that measures socioeconomic
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12 145 differences) [23], year of cancer diagnosis, age at cancer diagnosis, type of primary cancer and
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14 146 cancer treatment(s) received (i.e. no radiotherapy or chemotherapy , chemotherapy,
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17 147 radiotherapy or both). Finally, we performed several subanalyses, estimating models for each
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19 148 expenditure item and each type of primary cancer. Statistical significance was determined using
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22 149 $p < 0.05$. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).
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24 150 **Results**

27 151 **CCS characteristics**

29 152 A total of 5,353 FCCSS survivor patients and 382,757 controls were included in the study. The
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32 153 average number of controls per survivor patient was 71.5 (SD: 73.6). Approximately 46% were
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34 154 women and 51% were > 30 years old in 2011 (start of follow-up). The most common primary
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37 155 cancer (in childhood) was lymphoma (17.2%), followed by kidney tumor (15.1%),
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39 156 neuroblastoma (13.8%) and central nervous system (CNS) tumor (12.7%). Most survivor
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42 157 patients were treated after 1980s and 37.2% received both radiotherapy and chemotherapy
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44 158 (Table 1). The mean time between childhood cancer treatment and 2011 was 24.7 years (IQR:
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47 159 17–31). By the end of the follow-up (December 2018), 254 (4.7%) of the CSS had died.
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50 160 *Excess healthcare expenditure*

52 161 The annual mean excess healthcare expenditure confounded for all CCS was €3,920. As
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55 162 expected, this variable was positive skewed due to a few very high values among survivors
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57 163 (Supplementary Figure 1). Excess was higher in women than in men (€4,058 vs. €3,783), in
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164 older patients (€5,948 in patients over 40 years old in 2011), in those treated before the 1970s
165 (€5,836) and in CNS tumor survivor patients (€6,712) (Table 1). Patients who were treated with
166 chemotherapy alone had a 2.5 times lower excess than those who received only radiotherapy
167 (€2,279 vs. €5,917) but higher than patients not treated by radiotherapy or chemotherapy
168 (€1,830). Those who died during follow-up had a mean annual excess more than five times
169 higher than those who did not (€18,369 vs. €3,261).

170 Details of healthcare expenditure by healthcare items are reported in Table 2. Over the entire
171 cohort, the highest expenditure was for hospitalization (€1,552), which represented 39.6% of
172 the total excess, followed by pharmacy (€668) with 17%. These two healthcare resources were
173 used by > 70% of survivors. Other important items were medical devices (€324), sick leave
174 (€377) and disability benefits (€387). It should be noted that healthcare expenditure for
175 transportation was higher than for all types of medical visits.

176 **Excess healthcare expenditure by type of primary cancer**

177 Figure 1 shows the distribution of excess healthcare expenditure by item according to the type
178 of primary cancer. Although hospitalization was the main driver for the excess in most cancer
179 groups, pharmacy was the most important item among thyroid tumor survivors (€1,346),
180 representing 35.7% of their total excess (Supplementary Table 1). Pharmacy was also a major
181 item for kidney tumor survivors (€1,408) and gonadal tumor survivors (€1,037), representing
182 29.6% and 26.4% of the total excess, respectively. Sick leave was a major expenditure item in
183 the excess among neuroblastoma, lymphoma, soft tissue sarcoma, bone sarcoma and thyroid
184 tumor survivors, representing > 11% of the total excess, while medical devices was an important
185 expenditure item for bone sarcoma survivors (€986), with 22% of their total excess.

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187 **Figure 1. Distribution of excess health care expenditure by items by according to the type**
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2 188 **of primary cancer***. * Type of primary cancer: Lymphoma, kidney tumor, neuroblastoma,
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4 189 central nervous system tumor (CNS), soft tissue sarcoma, bone sarcoma, retinoblastoma,
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7 190 gonadal tumor, other solid cancer and thyroid tumor.
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11 191 Regarding CNS tumor survivors, almost 55% of the total excess was due to hospitalizations
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13 192 (€3,732). In addition, these patients had, on average, higher excess on physiotherapy, nursing
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15 193 and other health professional visits and transportation than the other primary cancer types.
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18 194 However, excess on sick leave among these patients was among the lowest of the other cancer
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20 195 types, with an annual mean excess of €186 (Supplementary Table 1).
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23 196 **Factors associated with excess healthcare expenditure**
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25 197 Table 3 presents estimations of the linear mixed model after adjusting for survivor
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27
28 198 characteristics. The increase in excess healthcare expenditure with each passing year among
29
30 199 survivors was €231 ($p \leq 0.01$). Annual excess healthcare expenditure was higher among
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33 200 survivors treated in the 1980s (€2306; $p \leq 0.01$), 1970s (€3848; $p \leq 0.01$) and before the 1970s
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35 201 (€4389; $p \leq 0.05$) compared to survivors treated after the 1990s (Table 3). CNS tumor survivors
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38 202 also had higher expenditure compared to survivors of other types of primary cancers.
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42 203 Total excess was not significantly higher among female compared with male survivors (€231;
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44 204 $p = 0.48$) (Table 3), except in lymphoma and soft tissue sarcoma survivors (Supplementary
45
46 205 Table 2). However, in the subanalysis of each item of the healthcare expenditure, being a woman
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48
49 206 was associated with a higher excess for specialist, physiotherapy and nursing visits, laboratory
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51 207 tests, technical medical procedures and sick leave expenditure (Supplementary Table 3).
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55 208 CNS tumor survivors had significantly higher excess expenditure for general practitioner,
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57 209 physiotherapy and nursing and other health professional visits, transport and hospitalization
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210 compared to survivors of other types of primary cancers (Supplementary Table 3). However,
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2 211 sick leave expenditure in CNS survivors was significantly lower. Bone sarcoma survivors had
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4 212 significantly higher excess expenditure for medical device and disability benefits, whereas
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7 213 thyroid tumor and kidney tumor survivors had significantly higher excess expenditure for
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9 214 specialist visits and laboratory tests compared to CNS survivors (Supplementary Table 3).
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13 215 Concerning treatment, survivors not treated by radiotherapy or chemotherapy (−€1910; $p \leq$
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15 216 0.01) and survivors treated by chemotherapy alone (−€1464; $p < 0.05$) had a significantly lower
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18 217 excess healthcare expenditure compared to those treated with only radiotherapy (Table 3).
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20 218 Survivors treated with radiotherapy and chemotherapy had higher excess, although not
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23 219 significant, than those treated with only radiotherapy, but it was significant in general
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25 220 practitioner, technical medical procedures and sick leave (Supplementary Table 3). Moreover,
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28 221 survivors treated with chemotherapy alone were associated with a lower excess in expenditure
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30 222 for general practitioner, specialist and physiotherapy visits, medical devices, laboratory tests,
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33 223 hospitalizations and disability benefits (Supplementary Table 3).
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35 224 **Discussion**

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39 225 In this study, we were able to compare healthcare expenditure in CCS with the general
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41 226 population and detail the cost attributable to childhood cancer in the long term. We found that
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43
44 227 the average annual excess healthcare expenditure for CCS was €3,920. Of note, this excess was
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46 228 mainly composed of hospitalization and pharmacy expenses. Higher excess was associated with
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49 229 CCS treated before the 1990s and with CNS tumor survivors, while lower excess was associated
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51 230 with CCS who had not received treatment with radiotherapy. This work fills an important gap
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54 231 in the literature regarding the economic burden of childhood cancer survivorship in a publicly
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56 232 funded healthcare system.
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233 Given the risk of developing late effects, CCS require significantly more healthcare resources
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2 234 over their lifetime than the general population [13]. Several studies have shown that CCS had
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4 235 a higher risk of hospitalizations [24–29], contacting their primary care physician [30, 31] and
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6 236 being economically dependent [32] and unemployed [10], particularly CNS tumor survivors
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8 237 [33], than the general population in high income countries. Consequently, CCS are more likely
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10 238 to experience financial hardship (e.g. higher out-of-pocket payments) as a result of medical
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12 239 costs more specifically in non-publicly-funded healthcare systems [14, 16]. While the cost
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14 240 attributable to adolescent and young adult cancer in the long term (age 15–35 years at their first
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16 241 cancer diagnosis) has been estimated at \$3,170 [34] in the USA, to our knowledge this is the
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18 242 first study that estimates the cost attributable to childhood cancer in the long term.
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25 243 Although we found in a previous study that female survivors had higher annual healthcare
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27 244 expenditure than male survivors [18], our current findings suggest that the excess was not
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29 245 significantly higher. However, this overall result masks the fact that being a female survivor
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31 246 was associated with a higher excess for physiotherapy and nursing visits, technical medical
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33 247 procedures, disability benefits and sick leave expenditure, extending the results of Streefkerk
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35 248 et al., which showed that female gender was a determinant for more primary care physician-
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37 249 based healthcare use [30].
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43 250 We also showed that CNS tumor survivors had the highest excess. This result is consistent with
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45 251 the results of several studies that have shown that CNS tumor survivors have a higher risk of
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47 252 having poor health and socioeconomic conditions, including having at least one disability
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49 253 indication condition [35], lower educational attainment [7] and higher risk of unemployment
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51 254 [10] and social security benefit uptake [11] than the cancer-free population.
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255 Regarding the influence of the period during which the patient was treated for cancer, we
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2 256 observed that having been treated before 1980 (during the periods <1970 and 1970-1979)
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4 257 compared with the > 1990 period was pejorative for the excess expenditure (about €4,300 and
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6 258 3,800, respectively). It was also the case, but to a lesser extent, for those treated between 1980
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8 259 and 1989 (about €2,300). This may reflect the therapeutic progress that has been made.
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11 260 Treatment of solid tumors has moved from a purely surgical approach to the addition of
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13 261 radiation therapy and then to multi-modality treatment based primarily on chemotherapy after
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15 262 the 1980s [36, 37].
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20 263 However, all other things being equal, the type of treatment received was influent on the excess
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22 264 expenditure. CCS treated with radiotherapy had an excess of more than €1,400 compared to
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24 265 those treated with chemotherapy and a higher excess compared to those not treated with either
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26 266 (€1,900). These findings are consistent with studies from The Netherlands in which survivors
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28 267 treated with radiotherapy had a particularly increased hospitalization rate for neoplasms,
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30 268 endocrine diseases and circulatory system diseases [26, 38] and were nearly 1.5 times more
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32 269 likely to contact their primary care physician compared with CCS treated with chemotherapy
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34 270 only [30].
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41 271 Efforts to reduce cumulative doses (e.g. protection of healthy tissues during radiotherapy or
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43 272 decreased chemotherapy doses) and improve monitoring are needed to reduce long-term
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45 273 toxicity and therefore costs. Newer types of radiation therapy, such as proton therapy, have been
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47 274 introduced to treat cancer with increasing promise to reduce both short-term and long-term
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49 275 toxicities [39, 40]. In France, proton therapy is shown to be a priority for children and young
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51 276 adults in all three of its centers [41]. Although establishing and operating proton therapy centers
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53 277 is very expensive, the opportunity cost of expanding the care of such centers should be
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55 278 considered if the reduction in late effects and future healthcare cost is greater than the cost of
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1 279 the centers in the long term. Future research should focus on the cost-effectiveness of proton
2 280 therapy in the long term in order to address this question.
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5 281 There were some limitations to this study. First, we considered only hospitalization in
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8 282 conventional hospital units because information regarding rehabilitation and psychiatric
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10 283 institution hospitalization was not available in the EGB sample. Thus, we have underestimated
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12 284 hospitalization costs, especially those related to mental health, where survivors of a CNS tumor
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14 285 are likely to be treated, for example. Nevertheless, the conventional hospital units treat more
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16 286 than 90% of all patients hospitalized in France [42]. Second, we could not address the
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18 287 association between excess healthcare expenditure and specific modalities of therapy (e.g.
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20 288 chemotherapy regimens and/or radiation doses) because this requires special considerations and
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22 289 will be investigate in separated publications. Lastly, the FCCSS included only patients from
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24 290 five non-profit private cancer treatment centers in France, which are not representative of all
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26 291 French childhood cancer treatment centers. Nevertheless, in a previous study we found that this
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28 292 did not impact the long-term survivor's medical expenditure [18].
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35 293 **Conclusions**
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37 294 Our results showed that long-term CCS have a high healthcare expenditure compared to the
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39 295 general population of the same age and gender, resulting in a important excess, especially
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41 296 among CNS tumor survivors and those who were irradiated. As the number of CCS is expected
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43 297 to increase, health authorities could use the findings of this article to improve the organization
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45 298 of care, in terms of medical follow-up and prevention of complications, in order to better
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47 299 anticipate the long-term effects and their associated medical expenses. Future research should
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49 300 focus on addressing the long-term cost-effectiveness of new approaches to childhood cancer
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51 301 treatment, especially those related to radiotherapy.
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1 Supplementary Information:

- 2 1. Supplementary Figure 1. Histogram of annual excess healthcare expenditure.
- 3 2. Supplementary Table 1. Annual mean of excess healthcare expenditures per patient in euros (%
4 of the total excess) by item according to the type of primary cancer.
- 5 3. Supplementary Table 2. Predictors of annual excess healthcare expenditures by each type of
6 cancer.
- 7 4. Supplementary Table 3. Predictors of annual excess healthcare expenditures by items.

Figure

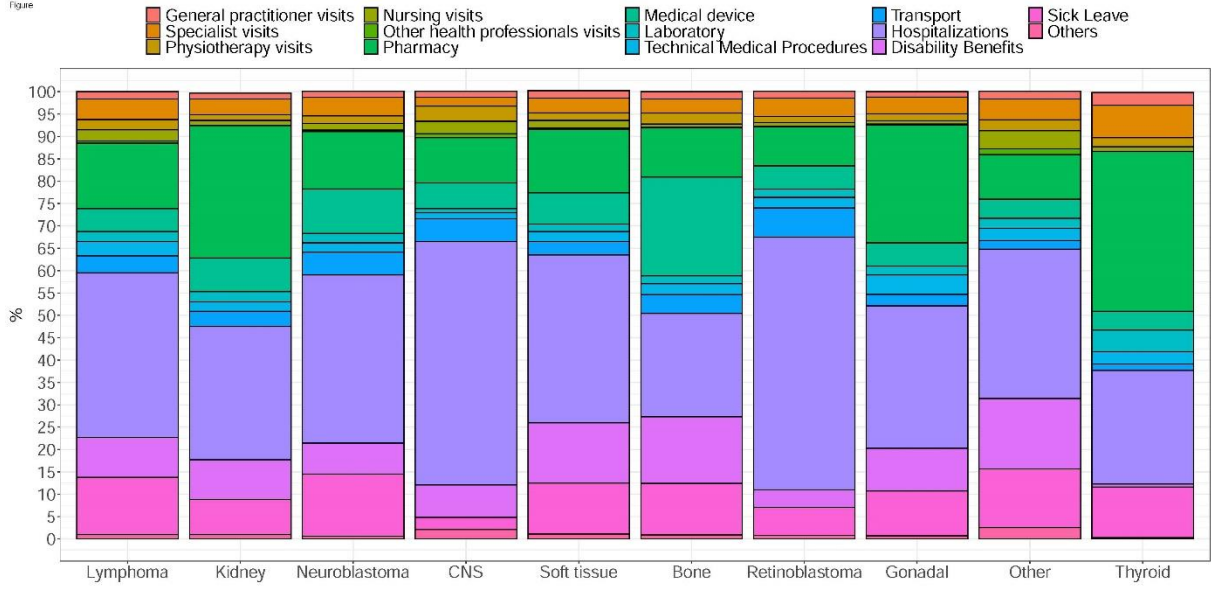


Table 1

	Number of patients (%)	Annual mean excess of healthcare expenditures per patient in Euros (95 % confidence interval)
All	5353	3920 (3539 ; 4301)
Gender		
Male	2919 (54.5)	3783 (3164 ; 4403)
Female	2434 (45.5)	4058 (3617 ; 4500)
Age at January 2011 (Start date)		
<20	818 (15.3)	908 (670 ; 1145)
20-30	1814 (33.9)	3042 (2552 ; 3532)
31-40	1699 (31.7)	3938 (2927 ; 4950)
>=41	1022 (19.1)	5948 (5200 ; 6695)
French geographical deprivation index 2009		
1 Quintile	2192 (40.9)	4120 (3319 ; 4921)
2 Quintile	970 (18.1)	3757 (3078 ; 4436)
3 Quintile	764 (14.3)	3757 (2972 ; 4541)
4 Quintile	712 (13.3)	3484 (2737 ; 4230)
5 Quintile	715 (13.4)	4209 (3328 ; 5089)
Status at December 2018 (Ending date)		
Alive	5099 (95.3)	3261 (2908 ; 3614)
Dead	254 (4.7)	18369 (15051 ; 21686)
Year of cancer diagnosis		
<1970	336 (6.3)	5836 (4662 ; 7010)
1970-1979	951 (17.8)	5798 (4540 ; 7056)
1980-1989	1780 (33.3)	4109 (3522 ; 4696)
>=1990	2286 (42.7)	1810 (1554 ; 2067)
Age at cancer diagnosis		
0-1	1277 (23.9)	2571 (2070 ; 3071)
2-4	1253 (23.4)	4495 (3280 ; 5709)
5-9	1183 (22.1)	3886 (3366 ; 4405)
10-14	1084 (20.3)	4918 (4080 ; 5757)
≥15	556 (10.4)	3892 (2969 ; 4815)
First primary cancer type		
Lymphoma	920 (17.2)	3962 (3240 ; 4683)
Kidney tumors	810 (15.1)	4594 (2979 ; 6209)
Neuroblastoma	738 (13.8)	2498 (1842 ; 3155)
Central nervous system tumor	679 (12.7)	6712 (5267 ; 8158)
Soft tissue sarcomas	583 (10.9)	4030 (3122 ; 4938)
Bone sarcomas	471 (8.8)	4283 (3471 ; 5094)
Retinoblastoma	467 (8.7)	1798 (1242 ; 2354)
Gonadal tumor	331 (6.2)	3750 (2410 ; 5089)
Other solid cancer	307 (5.7)	2609 (1519 ; 3698)
Thyroid tumor	47 (0.9)	3511 (1268 ; 5754)
Treatment Received		
No radiotherapy or chemotherapy	717 (13.4)	1830 (1256 ; 2404)
Radiotherapy	672 (12.6)	5917 (4807 ; 7028)
Chemotherapy	1974 (36.9)	2279 (1912 ; 2645)
Radiotherapy and chemotherapy	1990 (37.2)	5143 (4359 ; 5928)

* : Ecological Index measuring the deprivation, and based on the median household income, the percentage of high school graduates in the population aged 15 years and older, the percentage of blue-collar workers in the active population, and the unemployment rate. The fifth quintile represents the most disadvantaged area.

Table 2

Table 2. Excess health care expenditure by items

	Number of patients (%)	Number of claims	Total excess of health care expenditure over the follow-up period in million euros (%)	Annual mean excess healthcare expenditure per - patient in euros (95 % CI) *
General practitioner visits	5082 (94.9)	170039	2.2 (1.5)	60 (56 ; 64)
Specialist visits	5030 (94.0)	208804	5.3 (3.6)	142 (133 ; 152)
Physiotherapy visits	2428 (45.4)	166592	3.2 (2.2)	87 (74 ; 99)
Nursing visits	3797 (70.9)	154089	2.8 (1.9)	74 (54 ; 95)
Other health professional visits †	811 (15.2)	19879	0.6 (0.4)	17 (11 ; 23)
Pharmacy	5107 (95.4)	699570	24.8 (17)	668 (450 ; 886)
Medical devices	4447 (83.1)	72039	12.1 (8.3)	324 (272 ; 377)
Laboratory tests	4683 (87.5)	130378	2.9 (2)	77 (71 ; 83)
Technical Medical Procedures ‡	4790 (89.5)	65872	3.6 (2.5)	96 (85 ; 108)
Transport	1976 (36.9)	34006	6.0 (4.1)	162 (140 ; 185)
Hospitalizations	3773 (70.5)	42670	57.8 (39.6)	1552 (1355 ; 1749)
Disability Benefits §	384 (7.2)	17854	14.4 (9.9)	387 (305 ; 470)
Sick Leave	2731 (51)	49507	14.0 (9.6)	377 (337 ; 417)
Others	709 (13.2)	5076	1.9 (1.3)	49 (28 ; 70)
Total	5353	1836375	145.90 €	3920 (3539 ; 4301)

* Annual mean expenditure per-patient in € were calculated for the entire population (n=5,353). † Other health professional visits included expenditures related to visits to podiatrists, optometrists, speech therapists, and others. ‡ Technical medical procedures included expenditures mainly related to medical imaging techniques. § Disability benefits included all welfare payments or pensions made by the French Government to assist people with disabilities.

Table 3

Table 3. Multivariate analysis: Predictors of annual excess healthcare expenditures

	Beta	Pr > Z
Intercept	4217.94	< 0.01 ***
Time	231.63	< 0.01 ***
Age at January 2011	-13.01	0.8
Female (Ref = Male)	231.95	0.5
French geographical deprivation index (Ref = 1 Quintile)		
2 Quintile	-294.42	0.54
3 Quintile	-629.98	0.22
4 Quintile	-839.07	0.12
5 Quintile	-312.09	0.55
Age at first cancer	88.46	0.17
Year of Diagnosis (Ref = >1990)		
<1970	4389.18	0.01 ***
1970-1979	3848.18	< 0.01 ***
1980-1989	2306.94	< 0.01 ***
First primary cancer type (Ref = Central nervous system tumor)		
Lymphoma	-3166.94	< 0.01 ***
Kidney tumors	-2274.48	< 0.01 ***
Neuroblastoma	-3237.60	< 0.01 ***
Soft tissue sarcomas	-2555.28	< 0.01 ***
Bone sarcomas	-2681.82	< 0.01 ***
Retinoblastoma	-2936.16	< 0.01 ***
Gonadal tumore	-2930.01	< 0.01 ***
Other solid cancer	-3454.80	< 0.01 ***
Thyroid tumor	-4325.84	0.01 ***
Treatment (Ref = Radiotherapy)		
No radiotherapy or chemotherapy	-1910.54	0.01 ***
Chemotherapy	-1464.65	0.02 ***
Radiotherapy and chemotherapy	513.71	0.36

*** p<0.05

Title : Economic burden of the long-term effects of treatments for childhood cancer.

Keywords : Health care expenditures, hospitalisations, childhood cancer, survivorship, late effects, France.

Abstract : Childhood cancer survivors (CCS) may require lifelong medical care due to the late effects of cancer treatments. However, little is known about their healthcare utilization and expenditures at long-term, especially in publicly funded health care system. This thesis aimed to estimate and analyse the long-term health care expenditures and hospitalisation rates among CCS in France and to study their associated factors.

The research presented in this thesis was based on data from the French Childhood Cancer Survivors Study (FCCSS), which is a retrospective cohort of 7,670 5-year CCS diagnosed before the age of 21 years between 1946 and 2000 in France. The FCCSS is linked to the National Health Data System (SNDS), which contains comprehensive data on billing and reimbursement of the beneficiaries' health care expenditures since 2006.

We found that the annual mean healthcare expenditures among CCS was € 4,255 (SD: 18,790). Expenditures on hospitalization and pharmacy represented ~60% of total expenditures. Our results also showed that female gender and being survivor of a central nervous system (CNS) tumour were associated with increased health care expenditures.

We then estimated hospitalisation rates among CCS and detailed the hospitalisation-related clinical diagnoses compared with those of the French general population with the same gender, age and region of residence. We found that survivors were hospitalised more than twice as often as the matched reference population and they had more than three times as many in-patient bed-days. Our results showed that the highest risk for hospitalisation in CCS was related to neoplasm, followed by endocrine diseases, blood diseases, and diseases of the circulatory system. Finally, we compared the health care expenditures of the FCCSS with that of the general French population mentioned above and found that the annual mean excess healthcare expenditures for CCS compared with the median of the reference population was € 3,920 (95% CI: 3539 - 4301). A higher excess was significantly associated with having been treated before the 1990s and having survived a CNS tumour, whereas a lower excess was associated with not receiving treatment with radiotherapy.

In conclusion, this thesis showed that CCS are at higher risk of health care use and expenditure, leading to considerable excess compared with the median health care expenditure of the general population of the same sex and age. This high expenditure was related to high hospitalisation rates among CCS. Older survivors, CNS tumours survivors, and those treated with radiotherapy had a higher risk of health service use and expenditure. These results led us to recommend that special attention be paid to this population, especially in terms of follow-up and prevention of complications, and to support the development of effective innovative treatments.

Titre : Poids économique des effets à long terme des traitements des cancers de l'enfant.

Mots clés : Dépenses de santé, hospitalisations, cancer de l'enfant, survie, effets tardifs, France.

Résumé : Les survivants du cancer de l'enfant (CCS) peuvent avoir besoin de soins médicaux à vie en raison des effets tardifs des traitements anticancéreux. Cependant, on sait peu de choses sur leur utilisation des soins de santé et leurs dépenses à long terme, en particulier dans les systèmes de soins de santé financés par l'État. Ce projet de thèse avait pour objectif d'estimer et d'analyser les dépenses de santé et les taux d'hospitalisation à long terme des personnes atteintes d'un cancer dans l'enfance en France et d'étudier les facteurs associés.

La recherche présentée dans cette thèse est basée sur les données de la French Childhood Cancer Survivors Study (FCCSS) qui est une cohorte rétrospective de 7,670 CCS à cinq ans diagnostiqués avant l'âge de 21 ans entre 1946 et 2000 en France. L'étude FCCSS est liée aux données du Système National des Données de Santé (SNDS), qui contient des données complètes sur la facturation et le remboursement des dépenses de santé des bénéficiaires depuis 2006.

Nous avons constaté que le montant moyen annuel des dépenses de santé parmi les CCS était de 4 255 € (ét: 18 790). Les dépenses liées aux hospitalisations et à la pharmacie représentaient environ 60 % des dépenses totales. Nos résultats ont également montré que le sexe féminin et être survivant de tumeur du système nerveux central (SNC) étaient associés à des dépenses de santé plus élevées.

Lorsque nous avons estimé les taux d'hospitalisation parmi les CCS et détaillé les diagnostics cliniques liés à l'hospitalisation par rapport à ceux de la population générale française avec le même sexe, âge et région de résidence, nous avons constaté que les survivants étaient hospitalisés plus de deux fois plus souvent que la population de référence appariée et qu'ils avaient plus de trois fois plus de jours d'hospitalisation. Nos résultats ont montré que le risque plus élevé d'hospitalisation des CCS concernait les hospitalisations liées à des néoplasmes, suivies par les maladies endocriniennes, les maladies du sang et les maladies de l'appareil circulatoire. Enfin, nous avons comparé les dépenses de santé de la FCCSS à celles de la population française générale mentionnée ci-dessus et nous avons constaté que l'excédent annuel moyen des dépenses de santé pour les CCS par rapport à la médiane de la population de référence était de 3 920 € (IC à 95 % : 3 539 - 430). Un excès plus élevé était significativement associé au fait d'avoir été traité avant les années 1990 et d'avoir survécu à une tumeur du SNC, alors qu'un excès plus faible était associé au fait de n'avoir pas reçu de traitement par radiothérapie.

En conclusion, cette thèse a démontré que les CCS présentent un risque plus élevé d'utilisation de soins et de dépenses de santé, conduisant à un excès considérable par rapport à la médiane des dépenses de santé de la population générale du même sexe et du même âge. Ces dépenses élevées étaient liées à des taux d'hospitalisation élevés parmi les CCS. Les survivants plus âgés, ceux ayant eu une tumeur du SNC et les patients traités par radiothérapie présentaient un risque plus élevé d'utilisation des services de santé et de dépenses. Ces résultats nous amènent à recommander qu'une attention particulière soit accordée à cette population, notamment en termes de suivi et de prévention des complications, et de soutenir le développement de traitements innovants et efficaces.