Understanding the health effects of low doses of ionizing radiation from medical procedures: challenges for epidemiology

Elisa Pasqual

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Thesis supervisors

Dr. Elisabeth Cardis

Dr. Isabelle Thierry-Chef

ISGlobal Barcelona Institute for Global Health

upf. Universitat Pompeu Fabra Barcelona

Alla mia famiglia:

Mia mamma Patrizia, mio papá Daniele e mia sorella Laura

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“Occorre una grande fantasia, una forte immaginazione per essere un grande scienziato, per immaginare cose che non esistono ancora, per immaginare un mondo migliore di quello in cui viviamo e mettersi a lavorare per costruirlo"
(G.Rodari)

I feel particularly lucky to have dedicated almost four years of my life only to the Science. I am therefore deeply grateful to Elisabeth, my supervisor, who gave me this opportunity, trusted me since the very beginning, and supported me during this journey. I also want to thank my co-supervisor, Isabelle, for motivating me and for all the conversations we had in the last year.

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Along this PhD journey, I had the opportunity to reflect on what it means to do Science. These reflections are shared below here in a children's story I wrote.

An hour as a Scientist

A special science lesson was going to happen on that 11th of February 2019: a real scientist was coming to class!
Jeremy and Matilda were happy because that meant no homework for that day, Charlie was bored as usual ("science is boring, such as numbers", he went around saying) and Olivia did not believe that real scientists existed, because "there is nothing to discover anymore". Amelia was excited because she hoped they might use the microscope, the machine that she saw on television! George, the one that always got top grades in science, prepared a list of 100 questions for the scientist, because "scientists know everything". No one, not even the Teacher, could have imagined the incredible things that were going to happen to them!
A young lady with a big smile walked into the classroom: she was the Scientist! The Teacher thanked her for coming and told the students to listen carefully to her, because they would be tested on it later.
The Scientist started saying "Doing Science is a journey in search of an answer that doesn't exist yet. Are you ready to travel with me and see what I do everyday?" Charlie immediately shouted "YES!": travelling didn't sound at all like a boring science lesson!
Suddenly, the walls of the classroom disappeared and they found themselves sitting on the grass. They looked around and noticed that behind them there was a park, like the one where they used to go with their parents on Sundays. There were several large paths running throughout the park and a lot of people were walking around. In front of them, however, was a forest: a black and impenetrable forest. It was so thick that inside it was deep night, though the sun was shining.
The scientist explained "All of this is our world. Behind us, it's safe to walk because that's the world as we know it, as we have learnt it. People before us had worked a lot to build all those paths you see behind us. All people can walk over them and enjoy them, like on a Sunday in the park". She took a long breath and looked at the impenetrable forest "Over there you can find the answers to those questions that are still unanswered, and that's the place

where scientists go in search of them. If you want to know what's like working as a scientist, follow me there!". Charlie, Jeremy and Matilda were excited: finally some real fun! George was a bit disappointed of going into such a dark and dirty place. Olivia was impressed by the sheer size of the black forest: it looked like it was never ending! All of them, including the Teacher, felt a bit afraid; however, they followed the Scientist, because with her they felt safe.

There were several footpaths leading into the forest, they took one. While walking, they saw many smaller paths breaking off from the one they were on, and sometimes the Scientist turned onto one of them. She explained: "The work of a Scientist is to build footpaths. The one we are walking on now is the result of the work of many great scientists! To build something like this, first you need someone to open a way into the forest". There were some people along the footpath but, as they moved deeper into the forest, the people became less and less.

At one point the Scientist stopped and stepped out of the footpath, following a almost unnoticeable track: it was just about possible to see the trampled grass, probably the trace of the passage of no more than two or three people. Pointing to the track, the Scientist said: "Here is my working place! This is the way I am opening through the forest; hopefully one day it will become a footpath just like the one we were walking on before".

George started feeling afraid again. He was almost crying, complaining that it was dangerous and also he didn't have the right shoes for that: his mother would get angry if those shoes got dirty. Even the Teacher was afraid, really afraid, and he said it would be better to go back and let the children play in the big park they left behind. But Charlie suddenly said "No, let's keep going...it might be dangerous but it is fun and, think about it George, you might found the answers to the 100 questions you wrote"; then, turning to the Teacher, he added "It is the first time I enjoy the Science class". They kept going.

The passage was very difficult, the bushes and the plants were very flourishing. Sometimes they had to jump while other times they had to bend down. After a while they reached a river. The Scientist stopped and told the students: "This is the point where I am stuck. I am trying to find a way to cross the river." "We can help you!" replied Jeremy. "But I am tired", complained Olivia. The professor said: "We have walked a lot, they are children and they are tired. Let's go back, we cannot help the Scientist now". Amelia went to Olivia, gave her some sweets and some water and then, turning to all the others, said: "It is so beautiful here. We

can have some rest and in the meantime we can think about ways to cross the river". Jeremy and Matilda were talking excitedly to each other and after a while they screamed: "We have an idea!". They said that they would need a vine, one of those they saw while walking along the path. Then Matilda would swim (and she is a very good swimmer!) to the other side of the river, holding one end of the vine. The other end should be tied to a big, strong-looking tree. Once Matilda had reached the other side, she would secure the vine to another tree, so that the others could cross by holding it. The Scientist thought it was a good plan.

Once they found a suitable vine, Matilda started swimming towards the other side of the river. She tried once, twice, and countless more times but the current was too strong and it was impossible for her to advance. She came back crying: "We failed, we cannot cross the river". The Teacher was nervous and shouted at the Scientist: "See what you have done! This is too much for a child...and we have spent so much time on that, let's go back!". The Scientist, replied: "Yes it is true, a lot of time have passed, maybe you haven't noticed it, but here the time passes faster than outside...it is almost one year that we are walking, and Matilda have tried to cross the river for almost three months. If you want to go back, I understand." But at that point Jeremy hugged Matilda and told her: "You have done a great job. We have just failed this time; for sure there is another way to cross the river". And George said: "Yes! If we move a bit downstream, the current will probably be less strong, and it will be easier to cross!". So they started walking downhill, along the river. They were all tired, but they felt like there was an energy that was pushing them to keep going...the Scientist said that she used to call that energy "Curiosity".

After a while they found a point where the current seemed less strong. Matilda, and all the others after her, succeeded to cross, they were all very happy! However, Amelia was still a bit disappointed... It was a beautiful experience, but...all that effort for what? The Teacher understood her feeling and provoked the Scientist: "So... does this journey have an end?" The Scientist replied: "We can stop when we find a meaningful answer, when we open a path that interests someone else. Our end of the journey is the place that can be seen as a start of a new other journey. This passage that we created across the river does not exist if we're the only ones who used it."

Amelia and all the others understood. They should call the others and show them how to cross the river as they did. George said "Well, before calling other people, we should check that the

passage is safe enough". "Maybe we can put another vine, tie it to this tree and to that one on the other side, so that it will be easier to cross" said Jeremy. "Also, we need to tell them that the view from this side is beautiful and different from the other side, so they will follow us" said Amelia. While they were checking and making the passage safer, four people approached the class. They were four scientists who were working nearby; they heard the voices of the students and thought that something interesting was happening. The class helped them to cross the river. The four scientists asked many questions to the students, they wanted to know all the details about that passage across the river. They said that they could build a similar passage again, if they need to cross a river. And they concluded "That is a good passage. It is safe and no one has done this before. Others can go across this way, thank you for what you have done!".
At that point, they heard the bell ringing. Time has flown by so fast, thought Charlie! Suddenly they found themselves back in their classroom. The Teacher was behaving as usual, like he didn't remember anything about the journey in the forest. The Scientist was smiling to the students, as if to say: "Everything has been true, but do not expect the Teacher to remember". The Teacher gave homework, as usual: "Write a recap of the things you have learnt today", he said.

You should have seen the face of the Teacher when he read the essays of the students! No one was describing the biological effects of ionizing radiation that the Scientist had explained so well! Charlie wrote "We learnt that science can be fun!". Matilda and Jeremy wrote that they learnt to keep going and that there is always a way to find the answer. Amelia wrote: "I learnt how beautiful Science is, and how it is even more beautiful showing that to other people". George wrote: "I learnt that there is not an answer for all the questions, well, not yet...and searching for it is very hard." Olivia wrote: "It is incredible to see that the unknown is much more vast than what we know".

La logica è l'etica del pensare

** Logic is the Ethic of Thinking*

Roberta de Monticelli
"Esercizi di pensiero per apprendisti filosofi"

ABSTRACT

The application of ionising radiation (IR) in the medical sector is undoubtedly lifesaving. There are, however, risks associated with IR and there is growing concern among public health and radiation protection experts, in particular for the increasing medical radiological exposure in children. The aim of this dissertation is to contribute to a better characterisation of the IR risk in patients.

A hospital-based cohort study of childhood cancer survivors was developed as a basis for future analysis and, nested within the cohort, a cross-sectional study on neurodevelopmental effect after non-cranial radiotherapy was implemented. A descriptive analysis of the mental health status of the cohort is presented here.

The association between cumulative IR from medical diagnostic procedures and cancer (adult lymphoma and childhood/adolescent brain cancer), in two large international case-control studies, were estimated and a dosimetry estimation was developed.

Evidence of a neurodevelopmental effect at low-to moderate IR dose was synthesized in a systematic review and was found to be limited to inadequate.

The estimated effect at this low dose range requires greater effort from epidemiologists to design more informative studies, and collaboration with clinicians is key for future research in radiation epidemiology.

RESUMEN

La aplicación de la radiación ionizante (RI) en ámbito médico ha llegado, sin duda, para salvar vidas. Sin embargo, hay una preocupación entre los expertos de salud pública y protección radiológica con relación al incremento de la exposición medica a RI, sobretodo en pacientes pediátricos. Esta tesis tiene como objetivo contribuir a una mejor caracterización del riesgo de radiación en pacientes oncológicos.

Con ese fin, se creó un estudio de cohorte de supervivientes de cáncer infantil, como base para el análisis futuro y, anidado a esta cohorte, se implementó un estudio transversal sobre el efecto del neurodesarrollo después de haber recibido radioterapia no-craneal. Aquí se presenta un análisis descriptivo del estado de salud mental de la cohorte.

También se ha estimado la asociación entre la dosis acumulada de RI de los procedimientos de diagnóstico médico, como la exposición al radio-diagnostico y el cáncer (linfoma en adultos y tumores cerebrales en niños-adolescentes), en dos grandes estudios internacionales caso-control y dicho trabajo se unió a una estimación de dosimetría que puede ser aprovechada aún más para estudios similares.

En el marco de esta tesis, también, se sintetizó la evidencia actual de un efecto en el neurodesarrollo de la exposición a RI de dosis baja a moderada, en una revisión sistemática, concluyendo que la evidencia de este efecto es limitada e inadecuada.

La estimación de los efectos de radiación médica requiere grandes esfuerzos y la colaboración entre epidemiólogos y clínicos es un aspecto clave en este tema.

RESUM

L'aplicació de radiació ionitzant (RI) en l'àmbit mèdic ha portat indubtablement a l'estalvi de vides. No obstant això, hi ha preocupació entre els experts en salut pública i protecció radiològica pel que fa a l'augment de l'exposició mèdica a RI, especialment en pacients pediàtrics. Aquesta tesi té com a objectiu contribuir a una millor caracterització del risc de radiació en els pacients oncològics.

Amb aquesta finalitat, es va crear un estudi de cohort de supervivents de càncer infantil com a base per a futures anàlisis i, niats a aquesta cohort, un estudi transversal sobre l'efecte del neurodesenvolupament després de rebre radiació no cranial. Aquí es presenta una anàlisi descriptiva de l'estat de la salut mental de la cohort.

L'associació entre la dosi acumulada de RI dels procediments de diagnòstic mèdic, com ara l'exposició al radio-diagnòstic i el càncer (limfoma d'adults i tumors cerebrals en nens-adolescents), també s'han estimat en dos grans estudis cas-control internacionals. Aquest treball es va unir amb una estimació de dosimetria que pot ser més aprofitada per estudis similars.

En el marc d'aquesta tesi, també, l'evidència actual d'un efecte sobre el neurodesenvolupament de dosis baixes o moderades d'exposició RI va ser sintetitzada en una revisió sistemàtica, concloent que l'evidència d'aquest efecte és limitada i insuficient.

L'estimació dels efectes de la radiació mèdica requereix un gran esforç i la col·laboració entre els epidemiòlegs i els metges és un aspecte clau en aquest tema.

PREFACE

This thesis has been developed at the *Barcelona Institute for Global Health* (ISGlobal), previously the *Centre de Recerca en Epidemiologia Ambiental* (CREAL), between March 2015 and September 2019 under the supervision of Prof. Elisabeth Cardis and co-supervised by Dr. Isabelle Thierry-Chef. The thesis includes a compilation of 5 articles (1 accepted, 3 under review, and 1 in preparation).

The presented work contributes to the research on the health effect of low-to-moderate ionizing radiation dose which is currently a priority in radiation protection, considering, in particular, the increasing of medical radiation exposure in the general population.

This work contributed to this research line by:

1) **Building a structure for future research and analysis**:

- Setting-up epidemiological studies, in particular:
    a) A cohort of childhood cancer survivors (SPAIN-CCSS project);
    b) A study on neurocognitive effects in childhood cancer survivors following childhood cancer radiotherapy to sites other than brain (COGNITO study);
- Reconstructing doses from common conventional radiological examinations (dental intra oral, paediatric skull and neck X-ray) by patient age and time period entering x-ray parameters, as extracted in a literature review, to the PCXMC software for simulations.

2) **Providing estimates of health effects** of ionizing radiation at low-to-moderate dose levels:

- Exploring the risk of lymphoma in adults and of brain tumours in young people from exposure to diagnostic X-rays in case-control studies with self-reported medical radiation exposure
- Providing a synthesis of the current epidemiological evidence of neurodevelopment effect of exposure to low-to-moderate dose ionizing radiation in childhood adolescence using a Systematic Review methodology.

The candidate had the opportunity to work on all steps of epidemiological research from the design of protocols and questionnaires, grant applications, ethics approvals, conduction and coordination of multidisciplinary studies, analysis of data, interpretation of results and preparation of reports and scientific publications. In particular, the candidate worked in collaboration with the two major paediatric hospitals in Barcelona (Hospital San Joan de Deu and Hospital Vall Hebron) in the framework of the two epidemiological studies that were set up within this thesis. She designed and coordinated the COGNITO study on neurodevelopmental effect in childhood cancer survivors and she contributed to the grant writing phase of this study (KID-MEDRAD project funded by the Spanish Institute of Health). She obtained necessary authorizations from all appropriate ethics review committees. She also coordinated the childhood cancer survivors' cohort (SPAIN-CCSS project) and was involved directly in the data collection through medical record data abstraction.

The candidate has also co-supervised the work of a master student from *Universitat Politecnica de Barcelona* which led to estimating

organ doses from common dental radiological examination. These doses have been further used in the analyses of two international case-control studies in which the candidate was responsible for the analysis of risk from medical radiation exposure.

Finally, by leading a Systematic Review of epidemiological studies on neurodevelopmental effects of exposure to low-to-moderate IR, she contributed to the increased discussion, in the low dose radiation research communities, on the topic. Indeed, she was invited to present her work and discuss future research directions in two recent international scientific workshops: the 2019 EU MELODI workshop on non-cancer effects of low doses of ionising radiation in Sitges and in a dedicated workshop at the 2019 International Congress of Radiation Research in Manchester.

RATIONALE

Human beings have always been exposed to low dose IR from natural radioactive matter in the environment and from cosmic radiation. The discovery of radioactivity, at the start of the 20th century, was welcomed as revolution in several industrial sectors. The use of IR for energy production and in the medical sector is essential in today's society.

Since the introduction of radiation in medicine, diagnostic and therapeutic applications have dramatically evolved, resulting in major improvements in patient care. The medical exposure of patients is the largest anthropogenic source of radiation dose in the general population and continues to increase rapidly. It is therefore of societal importance to investigate the effects on health at low doses IR radiation and to improve our understanding of the dose-response relationship, in the low to moderate dose range (where information is lacking).

Radiation epidemiology is devoted to the study of the effects of radiation on the human population and aims to provide best estimates to understand these effects; to provide a sound scientific basis for setting radiation protection standards; and effective implementations of public health actions to optimise the use of radiation while minimising health impacts of its use.

Estimating risks from exposure to medical IR in epidemiological studies is challenging but it is an opportunity to study radiation risks in a specific context which is different from the atomic bomb survivors study (currently the reference study for radiation protection) and more relevant for radiation protection today. The exposure is fractionated, not uniformly distributed across the body,

and it is generally received by a non-healthy population. The health risk can thus be affected by other exposures (e.g. other treatments) and the baseline risk can be different from that of the general population.

In the present thesis, cancer and non-cancer outcomes are explored. Among cancer outcomes, risk of lymphoma in adults and of brain cancer in young people following lifetime medical diagnostic exposure is estimated. Among non-cancer outcomes, neurodevelopmental effects of low to moderate IR are explored.

AIM AND OBJECTIVES

The overall aim of this doctoral thesis is to investigate effects of low dose external IR received in the medical setting, particularly in paediatrics. The specific objectives are:

I. Estimating cancer risk from diagnostic radiological history:

a. Providing retrospective dose estimations for common conventional X-ray procedures based on typical settings used in different time periods and ages (*Manuscript I*, *supplement material of Manuscript III*).

b. Exploring the risk of lymphomas in adults from exposure to diagnostic radiation earlier in life within the Epilymph case-control study (*Manuscript II*)

c. Estimating the risk of brain tumours in young people from exposure to medical diagnostic radiation, in the MOBI-Kids case-control study (*Manuscript III*)

II. Investigating radiation induced neurodevelopmental effects:

a. A synthesis of the epidemiological evidence on neurodevelopmental effects induced by low-to-moderate IR doses received in childhood (*Manuscript IV*)

b. Studying the cognitive effects of low-to-moderate doses of IR among childhood cancer survivors treated for a tumour outside of the brain (*Study protocol I*)

III. Setting up a cohort of childhood cancer survivors:

a. Exploring mental health in a cohort of childhood cancer survivors (*Manuscript V*)

b. Conducting a neurocognitive evaluation in a subgroup of patients from the cohort (see Objective II.b).

OVERALL THESIS STRUCTURE

The present dissertation consists of five chapters. Chapter I includes an overall introduction aiming at summarizing the current epidemiological evidence of medical radiation effects. Chapter II, III and IV include the findings presented in the form of manuscripts. Chapter V is devoted to presenting a general discussion of the thesis. To help the reader navigate within the three central chapters, the different objectives and resulting publications are outlined in a single overall framework in Figure I.

Let's imagine a hypothetical follow-up of a population receiving low-to-moderate IR dose in medical context (black arrow of Figure I).

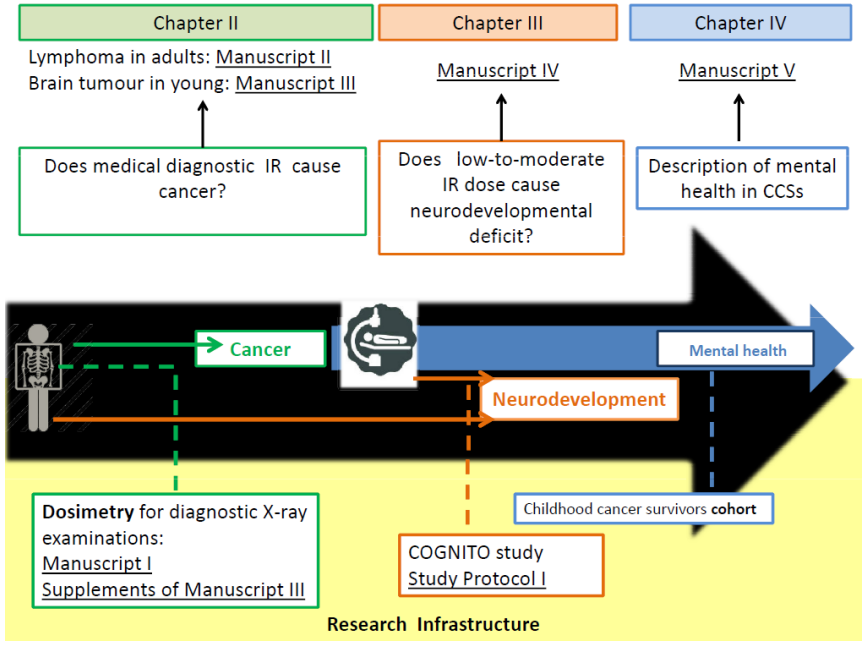

Figure 1: Thesis framework

In this population a number of cancers are observed. Thus, as a first research question, we might be interested in knowing if the observed cancers are causally related to the IR dose received previously during the medical procedures. Chapter II of the present

thesis aims to assess the effect of radiation dose from historical diagnostic procedures on the risk of lymphoma in adults and brain tumours in young people (Objective I) and includes two risk analyses manuscripts:

- *Manuscript II*: *"Association of ionizing radiation exposure from common medical diagnostic procedures and lymphoma risk in the Epilymph case-control study";*
- *Manuscript III*: *"Exposure to medical radiation during foetal life, childhood and adolescence and risk of brain tumour in young age: results from the MOBI-kids study"*.

To conduct the above mentioned analyses, a dosimetry assessment of common diagnostic medical procedures was carried out and detailed in *Manuscript I ("Trends in estimated thyroid, salivary glands, brain and eye lens doses from intraoral dental radiography over seven decades -1940 to 2009-")* and in the supplementary material section of *Manuscript III ("Exposure to medical radiation during foetal life, childhood and adolescence and risk of brain tumour in young age: results from the MOBI-kids study").*

In addition to cancer effect, radiation epidemiologists are increasingly interested in exploring non-cancer effects. Chapter III provides a critical synthesis of the current evidence of neurodevelopmental effects from low-to-moderate doses of IR (Objective II), by conducting a Systematic Review (*Manuscript IV*; *"The neurodevelopmental effects of low dose ionizing radiation exposure: a systematic review of epidemiological evidence"*).

Going back to the hypothetical population described in Figure I, radiation epidemiologists are also interested in exploring what is happening to patients after a cancer, as radiation exposure may

happen also in the context of cancer treatment. In the present thesis, in order to study the long term consequences of childhood cancers and their treatment, I coordinated the setting up of a childhood cancer survivor's cohort, at *Hospital Sant Joan de Deu in Barcelona*, with potential for extension at national level (Objective III). Chapter IV includes *the Manuscript V* (*"Aspects of mental health in childhood cancer survivors: results from a hospital-based cohort in Spain*") which describes the mental health outcomes in this cohort.

Neurodevelopmental effect is also an important outcome to be explored in childhood cancer survivors. Within the above mentioned cohort and using a comprehensive data base of cancer survivors from the other large paediatric cancer hospital of Barcelona (Hospital Vall d'Hebron), I set up a cross-sectional study of late neurocognitive effects in relation to radiation dose received in different parts of the brain during non-cranial radiotherapy. The study is ongoing with final testing of subjects expected by the end of 2019. The protocol of the study is presented in Chapter III.

LIST OF PUBLICATIONS ARISING FROM THIS THESIS

Manuscripts

Manuscript I: **Trends in estimated thyroid, salivary glands, brain and eye lens doses from intraoral dental radiography over seven decades (1940 to 2009)**

R.C. Fontana, **E. Pasqual**, D.L. Miller, S.L. Simon, E. Cardis, I. Thierry Chef
Accepted in Health Physics (30 May 2019)

Manuscript II: **Association of ionizing radiation exposure from common medical diagnostic procedures and lymphoma risk in the Epilymph case-control study.**

Elisa Pasqual, Michelle C Turner, Esther Gracia-Lavedan, Delphine Casabonne, Yolanda Benavente, Isabelle Thierry Chef, Marc Maynadié, Pierluigi Cocco, Anthony Staines, Lenka Foretova, Alexandra Nieters, Paolo Boffetta, Paul Brennan, Elisabeth Cardis, Silvia de Sanjose.
Under review in PLOS ONE (submitted on 1 March 2019)

Manuscript III: **Exposure to medical radiation during fetal life, childhood and adolescence and risk of brain tumor in young age: results from the MOBI-kids study**

Elisa Pasqual, Gemma Castaño-Vinyals, Isabelle Thierry-Chef, Noriko Kojimahara, Malcolm R Sim, Michael Kundi, Daniel Krewski, Franco Momoli, Brigitte Lacour, Thomas Remen, Katja Radon, Tobias Weinmann, Eleni Petridou, Maria Moschovi, Rajesh Dikshit, Siegal Sadetski, Milena Maule, Mariangela Farinotti, Mina Ha, Andrea 't Mannetje, Juan Alguacil, Nuria Aragonés, Roel Vermeulen, Hans Kromhout, Elisabeth Cardis
Under review in Neuroepidemiology (submitted on 14 September 2019)

Manuscript IV: **The neurodevelopmental effects of low dose ionizing radiation exposure: a systematic review**

Elisa Pasqual; Magda Bosch de Basea, Mónica López-Vicente, Isabelle Thierry-Chef, Elisabeth Cardis
Under review in Environment International (submitted on 24 of May 2019; revision submitted on 17 September 2019)

Manuscript V: **Aspects of mental health in childhood cancer survivors: results from a hospital-based cohort in Spain.**

Elisa Pasqual; Agnes Dumas, Lourdes Arjona-Camí, Laura Mangado-Aloy, Hector Salvador Hernandez…., Ofelia Cruz-Martinez, Elisabeth Cardis
In preparation

Conference presentations

*****= Invited presentation

The neurodevelopmental effects of low dose ionizing radiation exposure: a summary of current epidemiological evidence" (Oral)
Elisa Pasqual, Magda Bosch de Basea and Elisabeth Cardis
14-18 October 2019, European Radiation Protection Week, Stockholm

Brain tumour risk after exposure to medical ionizing radiation: results from the MOBI-kids study (Poster)
Elisa Pasqual, Gemma Castaño-Viñalis , Elisabeth Cardis and the MOBI-kids study group;
14-18 October 2019, European Radiation Protection Week, Stockholm

Brain tumour risk after exposure to medical ionizing radiation: results from the MOBI-kids study (Oral)
Elisa Pasqual, Gemma Castaño-Viñalis (presenter), Elisabeth Cardis and the MOBI-kids study group;
26 August 2019, International Society for Environmental Epidemiology, Utrecht

***The neurodevelopmental effects of low dose ionizing radiation exposure: a summary of current epidemiological evidence"** (Oral)
Elisa Pasqual, Magda Bosch de Basea and Elisabeth Cardis
26 August 2019, International Congress of Radiation Research, Manchester

***Cognitive effects of the exposure of the developing brain to low dose ionizing radiation: a systematic review & introduction to the COGNITO study"** (Oral)
Elisa Pasqual, Magda Bosch de Basea, Elisabeth Cardis
12 April 2019, MELODI meeting on non-cancer effect of low dose ionizing radiation, Sitges

Seguimiento epidemiológico en supervivientes de cáncer infantil: experiencia de una cohorte hospitalaria en el hospital Sant Joan de Déu de Barcelona (Poster)
Elisa Pasqual, Lourdes Arjona (presenter), Genoveva Maria Correa Llano, Ofelia Cruz Martinez, Elisabeth Cardis.
30-31 May 2019, XI Congreso Nacional de la Sociedad Española de Hematología y Oncología Pediátricas, Jerez de la Frontera

Neurodevelopment effects of the exposure to low-to-moderate ionizing radiation dose: a systematic review (Poster)
Elisa Pasqual, Magda Bosch de Basea, Elisabeth Cardis
22-26 September 2018, Radiation Research Society meeting, Chicago (US)

***Radiation Protection in medicine: the patient perspective** (Oral)
Elisa Pasqual
07 December 2017; University of Free State (South Africa)

Nested case control study in a cohort of patients exposed to CT scan during their childhood. (Oral)
E Pasqual, M Bosch De Basea, G Armengol Rosell, JF Barquinero, E Cardis
20-22 September 2016; European Radiation Protection week, Oxford

Cognitive effects after low - to moderate dose exposure: study plan in a cohort of childhood cancer survivors (Oral)
E Pasqual, H Salvador Hernández, L Mangado Aloy, C Boix LLuch, O Cruz Martínez, E Cardis
20-22 September 2016; European Radiation Protection week, Oxford

Nivel de instrucción en supervivientes de cáncer infantil: resultados de una cohorte de base hospitalaria (Poster)
Elisa Pasqual, Miguel Angel Flores Taico, Hector Salvador Hernandez, OfeliaCruz Martinez, Elisabeth Cardis
19-21 May 2016, IX Congreso Nacional de la Sociedad Española de Hematología y Oncología Pediátricas, Santander

Descriptive analysis from a hospital based childhood cancer survivors cohort: report from the project Spain-CCSS (Oral)
14-16 September 2016, 8th international conference on children's health and the environment.

Descriptive analysis from a hospital based childhood cancer survivors cohort: report from the project Spain-CCSS (Oral)
Hospital San Joan de Deu, to the clinicians of the haemato-oncological department

Self-reported mental health status in a hospital based cohort of childhood cancer survivors (Oral)
20-22 April 2016, Pan-European network for care of Survivors after Childhood and Adolescent Cancer meeting, Lisbon.

ABBREVIATION LIST

ABCC	Atomic Bomb Casualty Commission
CCSs	Childood Cancer Survivors
CT-scan	Computerized Tomography Scan
ERR	Excessive Relative Risk
EURADOS	European Radiation Dosimetry Group
EURAMED	European Alliance for Medical Radiation Protection Research
IR	Ionizing radiation
LNT	Linear Non-Threshold
LSS	Life Span Study
MELODI	Multidisciplinary European Low Dose Initiative
MIBG	yodo-131-metayodobenzilguanidina
MRI	Magnetic Resonance Imaging
NRCP	National Council on Radiation Protection
OR	Odds Ratio
PACS	Picture Archiving System
RERF	Radiation Effects Research Foundation
RR	Relative Risk
RRR	Relative Risk Ratio
SEHOP	Spanish Society of paediatric oncology and haematology
UNSCEAR	The United Nations Scientific Committee on the Effects of Atomic Radiation
WHO	Word Health Organization

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CHAPTER I: General Introduction

This chapter intends to provide the reader with an overall picture of the context in which this thesis was conducted, i.e. the state of the art in radiation epidemiology research concerning the topic under study: the health effects of low-to-moderate doses of medical Ionizing Radiation (IR), particularly in paediatric populations.

The introduction starts by giving an overview of the characteristic of the exposure of interest, which will help the reader understand terminology and issues addressed in each manuscript.

We then summarize key epidemiological studies of individuals exposed to different sources of medical radiation, selecting those which most contribute to current knowledge. Here we also detail the current status of Childhood Cancer Survivor's (CCSs) research by describing the ongoing larger cohorts.

The introduction ends with a paragraph summarizing current knowledge and research gaps concerning the health effect of low-to-moderate radiation dose, detailing, mostly, the outcomes included here (cancer and neurodevelopment).

1 LOW DOSE IONIZING RADIATION

1.1 Definition of ionizing radiation

Ionizing Radiation consists of energy released by atoms which travels in the form of electromagnetic waves, such as X-rays or γ–rays, or of subatomic particles, such as protons, neutrons, and α- and β–particles. It is called "ionizing" because it has enough energy to ionize the matter it passes through (i.e. makes atoms of that matter gain a positive or a negative charge) (National Research Council (U.S.), 2006).

In the present thesis, we mainly focus on X-rays, which are predominantly used in medicine, and in particular, in the low and moderate dose ranges. Low is generally defined as below 100 mGy (ICRP, 2005; National Research Council (U.S.), 2006); the definition of moderate is less standardized; in the current context we will take it to range from 100 to less than 5 Gy of external photon (here X-ray) radiation (Berrington de Gonzalez et al., 2013).

1.2 How ionizing radiation is measured?

1.2.1 Quantities in radiological protection

In radiation protection and radiation dosimetry, different quantities are used to measure radiation, according to the specific aim:

a) Measuring the amount of radiation released by a material. The term "radioactivity" refers to the amount of IR released by a material and represents the numbers of atoms that decay in a given time period in that material. The unit of radioactivity is the Becquerel, which is the number of disintegrations per second. As a radionuclide decays it can emit α-- or β particles, γ- rays, X-rays, protons or neutrons. As an example, the radioactivity of the ground

or of water (that is, their content in naturally occurring radionuclides or in radionuclides deposited after an accident) can be measured. Comparison of health indicators across areas with different levels of radioactivity are often used in ecological studies (Black et al., 2013; Evrard et al., 2006).

b) Measuring the exposure. The ability of radiation to ionize the air can be measured in Roentgen or in Coulomb/Kg. Also, Air-kerma, defined as kinetic energy of radiation released per unit mass of air (J/Kg), is a measure of exposure. These quantities are not used in radiation epidemiology for risk estimation, because they do not measure the dose deposited in tissues.

c) Measuring the dose. For the assessment of IR dose, two quantities have been developed and are used in radiological protection as well as in epidemiological studies for risk estimation. They measure the actual amount of energy deposited into the tissue or organ through which the radiation passes (ICRP, 2007a):

- The **absorbed dose** measures the quantity of energy that is absorbed by a unit of mass, it is measured in Joules /kg or Gray (1 Gy=1 J/kg). Historically this quantity was measured in rad (1 rad= 0.01 Gy).

- The **equivalent dose** in a given **tissue or organ** is the absorbed dose in Gy to that tissue or organ adjusted by a **radiation weighting factor** (W_R) that account for the effectiveness of the type of radiation in inducing a particular biological stochastic effect (ICRP, In press). It is measured in Sievert ($Sv=J/Kg*W_R$). Two main types of IR are distinguished based on the density of the ionizations (energy transfers) on the radiation track through a material or tissue: low Linear Energy Transfer (LET) and high LET radiations (Fig. 2). For low LET radiation types (X-rays, β- and γ- radiation), such as those

delivered by most medical radiation equipment, the W_R is set to one and the dose equivalent is therefore numerically identical to the absorbed dose. By contrast, weighting factors for higher LET particles such as α-particles or neutrons are greater than one, leading the equivalent dose to be higher than the absorbed dose. The equivalent dose has traditionally been used in analyses of the Life Span Study (LSS) of atomic bomb survivors to adequately combine doses from γ-rays and neutrons in estimating the risk per unit dose. Radiation weighting factors are revised periodically based on improved knowledge; the most recent published estimates are provided in ICRP Publication 103 (ICRP, 2007a, p. 103).

d) Other purposes. The equivalent dose must not be confused with the "Effective dose", which is the sum of the equivalent doses absorbed over all organs and tissues exposed, each one multiplied by their respective tissue factor accounting for the estimated relative radiation-sensitivity of different tissues. The effective dose allows comparisons of different type of exposures (including whole body and partial body) and is the main quantity used for setting limits in radiation protection; it is of little use in epidemiology, however, as it implicitly incorporates an element of risk in the tissue factors (a risk which the epidemiological studies are set up to estimate) and as dose may vary vastly across different organs particularly for partial body exposures.

In Table 1 we show the most frequently used units, their symbol and the rationale for use of each one.

Table 1. Ionizing Radiation related physical quantity

Quantity	Unit	Symbol	Use
Radioactivity	Becquerel	Bq	SI unit of radioactivity. 1 Bq=1 disintegration per second.
	Curie	Ci = 3.7×10^{10} Bq	Traditional quantity of radioactivity, not generally used anymore.
Exposure	Coulomb per Kg	C/kg	SI unit of exposure. Measuring the electrical charge produced by the IR ray.
	Roentgen	R= 2.58×10^{-4} C/kg	Conventional unit of exposure. One roentgen equals the amount of X-ray or γ- radiation required to produce ions carrying a charge of 1 electrostatic unit (esu) per cubic centimeter (2.58×10^{-4} Coulomb per kg) of dry air under standard conditions.
	Air-Kerma (Kinetic Energy Released per unit mass of air).	Gy= J/Kg	It is the amount of radiation energy (Joules), released in a unit mass (kg) of air. It is considered a measure of exposure, rather than dose.
Absorbed dose	Gray	Gy= J/Kg	The SI unit of absorbed dose
	Rad	Rad= 0.010 Gy	Historical unit of absorbed dose.
Equivalent dose	Sievert	Sv= J/Kg*Radiation weighting factors	For low-LET radiation this quantity is equal to the absorbed dose in a particular tissue or organ (in Gy) multiplied by a factor which takes into account the relative effect of the radiation type on the risk of radiation induced stochastic effect. Equivalent dose is a low dose concept.
	Rem	Rem=0.01 Sv	Historical unit of equivalent dose.
Effective dose	Sievert	Sv= $\sum \mathrm{J/Kg} * \mathrm{W_T}$	The weighted sum of effective doses over all organ/tissues in the body, weighted by a tissue weighting factor W_T which estimates the relative risk of stochastic effect in that particular organ This is a radiation protection quantity used to establish radiation limits
	Rem	Rem=0.01 Sv	Historical unit of equivalent dose.

SI: International System units

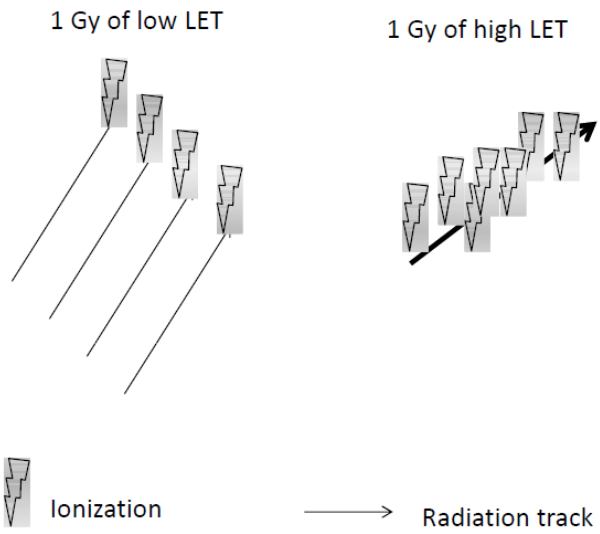


Figure 2: High LET and low LET radiation type
LET is the density of ionizations deposited by each radiation type along its track. The distinction between low and high LET depends on the number of ionizations that each track is capable of generating within matter
Figure adapted from (Chang et al., 2014)

1.2.2 Target organ

In estimating a specific effect of radiation, it is important to identify the target organ. As an example, if we estimate brain cancer risk after radiation exposure, we should estimate the dose absorbed by the brain and use this quantity for the risk estimation. This is particularly important for medical exposures, where dose is generally not uniformly distributed in the body. Actually, organs that fall into the radiation field will absorb most of the dose, while organs outside the field will receive much lower doses, if any. Thus, the resulting effective dose (weighted sum across the organ) will differ largely from the dose absorbed at the level of organs inside the radiation field. Table 2 shows estimated effective and absorbed doses to the brain, lung and stomach dose from typical skull, chest and abdomen CT-scans.

Table 2. Effective doses and organ absorbed doses from common CT-scan examinations

CT- Scan	Effective Dose	Absorbed dose at the level of the organ		
		Brain	**Lung**	**Stomach**
Skull	2 mSv	40 mGy	0 mGy	0 mGy
Chest	7 mSv	0 mGy	20 mGy	6 mGy
Abdomen	8 mSv	0 mGy	0 mGy	20 mGy

Values from (Lee et al., 2018)

1.2.3 Individual doses across different sources of IR exposure

Exposure from IR can come from different sources, both natural and human-made. Table 3 compares the effective doses from different sources of IR. From natural background radiation, each individual receives, on average, 2.4 mSv/year. A dental X-ray corresponds approximately to one hour of background radiation, while a chest CT-scan corresponds to two years of natural background radiation dose. Figure 3 shows the range of doses in common radiological procedures in medicine (diagnostic and therapeutic).

In epidemiological studies, dosimetrists play a key role in providing estimates of the dose received by each individual of the population under study. Figure 4 details the mean and range of absorbed doses in key radiation epidemiological studies (Cardis et al., 2007; Kashcheev et al., 2015; Ozasa et al., 2018; Vostrotin et al., 2019). The atomic bomb survivors study (Ozasa et al., 2018) represents the reference study and the current radiation protection system is mainly based on its findings.

Figure 5 details the dose ranges of large epidemiological studies conducted on medically exposed populations (Bithell and Stewart, 1975; Lundell et al., 1990; Pearce et al., 2012a; Ronckers et al., 2010; Sadetzki et al., 2005; Weiss et al., 1994).

As shown in Figures 4 and 5, most of the non-medical radiation epidemiology studies overlap in terms of doses with those of medically exposed populations. Thus, in principle, risk estimates calculated in non-medical radiation studies can be used as a guide for building radiation protection structures including protection of the exposed patients. However, it is important to note that the exposure from medical devices has special characteristics:

- Exposure is generally fractionated;
- Range can vary a lot: therapeutic procedures include also very high dose ranges
- Dose is not uniformly distributed across organs: dose to the target organ can be high, whereas it can be almost zero to other distant organs
- Dose reconstruction implies tackling two levels of uncertainty: the collection of number and type of procedures and the estimation of dose for each single examination.

Table 3: Effective dose from different source of radiation exposure

Source	Approximately effective dose	Reference
Average yearly annual dose from natural background radiation	Mean worldwide 2.4 (range 1-13)	(UNSCEAR, 2008a)
Eating one banana	0.0001 mSv	
Air plane flight (cosmic radiation)	0.003 mSv (Frankfurt-Rome) to 1.1 mSv (Frankfurt- San Francisco)	(UNSCEAR, 2008a)
Radiation worker annual dose limit	20 mSv/year	(European Commision, 2013)
Annual dose limit to the general public	1mSv/year	(European Commision, 2013)
Dental x-ray (intraoral)	0.02 mSv (weighted average across level I countries)*	(UNSCEAR, 2008b)
Chest x-ray	0.07 mSv (weighted average across level I countries)*	(UNSCEAR, 2008b)
Chest CT scan	7.8 mSv (weighted average across level I countries)*	(UNSCEAR, 2008b)
Low dose boundary definition	100 mSv	(National Research Council (U.S.), 2006)

(*) Level I countries are considered thos with at least one physichian every 1000 inhabitants (UNSCEAR, 2008b)

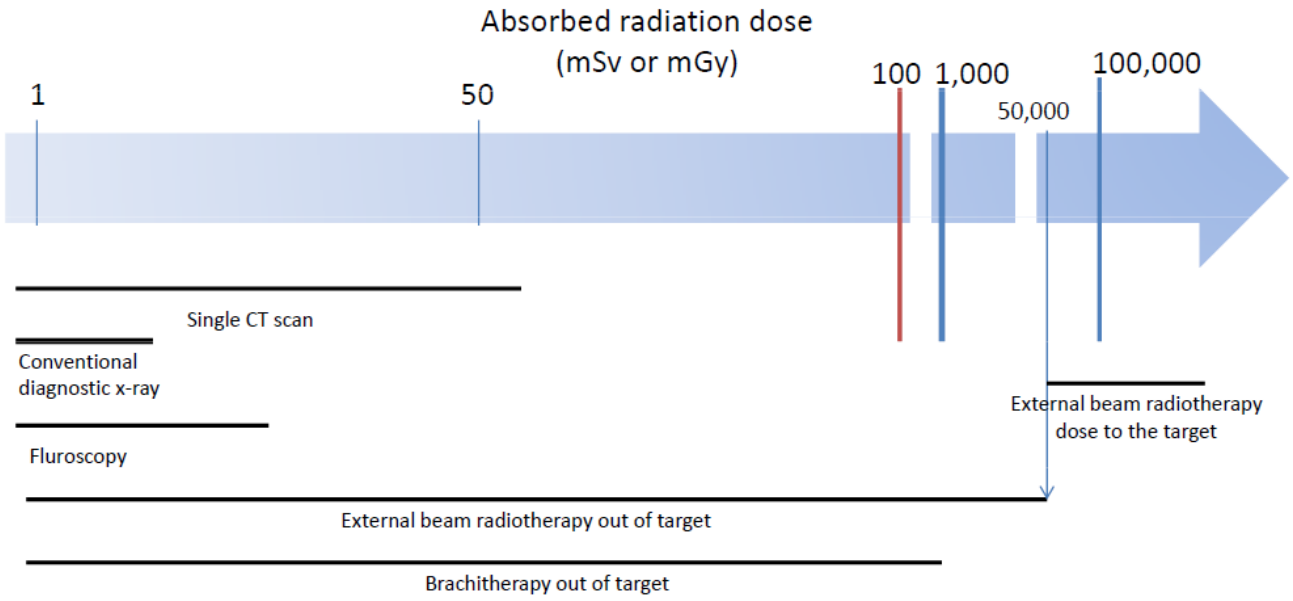


Figure 3: Approximate level of organ dose across common medical radiological procedures

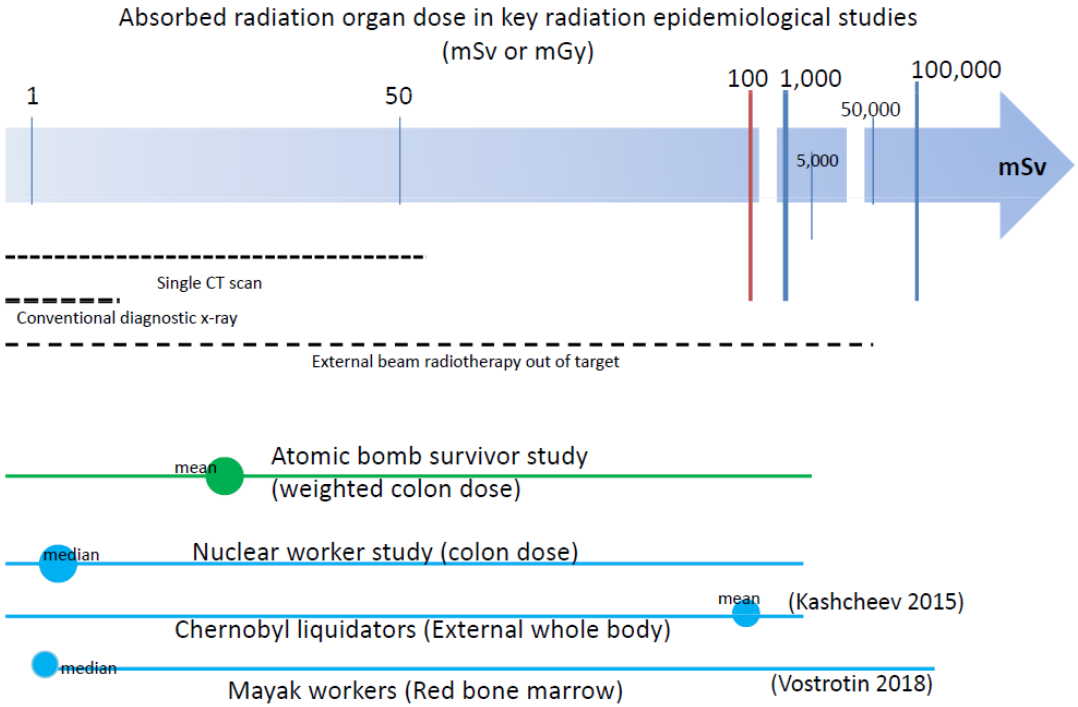


Figure 4: Dose range in key epidemiological studies (excluding medically-exposed populations)

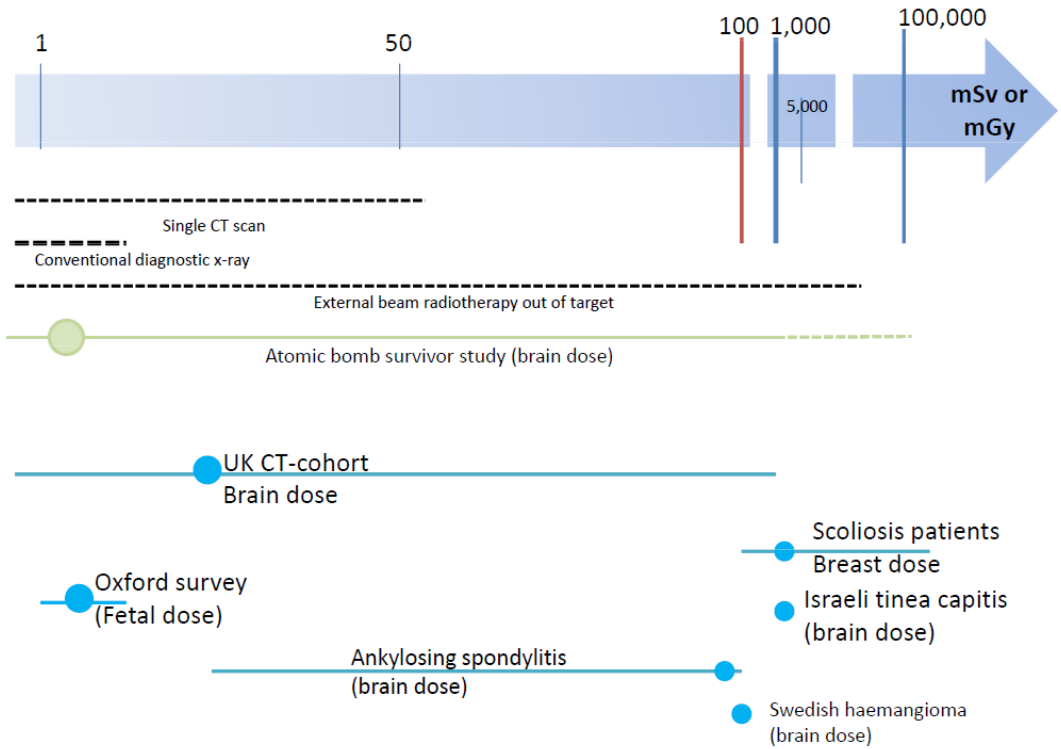


Figure 5: Dose range (Absorbed dose in mGy or mSv) in key radiation epidemiological studies of medically exposed populations

1.2.4 Dosimetry work in the present doctoral thesis

As indicated above, obtaining adequate dosimetry is crucial for any epidemiological study, and risk estimates should be based on the dose to the target organ. Within this thesis, dose reconstruction was carried out in the different study populations.

Historical doses from radio-diagnostic imaging were generally not recorded in radiological records and need to be estimated. Doses can be estimated from the parameters set by the radiographers at the moment of doing the radiography, such as X-ray tube voltage, collimation, entrance Air-Kerma, X-ray-Image receptor distance (Fig. 6). However, historically, such parameters were not systematically stored in radiological records, challenging any retrospective study of the effects of medical imaging. For this reason, most studies of the effects of diagnostic exposures are based on numbers of procedures rather than doses (Linet et al., 2012).

An alternative approach is to estimate organ doses from commonly used parameters for different diagnostic procedures in different time periods. For the analyses performed in *Manuscript II and III*, we estimated common dose parameters for the main time periods of concern. The manuscript "*Trends in estimated thyroid, salivary glands, brain and eye lens doses from intraoral dental radiography over seven decades (1940 to 2009)*" (*Manuscript I*, Chapter II), accepted for publication in *Health Physics,* illustrates the process for the reconstruction of dose to the brain, thyroid and salivary glands from dental intraoral procedures. The same procedure was followed for skull, sinus, and neck x-ray and the details can be found in the Supplementary material of *Manuscript III* (Chapter II)

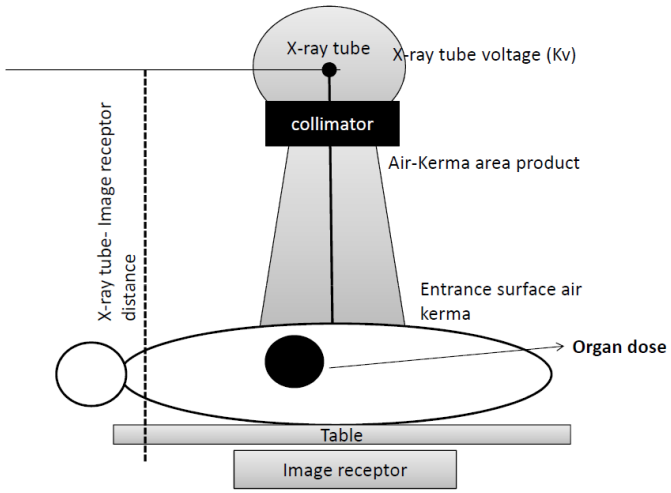


Figure 6: Radiography technical parameters

1.3 The use of IR in medical settings

1.3.1 The use of IR has significantly improved patient care.

The application of IR in medicine started soon after the discovery of X- rays, at the beginning of the 20th century. In his first publication "On a new kind of rays" (Röntgen, 1896), Rontgen showed the phenomenon he discovered with the famous picture of the bones of his wife's hand with a ring (Figure 7). This image suggested clearly the historical importance of the discovery and Roentgen sent a copy of the paper together with some early X-ray photographs to several physicians he knew (Feldman, 1989). A few weeks later, several experiments were already ongoing and the first radiograph in a medical setting was taken by John Francis Hall-Edwards in Birmingham (11 January 1896). Radiation started to be applied as

a tool in the diagnostic process because of the capacity of the X-ray to pass through material and to impress a photography sheet.

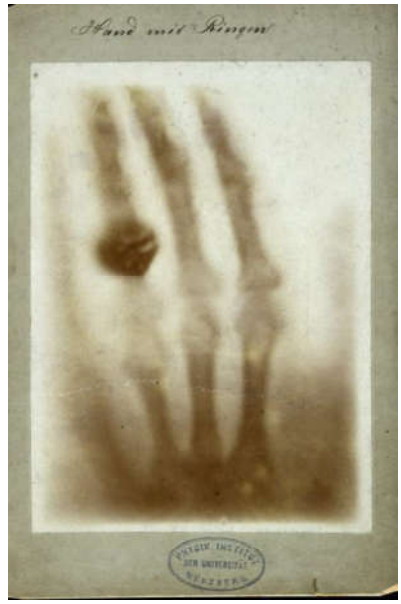


Figure 7: The first X-ray image, "Hand mit Ringen" by Roentgen, 1895.

The other important characteristic of radiation, induction of cellular death, made IR a useful therapeutic agent, in particular in cancer treatment. Almost contemporary with Roentgen's discovery, Marie Skłodowska-Curie, Pierre Curie and Henry Becquerel discovered the phenomena of radioactivity. Marie Skłodowska-Curie established the Curie institute in Paris, which can be considered as the first cancer therapy centre using radioactive isotopes.

The introduction of IR in medicine has, without any doubt, drastically improved the diagnostic and therapeutic process. Nowadays it is applied in all fields of medicine to save lives.

1.3.2 Sources of Ionizing Radiation in medical setting

IR is used, both internally and externally, for diagnostic procedures. Conventional X-rays and CT-scanners use an external radiation beam directed to the anatomical area that needs to be examined. The two procedures differ in the amount of energy of the X-ray beam (generally higher in CT-scan) and in the direction of the X-ray. In the CT-scan, the X-ray beam rotates around the patient, which increases the duration of exposure compared to conventional X-ray. The rotation allows a 3D reconstruction of the image. Both of these radio-diagnostic tools may also be used to guide interventional radiology procedures. Radiation dose to the target organ may vary a lot between different interventional procedures and it increase with the complexity of the procedure as higher screen time is required. In diagnostic radiology, internal radiation is also used in nuclear medicine diagnostic procedures, requiring the ingestion, injection or inhalation of a radioactive material that releases its energy in the patient's body.

In Table 4, common diagnostic procedures are listed together with their clinical applications and approximate effective dose, provided here as a tool for comparison.

Radiotherapy is also implemented for treatment of malignant disease as well as for some benign disease (i.e. hyperthyroidism). The aim of the radiotherapy treatment is to induce cell death in a targeted volume of cells (malignant cells, for example), thus doses in the target volumes are required to be considerably higher (up to 100 Gy (Xu et al., 2008)) than those used for diagnostic purposes. Radiation exposure in radiotherapy can also be external or internal. Table 5 details the most common radiotherapy modalities.

Table 4: List of common diagnostic procedures and definition

Procedure	Characteristic of the procedure	Common clinical applications (example)[a]	# of procedure/ 1000 individuals[b]	Dose range (effective dose, mSv)
External radiation				
Conventional x-ray	The x-rays pass through the body and are captured by a detector (film sensitive or a digital detector.)	**Dentistry:** Assessment of dental pathologies; **Respiratory**: Assessment of lung pathology; **Surgery**: Abdominal obstruction, free air or free fluid within the abdominal cavity; **Orthopaedics**: Assessment of bone structure, fractures diagnosis, bone pathology	Dental x-ray: 351 Medical diagnostic: 1177	Dental: 0.02 mSv Chest: 0.02 mSv; Pelvis: 1.2 mSv Abdomen: 0.82 mSv (UNSCEAR, 2013)
CT scan	In the CT-scan the x-ray tube produces an x-ray beam that is captured by the detectors placed all around the patient.	**Neurology**: detect brain pathology including neurovascular disease, myelography; **Oncology**: diagnosis and therapy planning; **Cardiology**: Cardiac CT; **Respiratory:** vascular and lung pathology **Emergency medicine**: assess of trauma patients, abdominal and pelvic pathologies; **Orthopedics**: Assessment of bone structure, fracture diagnosis, bone pathology	CT scan: 128	Head: 0.9-4 mSv Abdomen: 3.5–25 mSv Chest: 4.0–18.0 mSv (UNSCEAR, 2013)
Fluoroscopy	During fluoroscopy, x-	**Barium studies**: Barium swallows	Chest	Barium swallow: 1.5

Procedure	Characteristic of the procedure	Common clinical applications (example)[a]	# of procedure/ 1000 individuals[b]	Dose range (effective dose, mSv)
	ray beams are continually emitted and captured on a screen, producing a real-time, dynamic image.	barium meal and follow-through, barium enema for evaluation of the gastro-intestinal tract. **Gynecology:** **Hysterosalphingography (HSG)** for evaluation of the uterine cavity and the fallopian tubes. **Urology: Retrograde urethrogram, micturating cysto-urethrogram** for the evaluation of abnormalities of the urinary system.	fluoroscopy, colechisto-graphy, urography: 27.2	mSv Barium enema: 2.0–18.0 mSv Hysterosalpingo-gram: 1.2 mSv Cystourethro-graphy: 1.5 mSv (Mettler Jr et al., 2008; UNSCEAR, 2013)
Interventional procedures	X-ray beam (Concentional or CT-scan) are used to guide surgical interventions on the patients	**Interventional cardiology:** valve replacement, angioplasty and stenting, aortic surgery **Biopsy procedures** **Renal and genitourinary interventions:** Percutaneous nephrostomy **Percutaneous biliary drainage** **Fertility treatment**		50-70 mSv (Mettler Jr et al., 2008)
Internal emitters				

Procedure	Characteristic of the procedure	Common clinical applications (example)[a]	# of procedure/ 1000 individuals[b]	Dose range (effective dose, mSv)
Nuclear medicine	Involves injection, inhalation or ingestion of radioactive tracers to visualize various organs. The radioactive tracer emits γ- radiation, which is then imaged using a γ-camera.	**Bone scan**; to assess metabolic activity of the bones. Commonly used for oncology staging, arthritis, fractures. **Myocardial Perfusion scan**; to compare the blood flow to the myocardium at exercise and rest. **Renal scan;** to determine the perfusion and drainage of the kidneys and allow for calculation of differential function. **Lung scan:** to allow for comparison of ventilation and perfusion of the lungs to diagnose pulmonary embolism. **Thyroid scan;** to assess the appearance and function of the thyroid gland.	Nuclear medicine procedures: 9.2	Bone (99mTc-MDP): 6.3 mSv Cardiac rest-stress test (99mTc-sestamibi 1-day protocol): 9.4 mSv Lung perfusion (99mTc-MAA): 2 mSv Renal (99mTc-DMSA):3.3 mSv Thyroid scan (sodium iodine123): 1.9 mSv (Mettler Jr et al., 2008; UNSCEAR, 2013)

a The list of application is not meant to be exhaustive.
Sources https://www.who.int/diagnostic_imaging/imaging_modalities/en/
b (Weighted average across level I countries)
c (UNSCEAR, 2008b)
d (Mettler Jr et al., 2008)
Level I countries are defined in UNSCEAR report as at least one physician for every 1,000 people in the general population

Table 5: List and definition of common radiotherapy modalities

Radiotherapy modalities	Radiation type	Common clinical application (Reference *)	Dose to the target organ #	Range of out of field dose a
External beam	Photons, electron, protons, neutrons	**3-D conformal radiation therapy:** it allows to delivers beams from many directions, according to a precise shape planned before **Intensity-modulated radiation therapy (IMRT)** Similar to the 3D conformal radiotherapy, but in addition allows to modulate the intensity of the beam in specific point **Image-guided radiation therapy (IGRT).** It is a type of IMRT where imaging is obtained during treatment to allow changing also during treatment **Tomotherapy:** It is a type of IMRT where radiation is delivered in a spiral pattern (slice by slice) **Stereotactic radio surgery:** many small beams of radiation are aimed at the tumor from different directions (Gammaknife is a type of stereotactic radiosurgery)	Up to 100 Gy	Depending on the distance from the target: a)Highest distance: 0 to < 5Gy b)Intermediate (5-50 Gy) c)Radiation beam border: > 50 Gy (Xu et al., 2008)
Brachytherapy	Ra-226, Cs-137, Ir-192, I-125	Internal radiation therapy in which seeds, ribbons, or capsules that contain a radiation source are placed in the body. Often used to treat cancers of the head and neck, breast, cervix, prostate, and eye.	~60 Gy	0 to ~1Gy (Xu et al., 2008)

Radio-immunotherapy (RIT) (Larson et al., 2015)	Photons, electron, α-particles (Y-60, Bi-214…)	Use of mono-clona antibodies to carry radionuclides to a specific target cell type. It is applied mainly to treat leukaemia and certain types of lymphomas.	~100 Gy	~10 Gy to 0 (Xu et al., 2008)
Sources: (*) https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy, (#) dose reported here are for cancer treatment. For benign disease, dose may vary				

1.3.3 Pattern and trends in exposure from medical IR

The use of medical IR is increasing (NCRP Report No. 160, 2009; UNSCEAR, 2008b) and IR from medical sources has become the largest human-made source of IR exposure for the general population. In the US, the per capita annual dose from all IR sources has nearly doubled between the early 1980's and 2006 as a consequence of a 7-fold increase in per capita medical annual dose (Fig. 8) (NCRP Report No. 160, 2009). In other high income countries, it is estimated that each person receives on average 2mSv/year from medical procedures (UNSCEAR, 2008b).

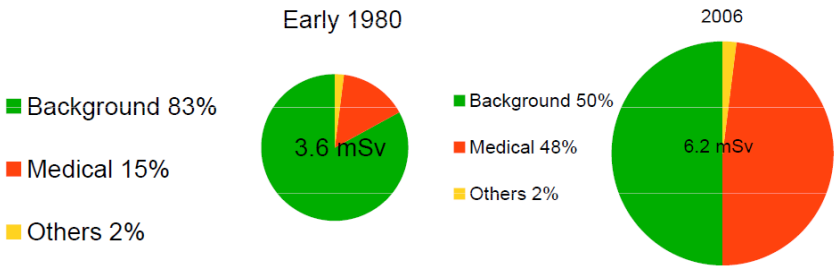


Figure 8: Per capita annual IR dose from all sources.
Adapted from NCRP report 160.

This increasing use of medical IR has raised concerns among public health and radiation protection experts, and efforts are made to reduce such doses. Technological improvement and optimization of protocols have led to dose reduction and increased image quality in diagnostic radiology. Melo et al. estimated the dose to different organ from common conventional radio-diagnostic procedures in each decade from 1930 to 2010 and found a decrease of dose of the order of 22 fold, mainly in the most recent decades (1990s-2000s)(Melo et al., 2015).

The technological advances in CT-scan protocols have also produced a great benefit in terms of dose reductions. In particular, for paediatric CT-scans, the implementation of paediatric CT

protocols in about 2000 has resulted in a substantial dose decrease in children (Lee et al., 2018).

In addition, analysis of trend in radiological practice in US and Canada for the current period (2000-2016) have shown that the rate for CT scan in adults are increasing, especially for the older adults (>65 years), however, for the younger adults, such increase appears to be at slower pace (Smith-Bindman et al., 2019). In children, the CT rate appears to be stabilized or indeed decreasing (Smith-Bindman et al., 2019). This decreasing trend may be the result of recent awarness campaign around the concern of IR exposure in the medical sector (Frush et al., 2003; WHO, 2016).

2 MAIN EPIDEMIOLOGICAL STUDIES ON POPULATIONS EXPOSED TO MEDICAL RADIATION

The study of the effects of medical radiation exposure has been identified as a key research gap in radiological protection (EURAMED, 2017; Kreuzer et al., 2017). Currently, there is a need to answer public health and radiation protection concerns, considering the increasing trend of medical radiation exposure and the consequent rise in population average annual doses. In addition, from a research point of view, it is of interest to:

- Study radiation effects when exposure is at low levels, fractionated, and non-uniformly distributed across organs. Such exposure is different from the whole-body near instantaneous exposure which happened in the atomic bombings (the main reference for estimating radiation risks for radiation protection is the atomic bomb survivors study).
- Estimate cancer risk for specific cancer and non-cancer outcomes in populations with different baseline risks than those of the Japanese atomic bomb survivors
- Estimate radiation risk in the context of multiple exposures (including pharmacological treatment). This is particularly important in cancer survivors study.

Epidemiological studies in medically exposed populations share several challenges, however, including:

- Reaching adequate study power: to estimate effects as such low dose levels, a very large sample size is needed.
- Dealing with uncertainty related to the exposure: the assessment of the exposure is a source of uncertainty at least on two main levels: a) the collection of number of each

type procedures (self report or medical record based), b) the retrospective reconstruction of organ dose in the absence of detailed technical records.

- Considering that diagnostic procedures, such as CT scanning, may be used because of suspicion of cancer, raising issues of reverse causation.
- Dealing with possible biases due to underlying medical conditions: populations exposed to medical radiation may be different from the general population; they might also have underlying medical conditions which could confound the association under study.

Statistical power and dosimetry uncertainty are mainly a concern in diagnostic imaging studies and such issues are shared also with low dose radiation epidemiological studies (occupational studies, environmental exposure and atomic bomb survivors).

In the following paragraph and in Table 6 and 7, studies conducted on medically exposed populations thath mostly contributed to the current scientific knowledge are listed, highlighting main methodological characteristics. This list is not meant to be exhaustive, and studies reporting radiation risk after medical radiation have been systematically reviewed elsewhere (Bernier et al., 2015; Doll and Wakeford, 1997; Kleinerman, 2006; Krille et al., 2012; Linet et al., 2012, 2009; Mulvihill et al., 2017; National Research Council (U.S.), 2006; UNSCEAR, 2008b).

2.1 Studies on population exposed to medical diagnostic procedures

Table 6 details the study characteristics of the main epidemiological studies conducted on population exposed to low IR dose from diagnostic procedures (Berrington de Gonzalez et al.,

2016; Bithell and Stewart, 1975; Boice et al., 1991, 1978; Howe, 1995; Pearce et al., 2012a; Preston-Martin et al., 1988). Fig. 5 outlines the approximate range of doses in these studies.

The question around potential cancer risk from diagnostic radiological exposure was explored within case-control design: a) The UK case-control study on childhood cancer and foetal diagnostic irradiation (Bithell and Stewart, 1975); b) Two case-control studies of risk of cancer after exposure to diagnostic medical radiation (Boice et al., 1991; Preston-Martin et al., 1988): Boice et al. collected information from medical records, while Preston-Martin et al. based risk estimation on self-reported medical radiological history. In early times, also, two cohort studies of populations receiving multiple fluoroscopies for follow up of tuberculosis were set up (Davis et al., 1989; Howe, 1995).

More recently, a large scale study was conducted in a cohort of UK paediatric patients who underwent CT-scanning (UK-CT cohort) (Pearce et al., 2012a). This study, and other more recent national studies of paediatric CT-scans (Huang et al., 2014; Journy et al., 2016; Krille et al., 2015; Mathews et al., 2013; Meulepas et al., 2019), have raised a debate around the relatively high risk of brain tumours found, compared to what was expected from the atomic bomb survivors study. Results of a large scale European study (EPI-CT) (Bernier et al., 2018; Bosch de Basea et al., 2015) are expected shortly.

2.1.1 Patients treated for benign conditions

Several cohort studies of patients who received radiation treatment for benign conditions have been carried out. The level of doses considered in these studies are generally considerably higher than those in diagnostic exposed population (Fig. 5), but, for sites far

from the treatment site, these studies still remain informative for low-to-moderate dose radiation epidemiology. Risk from internal radiotherapy has been also studied (Adams et al., 2010; Kitahara et al., 2019), but is not reviewed here, as the main focus of the present doctoral thesis is on external medical radiation exposure. Table 7 lists the largest studies conducted to date in populations exposed to external therapeutic irradiation for benign conditions. Treatment of tinea capitis, a cutaneous fungal infection of the scalp nowadays treated only with antifungal drugs, was performed with ionising radiation in various countries and, in particular, in Israel between 1948 and 1960. At that time, the Israeli Ministry of Health treated all the children immigrating from North-Africa and the Middle East suffering from this disease with irradiation. A tinea-capitis cohort was also assembled in the US (patients treated between 1940-1959) (Shore et al., 2003) but with lower sample size. In Sweden, two cohort of patients followed up after irradiation for haemangioma were established (Lindberg et al., 1995; Lundell and Holm, 1996). In the middle of the 20th century, Ankylosis Spondylitis (an inflammatory disease which involves the spine joints) was also treated with radiation and a follow up of these patients was set up in the US (Weiss et al., 1994) and in the UK (Darby et al., 1987). Other relatively smaller studies conducted in populations exposed to radiotherapy for benign disease are reviewed elsewhere (UNSCEAR, 2006).

2.1.2 Radiotherapy for cancer treatment

Shortly after the discovery of radioactivity, Marie Curie founded the first cancer treatment institute (Institut Curie, 2019) and IR started to be applied for cancer treatment. Today it is an important contribution in increasing cancer survival rate, in adults as well as

in children and adolescents. The increasing number of cancer survivors has raised concerned among clinicians and public health expert around possible late effect in such population. Studies of atomic bomb survivors and of other populations exposed to IR have clearly shown that radiation can be particularly harmful for children who are more sensitive to IR-induced long term effects and have longer life spans to develop late-effect (UNSCEAR, 2013), thus there is greatest interest in the follow up of this paediatric population. In addition, considering the continuous increase in CCSs rate, there is a clinical and public health interest in establishing adequate follow up guidelines to reduce the burden of late health effects in this population (Armenian and Robison, 2013; COG, 2018; Haupt et al., 2018; Jankovic et al., 2018).

Radiation effects after cancer radiotherapy during childhood have been studied in numerous studies, and they have been extensively reviewed (Berrington de Gonzalez et al., 2013; Morton et al., 2014b; National Research Council (U.S.), 2006; UNSCEAR, 2006).

2.1.2.1 Childhood Cancer Survivors: public health and clinical concern

Childhood cancer survival rates are rising, thanks to the enormous advance in treatment (Gatta et al., 2014, 2005). Today, in high income countries, survival rates at five years are around 80% (Trama et al., 2016). There is therefore an increasing public health concern about the long term health and well-being of this population, which has been exposed early in life to aggressive treatment, including IR. Secondary cancers, cardiovascular effects, endocrine effects, cognitive effects are some of the major late effects that this population may experience later in life (COG, 2018; PDQ Pediatric Treatment Editorial Board, 2002). A long term

medical follow up of this population is recommended for survivors both in terms of physical and mental health (Jain et al., 2019; Reynolds et al., 2019). Radiation epidemiologists can work jointly with clinicians in setting-up this surveillance, which should involve different professionals in the field of cancer care. Actually, CCSs experience late effects not only due to radiation but also related to other types of treatment (surgery, chemotherapy agents), to the cancer itself and related to patient specific characteristics. An epidemiological follow-up, jointly with a clinical follow-up, is of particular interest, as it can be informative to inform on the appropriate preventive actions to be implemented (Bhatia et al., 2015).

2.1.2.2 Current ongoing large studies and main findings

Table 8 lists current major follow up studies of CCSs currently active. Additional effort is ongoing at the European and International level to build large consortia bringing together national or regional CCSs cohorts (Bhatia et al., 2015; Grabow et al., 2018; Tikellis et al., 2018; Winther et al., 2015). A variety of health outcomes has been addressed in previous studies, which have substantially contributed to raising the knowledge of the health effects experienced by this population, and to improving clinical follow-up guidelines. Indeed, such population is at risk of various health outcomes, as result, not only of the radiation treatment, but also other type of treatment or of the complication related to the tumor itself. Table 9 listed potential health effects that have been associated to putative therapeutic agents.

2.1.2.3 Research questions of interest for radiation epidemiologist in CCSs follow up

Radiotherapy for cancer treatment delivers very high dose to the target organ; however, the dose to organs out of field can be in the range of low-to-moderate doses (from close to 0 in organs far away from the target up to 5 Gy for organs close to the target, while the dose to the organ in the field is of the order of 50-60 Gy). Thus, studies on cancer survivors are informative for radiation protection both in the high dose range, where there is a need to better characterize the shape of the dose response when dose is fractionated (Berrington de Gonzalez et al., 2013), and in the low-to-moderate dose range, outside of the radiation field for various outcomes of interest.

It is also important to understand how risk estimates may vary in such very complex exposure setting, in which children are exposed to a variety of risk factors related to treatment (chemotherapy, surgery) or medical conditions (genetic variants, concomitant medical conditions) which may affect their long-term health. Finally, studies of CCSs are important to compare short- and long-term risks across different radiotherapy modalities. The continuous evolution of radiotherapy modalities (e.g. the recent advancing in using proton therapy) challenges radiation epidemiologists and clinicians to evaluate long term safety and outcome of these treatment procedures.

2.1.3 Childhood Cancer Survivors in the present thesis

Within this doctoral thesis, I have coordinating the setting-up of a hospital-based cohort of CCSs in Barcelona, and I am pursuing efforts with the Working-Group on Long Term Effects of the Sociedad Española de Hemato-Oncologia Pediátrica (SEHOP,

Spanish Society of pediatric oncology) to build a nationwide CCSs study, which could contribute to the monitoring long term effects in the framework of European and National collaborations. We presented two posters on the topic at SEHOP meetings (2016, 2019) which can be found in the Annex II of the present thesis. In this thesis I present a draft of the research article describing the hospital based study (*Manuscript V*, Chapter IV), as well as a descriptive analysis of the mental health status in this population, which should be further explored by enlarging the cohort and completing collection of treatment data.

Table 6: Characteristic of main studies in medical radiation epidemiology

Reference	Study population	Outcomes	Collection of procedures and dose estimation	Methodological Strength/limitation
UK CT-cohort (Berrington de Gonzalez et al., 2016; Pearce et al., 2012a)	Cohort of 178,587 patients undergoing a pediatric CT scan	Leukemia, Brain cancer	**Collection**: CT scan procedures were collected retrospectively using the electronic record radiology information (RIS). **Dosimetry:** Absorbed dose was estimated using typical machine setting parameters using in UK during the study period	-Very large sample size -Ascertainment of cases based on hospital record/tumor registry -Impact of underlying medical conditions: The subsequent paper by Berrington et al. took in to account predisposing conditions. Limitations in individual dosimetry – doses assigned from look-up tables based on typical machine settings
Tuberculosis fluoroscopy cohort: **US (Massachussets):** (Boice et al., 1978; Davis et al., 1989; Little et al., 2016); **Canada:** (Howe, 1995; Miller et al., 1989; Zablotska et al., 2014) **Combined:** (Tran et al., 2017)	Cohort of patients receiving Multiple fluoroscopy for TB treatment: US: 6,282 irradiated + 7100 non-irradiated Canada: 64,172	Cancer and non cancer (cardiovascular) mortality.	**Collection:** medical record review. **Dosimetry**: Based on information on the beam quality, patient orientation, and imaged anatomy obtained from physician interviews and medical record abstraction.	-Large sample size and long term follow up -Uncertainty in dosimetry
Case control	412 matched case-	Acute	**Collection:** Self-reported based	Potential for biases as information

Reference	Study population	Outcomes	Collection of procedures and dose estimation	Methodological Strength/limitation
studies of cancer and diagnostic X-rays (Los Angeles County) (Pogoda et al., 2011; Preston-Martin et al., 1988; Preston-Martin and Pogoda, 2003)	controls pairs	myeloid leukaemia and parotid gland cancer	on an in-person interview **Dosimetry:** Dose for each procedure was estimated from values collected in the literature	on radiological history was self-reported Relatively high uncertainty in the dose estimation
US case control study of leukaemia, lymphoma and multiple myeloma (Boice et al., 1991)	1121 cases + 1390 controls		**Collection:** Medical record review of the procedures registered in the Kaiser Permanente health insurance plan. **Dosimetry:** None. Analysis by number of procedures	Potential for biases as medical record review did not cover the whole lifetime of the subject (median age at entry in the Kaiser health plan was 45 year)
Oxford Survey Childhood Cancer (Bithell and Stewart, 1975)	15300 case-control pairs of childhood cancer	Paediatric cancer	**Collection:** Mother-reported radiological examination during pregnancy further validated (Stewart et al., 1958). **Dosimetry:** None (comparison by number of examinations)	Possible recall bias, however data validation at hospital level was performed (Stewart et al., 1958) Lack of dosimetry, however less problematic as pelvimetry back in time was quite standardised procedure

Table 7: Main epidemiological studies on populations receiving external radiotherapy for benign conditions

Reference	Study population	Outcome	Dose reconstruction	Methodological Strength/limitation
Israeli tinea capitis (Sadetzki et al., 2011, 2006, 2005; Vered et al., 2016)	10,834 patients treated between 1948 and 1960 in Israel for tinea capitis (mainly children, newly arrived immigrants from North Africa and to a lesser extent from the Middle East were treated for tinea capitis by irradiation by the Israeli ministry of health)	Cancer (brain, thyroid) Non-cancer (mental diseases, dental pathologies)	Retrospective dose reconstruction based on medical record review	Large sample size Ascertainment of cases based on hospital records/tumor registry Uncertainty in dosimetry for specific sites (thyroid)
Swedish Haemangioma cohorts (Goteborg and Stokholm) (Blomstrand et al., 2014; Eidemüller et al., 2015; Hall et al., 2004; Lindberg et al., 1995; Lundell and Holm, 1996)	11,807 Children treated with irradiation for cutaeous haemangioma in Sweden between 1930 and 1965	Cancer (brain, breast, thyroid) and non-cancer (cognitive effects)	Retrospective dose reconstruction based on medical records review	Large sample size Ascertainment of outcome based on hospital record/nationwide registry (tumour registry, cognitive results from military testing)
Ankylosing spondilitis patients (Weiss et al., 1994)	15,577 ankylosing spondylitis patients diagnosed between 1935 and 1957 in the UK	All cancer mortality	Retrospective dose reconstruction based on medical records review (only for 1 in 15 patients dose was reconstructed)	Limited dosimetry

Table 8: Ongoing major Childhood Cancer Survivors follow up studies

Cohort	Size	Coverage	Reference
US cohort of CCSS	First enrolment: 14,000 Second enrolment: 10,000	First enrolment: 5-year survivors of childhood and adolescent cancer diagnosed between 1970 and 1986. Second enrolment: 5-year survivors diagnosed and treated between 1987 and 1999	(Childhood Cancer Survivor Study, 2007; Robison et al., 2009)
French Childhood Cancer Survivor Study (FCCSS)	12 000 (6000 more to be enrolled)	All 5 years survivors diagnosed between 1946-1999, aged 0-19	(Allodji et al., 2019)
British Childhood Cancer Survivor Study (BCCSS)	34490	All 5 years survivors diagnosed between 1940-2006, aged 0-14 years old	www.bccss.bham.ac.uk
The Dutch Childhood Oncology Group (DCOG) LATER study,	6168	All 5 years survivors diagnosed between 1963-2002, aged 0-17	www.skionlaterstudie.nl/english/
The Adult Life After Childhood Cancer in Scandinavia (ALiCCS) Denmark Finland Iceland Norway Sweden	33160	All 1 year survivors diagnosed between 1943-2008 when they were 0-19 years old	(Asdahl et al., 2015) www.aliccs.org

Swiss Childhood Cancer Survivor Study (SCCSS).	4405	All 5 years survivors from 1976 when they were 0 to 20 years old	www.childhoodcancerregistry.ch
Italian Study on off-therapy Childhood Cancer Survivors (OTR)	3029 (1000 more to be enrolled)	All 2 years survivors from 1980 aged 0-18 at the time of cancer	(Winther et al., 2015)

Table 9: List of adverse effects related to cancer treatment in childhood

Treatment group	**Therapeutic agents**	**Health effect**
Any	Any cancer experience	Adverse psychological/quality of life; Mental health disorder; Risky behaviour; Fatigue/ sleep problems; Limitation in health care and insurance access
Chemotherapy	Alkylating agents	Testicular/Ovarian dysfunction; Reduced ovarian follicular pool/Impaired spermatogenesis; Acute myeloid leukaemia/ Myelodysplasias; Pulmonary fibrosis; Cataracts; Bladder malignancy; Renal toxicity
	Anthracycline Antibiotics	Acute myeloid leukaemia/ Myelodysplasias; Cardio-toxicity
	Anti-tumour Antibiotics	Pulmonary toxicity
	Antimetabolites	Neurodevelopmental deficits; Hepatic dysfunctions; Reduced bone mineral density; Clinical leukoencephalopathy
	Any chemotherapy	Dental abnormalities

Treatment group	Therapeutic agents	Health effect
	Corticosteroids	Reduced bone mineral density; Osteonecrosis; Cataracts
	Epipodophyllotoxins	Acute myeloid leukaemia/ Myelodysplasias
	Heavy metal	Ototoxicity; Peripheral sensory neuropathy; Renal toxicity
	Plants Alkaloids	Peripheral sensory neuropathy; Vasospastic attacks
Hematopoietic cell transplants	Graft versus host disease	Xerophtalmia; Oral toxicity; Pulmonary toxicity; Immunological complications; Functional asplenia; Esophageal stricture; Vaginal fibrosis/stenosis; Joints contractures
	Hematopoietic cell transplants	Acute myeloid leukaemia/ Myelodysplasias; Secondary neoplasm; Hepatic dysfunctions; Osteonecrosis; Reduced bone mineral density; Renal toxicity
Other treatment	Blood transfusion	Hepatitis B, C and HIV infections (diagnosis prior 1985)
	Systemic radiation (I131)	Hypothyroidism
	Systemic radiation (MIBG)	Hypothyroidism; Thyroid nodules
Radiation	All fields	Secondary neoplasm; Dermatologic toxicity
	Brain/cranium	Neurodevelopmental deficits; Brain tumours; Clinical leukoencephalopathy; Cerebrovascular complications; Craniofacial abnormalities; Chronic sinusitis
	Breast	Breast cancer; Breast tissue hypoplasia

Treatment group	Therapeutic agents	Health effect
	Ear	Ototoxicity
	Eye	Cataracts; Ocular toxicity
	GI/Hepatic system	Esophageal stricture; Diabetes mellitus; Dyslipidemia; Hepatic dysfunctions; Cholelitiasis; Bowel obstruction; Chronic enterocolitis; Colorectal cancer
	Heart	Cardiotoxicity
	Lungs	Pulmonary toxicity; Lung cancer
	Muscolar system	Musculoskeletal growth problems; Scoliosis; Radiacion induced fractures
	Neck/Thyroid	Thyroid nodules; Thyroid cancer; Hypothyroidsm; hyperthyroidsm; Carotid artery disease; Subclavian artery disease
	Neuroendocrine axis	Overweights/Obesity; Growth hormon deficit; Precosious puberty; Hyperprolactinemia; Central hypothiroidism; Gonadotropine deficiency; Central adrenal insufficiency
	Oral cavity	Xerostomia, salivary gland dysfunction; Dental abnormalities; Osteonecrosis
	Reproductive system	Testicular/Ovarian dysfunction; Reduced ovarian follicular pool/Impaired spermatogenesis; Uterine vascular insufficiency; Vaginal fibrosis/stenosis
	Spleen	Functional asplenia
	Urinary tract	Renal toxicity; Urinary track toxicity; Bladder malignancy

Treatment group	Therapeutic agents	Health effect
Surgery	Amputation	Reduced mobility
	Central venous catheter	Thrombosis, Vascular insufficiency
	Enucleation	Impaired cosmesis; Orbital hypoplasia
	Hysterectomy	Pelvic floor dysfunction; Urinary incontinence; Sexual dysfunction
	Laparotomy	Bowel obstruction
	Nephrectomy	Renal toxicity
	Neurosurgery (Brain)	Neurodevelopmental deficits; Seizure; Hydrocephalus; Overweight/Obesity; Diabetes insipidus
	Neurosurgery (Spinal cord)	Urinary incontinence; Fecal incontinence; Psychosexual dysfunction; Scoliosis
	Pelvic surgery	Urinary incontinence; Fecal incontinence; Psychosexual dysfunction
	Splenectomy	Asplenia
	Thoracic surgery	Pulmonary dysfunction; Scoliosis
	Thyroidectomy	Hypothyroidism
Adapted from (COG, 2018)		

3 THE EFFECTS OF LOW DOSE IONIZING RADIATION EXPOSURE

There is major public and radiation protection interest in better understanding the effects of radiation at low levels of dose, in the general and working environments and, in particular, in medicine. To date, for radiological protection, international standards and recommendations are based on cancer risk using the Linear No-Threshold Hypothesis (LNT) (ICRP, 2007b, 2005). However, there is still uncertainty regarding the magnitude of cancer risk from low doses of IR (McLean et al., 2017a; National Research Council (U.S.), 2006; Richardson et al., 2015; Salomaa et al., 2013; UNSCEAR, 2018) and factors which may modify the risk (Kreuzer et al., 2017; Salomaa et al., 2013).

In recent decades, the body of evidence concerning non-cancer effects of radiation has grown rapidly, in particular for cataracts and vascular effects at moderate doses in the range 500 mGy to 2 Gy. There is still uncertainty about both the existence of an effect at low-to-moderate doses and about the possible mechanisms of induction of these effects. The issue is very important as radiation protection standards, apart from those related to dose to the eye (recently revised following the observation of an increased risk of lens opacities in Ukrainian clean-up workers), are mainly based on cancer risk.

Undoubtedly, it is important to reduce uncertainty around risk estimates for our society (McLean et al., 2017b; MELODI, 2015).

In the following paragraph we will review some of the main studies wich have been informative and mostly contributing to the current knowledge around radiation induced cancer. This list is not meant to be exhaustive, and studies reporting radiation risk have been

extensively reviewed (Bernier et al., 2015; Doll and Wakeford, 1997; Kleinerman, 2006; Krille et al., 2012; Linet et al., 2012, 2009; Mulvihill et al., 2017; National Research Council (U.S.), 2006; UNSCEAR, 2008b).

3.1 Cancer effects

The fact that cancer may be induced by IR was first observed among the first radiation workers, including Marie Skłodowska-Curie and other pioneers who died from leukaemia and other radiation induced injuries. An increased risk of leukaemia was also observed among early radiologists (Linet et al., 2005; March, 1950; Mohan et al., 2003), as well as an increased incidence of bone cancer (sarcoma) in radium dial painters, young women who painted fluorescent clock dials with radium containing paint and who ingested radium as they licked the point of their brush to make it finer (Polednak et al., 1978; Rowland et al., 1978).

However, the scientific evidence concerning the magnitude of radiation induced cancer risk came mainly from the observation of the among atomic bomb survivors cohorts.

3.1.1 Evidences from the atomic bomb survivors study

The life span study (LSS) cohort includes around 120,000 atomic bomb survivors and was assembled in the 1950s by the Atomic Bomb Casualty Commission (ABCC) and now mantained by the Radiation Effects Research Foundation (RERF). The aim of the study is to investigate late health effects of atomic bomb radiation and its trans-generational effects (Ozasa et al., 2019, 2018). The majority of survivors in this cohort (around 97%) received doses lower than 1 Gy. The LSS has several strengths including: the large sample size, the long follow up (1950-up to now), an

extensive and detailed estimation of dose, high quality mortality data since the 1950s and cancer incidence data since the mid-1970s. Subjects were exposed in different ages, including during foetal life, allowing testing for effect modification with age at exposure. Regarding cancer risk estimation after IR exposure, the key findings of the atomic bomb survivors study are:

- Increase risk of leukaemia with increasing dose to the bone marrow (best fit by a linear-quadratic dose-response function). Leukaemia has also a much higher relative risk per unit dose relative to solid cancer (Hsu et al., 2013)
- Increase risk of solid cancer (all combined) with increasing dose to the stomach (linear dose-response) (Ozasa et al., 2012).
- Among solid cancer the highest ERR/Sv was found for female breast cancer and thyroid cancer following childhood exposure. Dose-related increases have also been observed for many other cancer types including cancers of the bladder, lung, brain, thyroid gland, colon, esophagus, ovary, stomach, liver and skin (excluding melanoma) (National Research Council (U.S.), 2006; Ozasa, 2016) and central nervous system tumours (Preston et al., 2002).
- Increase of leukaemia risk was started to seen 2 years after the bombing and peacked at 6-8 years after the bombing. For solid cancer, increase risk was started to be observer later (10 years) after the bombing and still today found to be elevated (Ozasa et al., 2019).
- Analyses of the LSS study have clearly shown that, for many cancers, exposure in childhood entails a higher risk per unit dose than exposure later in life (Preston et al., 2003; UNSCEAR, 2013).

3.1.2 Evidence from studies on non-medically exposed population

While the atomic bomb study populations were the main basis for radiation protection standards in the past, recent decades have seen a number of publications from large scale populations with low dose protracted exposures suggesting an increased risk at low doses. Indeed, additional evidence of radiation induced cancer effect comes also from large nuclear workers cohort studies. In the occupational setting, exposure is protracted during life and cumulative doses are low, thus exposure context is different from the single-time whole body exposure received by the atomic bomb survivors. Effort was done to build large international nuclear workers cohort studies to obtain sufficient statistical power to detect an effect, if any. An increase ERR for leukaemia was found in a recent study on 308,297 workers (Leuraud et al., 2015). Increased ERR of solid cancer was also reported in the former large cohort analysis and in the re-analysis of this sub-cohort (Cardis 2007, Richardson 2019).

The follow up of populations exposed to radioactive contamination of the Techa river from the Mayak plutonium facility (Davis et al., 2015), and of the Chernobyl cleanup workers (Kashcheev et al., 2015) have also shown an increased risk of cancer, in line with the atomic bomb survivor study. Table 10 summarizes results of cancer risk estimates from major studies conducted in non-medically exposed populations.

3.1.3 Evidences from studies on medically exposed populations

Results of risk estimates from studies conducted in medically exposed population (for diagnostic or treatment purpose) have

been summarized in Table 11 (Characteristic of these studies were outlined above in Table 6 and 7).

The Oxford Survey of Childhood Cancers (OSCC), a case-control study exploring the effect of prenatal diagnostic irradiation and cancer in offspring (Bithell and Stewart, 1975), was the first study to show a statistically significant increase cancer risk at very low doses (10mGy). Such results have been under debate for several years, because they were based on self-reported number of X-ray examinations, thus uncertainty around doses was particularly high. However, radiation protection experts have been particularly receptive to the results of the OSCC study, resulting in a drastic drop of numbers of X-ray procedures in pregnant women. In subsequent studies, foetal doses were consequently much lower and risk estimation were not statistically significant (Linet et al., 2009). The cohort studies of people receiving fluoroscopy for tuberculosis follow up show an increase risk for breast cancer, but generally not for other cancer sites (Davis et al., 1989; Miller et al., 1989). Recently, the results coming from the UK paediatric CT-scan cohort show an ERR/Gy higher than what should be expected from the atomic bomb survivors estimations (Pearce et al., 2012a). This has raised criticism around possible reverse causation bias or confounding by indication (Boice, 2015). However, a recent reanalysis excluding predisposing conditions, resulted in generally lower, but overall comparable ERR estimations (Berrington de Gonzalez et al., 2016).

Large studies have been conducted in survivors of benign condition treated with radiotherapy (i.e. tinea capitis (Sadetzki et al., 2005), and childhood haemangioma (Karlsson et al., 1998)). The doses, here, are relatively higher respect of the previous listed studies (Fig. 5). In the Israeli tinea capitis study (Sadetzki et al., 2005), an

increase RR for brain cancer was reported, consistent with the atomic bomb survivors study. Also increase cancer risk of leukaemia and all cancer except leukaemia were shown in the Ankylosis Spondylitis study (Weiss et al., 1995, 1994).

Considering all the current evidence coming from epidemiological studies on medically exposed populations, overall, we can conclude:

- Studies conducted in medically exposed population have been informative for the estimation of cancer risk at low dose radiation level. Overall, the risk is small and compatible with the atomic bomb survivors risk estimation.
- Regarding diagnostic medical exposure, the OSCC provided evidence for an increase risk even at very low level of dose (Doll and Wakeford, 1997). Recent CT-scan cohort studies are also showing an increase risk at relatively low dose level (Berrington de Gonzalez et al., 2016; Huang et al., 2014; Journy et al., 2016; Mathews et al., 2013; Meulepas et al., 2019; Pearce, 2011). Other case-control studies conducted on medical diagnostic procedures have generally been less informative (Boice, 2015; Preston-Martin and Pogoda, 2003).
- The body of evidence from epidemiological studies, conducted in population exposed to low dose level, support the linear non threshold model of cancer risk, the model on which the whole radiation protection system is currently based.

Table 10: Main informative studies in low dose radiation research (excluding studies of medically exposed populations)

Population (ref)	Organ dose distribution	ERR/Gy for select cancer site	Relative risk at 100 mGy
Atomic bomb survivors (Grant et al., 2017; Ozasa et al., 2018)	45% below 5 mGy; 15% above 100 mGy; 2.6% above 1000 mGy ; Mean weighted colon dose= 30.8 mGy (Grant et al., 2017)	**Solid cancer (mortality):** ERR/Gy (95% CI) 0.47 (0.38; 0.56) (Ozasa et al., 2012) **Leukaemia** ERR/Gy= 3.10 (1.80; 4.30)	**Solid cancer** RR= 1.05 (1.04; 1.06) **Leukaemia** RR=1.3 (1.18; 1.43)
Nuclear workers (Cardis et al., 2007, 2005; Leuraud et al., 2015; Richardson et al., 2015)	Individual cumulative dose (mGy) : **colon** : mean 20.9 ; median 4.1; maximum 1332 (Richardson et al., 2015) **Bone marrow:** mean 15.9; median 2.1 (Leuraud et al., 2015)	All cancer excluding leukaemia: ERR/Sv= 0.48 (0.20, 0.79) (Cardis et al., 2005) (Richardson et al., 2015) ERR/Gy=2.96 (90% CI 1.17; 5.21) (Leuraud et al., 2015)	**All cancer excluding leukaemia:** RR= 1.05 (1.02; 1.08) **Leukaemia excluding CLL:** RR= 1.30 (1.17; 1.52)
Chernobyl liquidators (Kashcheev et al., 2015)	Median 102 mGy , the maximum dose is 1,240 mGy, and the minimum dose is 0.1 mGy	**All cancer incidence:** ERR/Gy= 0.47 (95 % CI 0.03; 0.96)	**All cancer** RR= 1.05 (1.003; 1.09)
Techa River residents (Davis et al., 2015; Krestinina et al., 2013)	Median 15 mGy (90 percentile 121 mGy)	For **all solid cancer**: ERR/Gy = 0.77 (95% CI 0.13-1.50); For **leukaemia** excluding CLL: ERR/Gy= 2.2 (95% CI 0.80–5.40)	RR for solid cancer= 1.08 (1.01; 1.15) RR for leukaemia= 1.22 (1.08; 1.54)

ERR: In radiation epidemiology, risk estimates are usually reported as Excess Relative Risk (ERR) which represent the excessive risk respect to the background risk and it is defined as ERR= RR- 1.

Table 11: Results from main epidemiological studies on medically exposed population

Population (ref)	**Organ dose distribution**	**Main results**	**Relative risk at 100 mGy** (if not otherwise specified)
Diagnostic medical radiation			
UK-CT-cohort (Berrington de Gonzalez et al., 2016; Pearce et al., 2012a)	**Bone marrow:** Mean (range): 11 mGy (0-50) **Brain:** Mean (range): 43 mGy (0-350)	**Brain cancer:** ERR/Gy= 23 (10; 49); after excluding predisposing condition: ERR/Gy=19 (8; 43) after excluding previous cancer: ERR/Gy= 16 (6; 37) **Leukaemia:** ERR/Gy= 36 (5; 120); after excluding previous cancer ERR/Gy= 33 (4; 114) No changes after excluding predisposing conditions	**Brain cancer:** RR= 3.3 (2.0; 5.9); after excluding predisposing conditions RR = 2.9 (1,8; 5.3) **Leukaemia:** RR= 4.6 (1.5; 12.0); after excluding previous cancer RR= 4.3 (1.4; 12,4)
Case control studies on exposure to diagnostic X-rays (Pogoda et al., 2011; Preston-Martin et al., 1988; Preston-Martin and Pogoda, 2003)	16 % with bone marrow dose above 1000 mGy	**Acute myeloid leukaemia:** No evidence for an increase risk **Parotid gland:** Positive significant association	**Parotid gland:** Relative risk for dose greater than or equal to 500 mGy = 3.4 (CI 1.02-11.46)
US case control study of leukaemia, lymphoma and multiple myeloma (Boice et al., 1991)	Number of X-rays used as exposure variable	No statistically significant association reported for lymphoma and leukaemia (CLL and non-CLL). Statistically significant increase risk of multiple myeloma was reported for receiving multiple X-rays	RR of **multiple myeloma** for receiving more than 4 procedures= 3.9 (CI not reported)

Population (ref)	**Organ dose distribution**	**Main results**	**Relative risk at 100 mGy** (if not otherwise specified)
Tuberculosis fluoroscopy cohort: US (Massachussets): (Davis et al., 1989); Canada: (Miller et al., 1989)	**US:** Mean dose to the: Breast = 800 mGy; Lung= 750 mGy; and active bone marrow= 90 mGy. **Canada:** Mean lung dose 1020 mGy (0; 24,200). Mean breast dose varied across region 2100 mGy in Nova Scotia and 790 mGy in other regions	**US: Breast cancer** mortality was increased (SMR = 1.4, n = 62). **Lung cancer** (SMR = 0.8, n = 69) and **leukaemia** (SMR = 1.2, n = 17) were not. **Canada:** Significant dose-response relationship for **breast cancer**. No increase risk for **lung cancer**	In the Canadian study: RR for **breast cancer** mortality = 1.36 (95% CI 1.11; 1.67)
Oxford SCC (Bithell and Stewart, 1975)	Approximately 10 mGy (foetal dose for an abdominal X-ray) (up to 5 radiography (~50 mGy)	OR for **all childhood cancer** =1.39 (1.30-1.49) (foetal exposure to maternal abdominal x-ray versus not)	No ERR model
Therapeutic medical radiation (benign)			
Israeli tinea capitis (Sadetzki et al., 2005)	Mean brain dose 1.5 Gy	Malignant brain tumour ERR/Gy= 1.98 (0.73-4.69)	**Malignant brain tumour** RR= 1.2 (1.07; 1.7)
Swedish Haemangioma cohorts (Goteborg) (Lindberg et al., 1995)	Mean thyroid dose= 120 Gy Mean brain dose:=77 Gy	ERR/Gy for **thyroid cancer**= 7.5 (CI 95% 0.4-18.1). ERR/Gy for **brain cancer**= 10.9 (CI 95% 3.7-20.5)	**Thyroid cancer** RR = 1.75 (1.04; 2.81) **Brain cancer** RR = 2.09 (1.37; 3.05)
Swedish Haemangioma cohorts pooled analysis (Karlsson et al., 1998)	Brain dose mean (range) 70 mGy (0- 11500 mGy)	**Brain cancer** ERR/Gy = 2.7 (95% CI 1.0-5.6).	**Brain cancer** RR = 1.27 (1.1; 1.56)

Population (ref)	**Organ dose distribution**	**Main results**	**Relative risk at 100 mGy** (if not otherwise specified)
Ankylosing Spondylitis patients (Weiss et al., 1995, 1994)	Mean total body dose 2640 mGy (860-4620) Brain: 200 mGy (30-400)	**All cancer** except leukaemia ERR/Gy= 0.11 (95% CI 0.04; 0.18) **Leukaemia** (no-CLL) ERR/Gy=12.4 (2.3; 52.1)	**All cancer except leukaemia** RR = 1.01 (1.004; 1, 02) **Leukaemia** RR = 2.24 (1.23; 6.52)

3.1.4 The dimension of the risk: expected number of cancer cases caused by medical radiation exposure

In the previous section, we reviewed risk estimates from epidemiological studies conducted in medically exposed populations (Tables 6, 7, and 11). Overall, they suggest that the risk coming from radiological procedures is small, however not null even at very low doses, and this is also supported by the current body of evidence from low dose studies (including the LSS, the nuclear workers studies and the study of the Techa River).

It is important to note that, for a risk benefit analysis from an individual point of view, when a procedure is well justified, the health risk of not undergoing the procedure may be much higher than the subsequent cancer risk from having it.

However, considering the large number of exposed individuals, even a small increase of risk can be translated in a large number of cancers. Thus, from a public health point of view, dose should be kept as low as possible; to reduce the future number of cases attributable to exposure to IR. In this sense, continuous effort to optimize the dose results in a reduction of individual risk associated with radiation exposure.

It has been estimated that, in developed countries, the proportion of total cancer attributable to previous medical radiation exposure range between 0.6% in the UK and 3.2% in Japan (Berrington de González and Darby, 2004a). On average, 700 cancer cases in UK, 5695 in US, 2049 in Germany and 7587 in Japan are expected, each year, to be due to medical diagnostic IR exposure (Berrington de González and Darby, 2004b). In Spain, it has been estimated that for the number of paediatric CT performed in 2013 (105,802 CT) about 168 cancer cases (95% Credibility Intervals: 30

- 421) are expected in the lifetime of the subjects exposed (Bosch de Basea et al., 2018). Around 64 cancer cases (90% Uncertainty Intervals: 38; 113) are expected to be induced by the 130,750 scans performed in the year 2015 in the UK (Journy et al., 2017).

3.1.5 Biological mechanisms

From a biological point of view, radiation induced cancer has been traditionally explained using the classical biological framework of the "DNA-target effect", which has been used as the logical basis for the linear-non threshold hypothesis. Briefly, IR tracks are capable of inducing a non-lethal DNA mutation through a direct (radiation ionize directly DNA) or indirect (ionization of water molecules generate reactive oxygen species which damage the DNA) mechanism. If the unrepaired mutation results in a non-lethal modification of genes involved in the control of regulatory cells pathways (such as the cell cycle, induction of apoptosis), the cells can start uncontrolled proliferation, which may in turn undergo additional mutations and generate a tumour mass. There is no evidence that at low dose radiation the mechanism of DNA damage is different from the one described above, which is the one postulated for high dose radiation, though the type and efficiency of DNA repair may differ between high and low doses (Hall et al., 2017).

DNA damage is not the only mechanism by which IR may influence cancer risk, however, and the recent decades have seen a lot of research on non-targeted effects of radiation, including genomic instability (Huang et al., 2003), bystander effect, adaptive response (Kadhim et al., 2013). While all of these mechanisms have been found to be radiation-induced, it is not clear which of these are active following low doses of IR, nor how they all combine, together

with DNA mutation, to affect cancer risk (Burtt et al., 2016). Figure 9 aims to illustrate target and non-target mechanism of radiation induced biological effects.

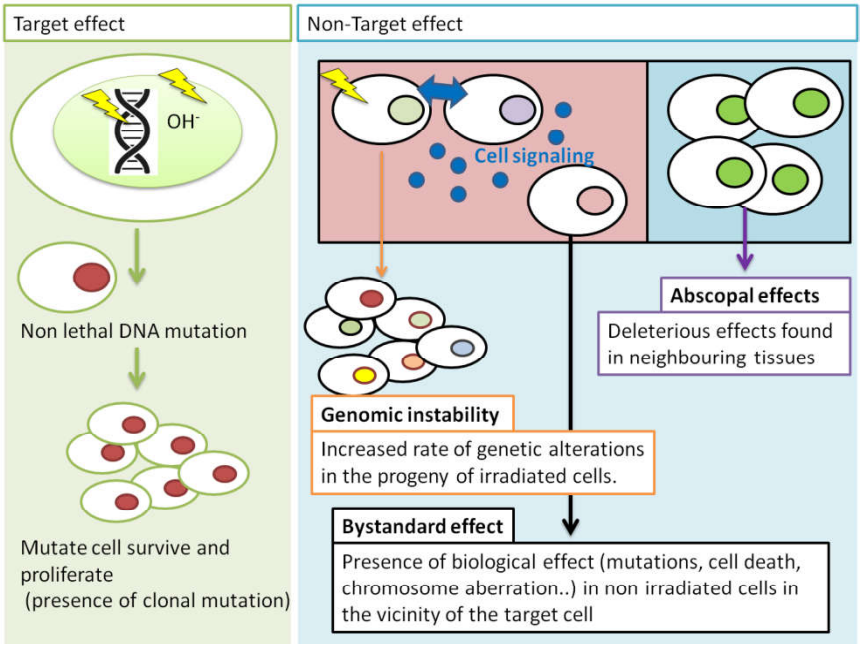


Figure 9: Biological effect of IR (target and non-target). Figure adapted from (Kadhim et al., 2013)

3.1.6 Dose response shape

As reviewed above, the current epidemiological evidence suggests that the relationship between radiation dose and subsequent cancer is linear (or linear quadratic) without threshold.

The linear non-threshold model (LNT) (curve "*a*" in Fig. 10) has been the object of debate for many decades. The consequence of an erroneous assumption of the LNT might be an increase cost of radiation protection (in case the true risk is lower, curve "d" or "c" in Fig. 10) or an insufficient radiation protection system (in case the true risk is higher, curve "b").

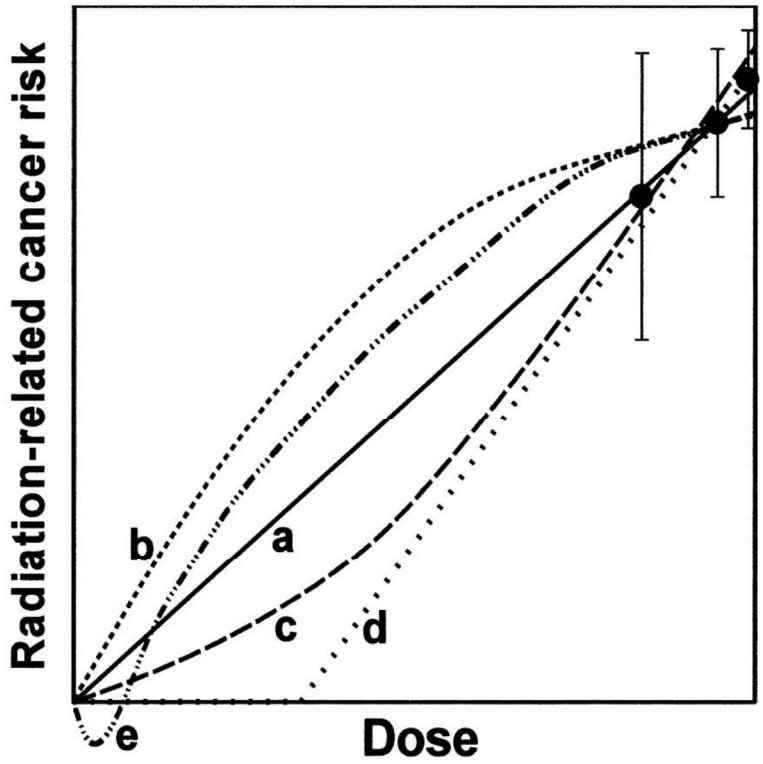


Figure 10: Dose-response curves compatible with the data from epidemiological studies.
Figure from (Brenner et al., 2003)

In favour of the non-linear threshold dose response, the integration of epidemiological and biological observation gives important argument, known as the "biophysical argument":

- At 10 mGy dose at the level of the organ, there is epidemiological evidence of an increased risk (Doll and Wakeford, 1997).
- At 10 mGy, few electron tracks may cross cell nuclei (Box b in Fig 10) and it is hard to imagine that electron track can act in a cooperative way in this situation, as the chance that they hit together the same structure are very low (Brenner et al., 2003).
- At dose lower than 10 mGy, even fewer electron tracks will cross the cells and we can also exclude that there is any type

of interaction between electrons tracks that cross cells (Box c in Fig 10).

- As a result, we expect a lower number of interactions of the electron track with the DNA with the decreasing levels of dose and consequently a fewer number of DNA damage.
- Thus, the chance of carcinogenesis at lower dose decreases (because the number of interactions with DNA decreases), but even one radiation track could lead to cancer.

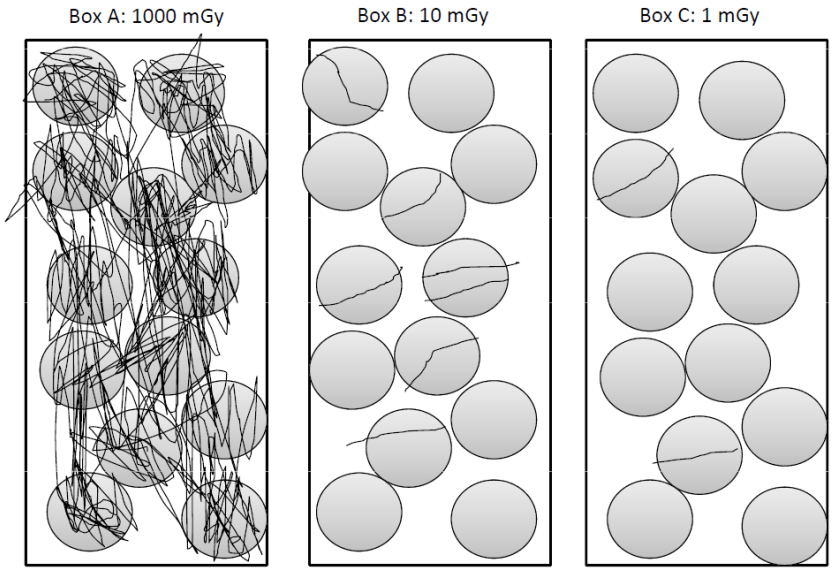


Figure 11*: Illustration of the biophysical argument.*
Circles represent cells, line represent electron tracks.
Adapted from Brenner 2015 (presentation at Radiation epidemiology and dosimetry course at NCI).

Though the biophysical argument provides clear support for LNT, the actual magnitude of the carcinogenic effect at low doses is currently unknown, as it also depends on the dose-dependence of all other, non-targeted, dose-dependent effects of IR. It is therefore difficult, purely from the biological point of view, to draw conclusions concerning the resulting effect. Large, careful epidemiological studies of populations having received low doses

of IR are still, currently, the most relevant approach for directly estimating risk.

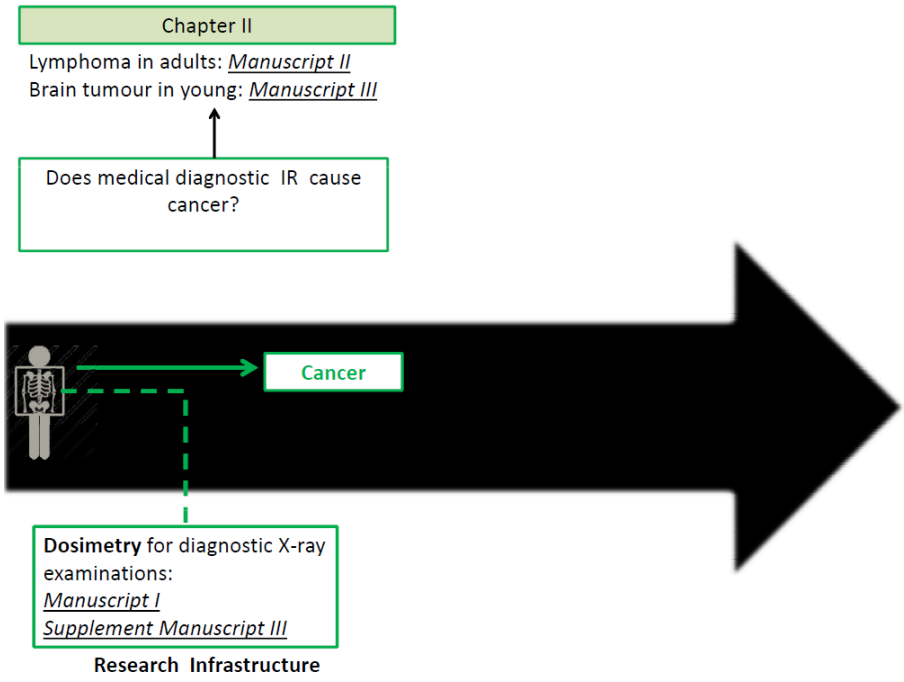
3.1.7 Cancer effect explored in the present thesis

In the present thesis we explored the risk of brain cancer in young people and of lymphoma in adults after exposure to diagnostic medical IR within two case-control studies with very similar methodology. Both are large international case control studies with common core protocols in which self-reported medical radiological history was collected in an in-person interview. In both studies we aimed to estimate radiation risk using the dose to the target organ, instead of using the number of reported examinations, the approach commonly used in similar case control studies in radiation epidemiology.

3.2 Non cancer effects

Apart from cancer, there is growing evidence that radiation may cause cataracts, cardiovascular, immunologic, metabolic, endocrine and cognitive effects even at low doses. The study of such effects is currently considered a priority in radiation protection (Kreuzer et al., 2017). The present thesis focused on neurodevelopmental effects, through 1) a systematic review (*Manuscript IV*, Chapter III) that summarized the current evidence concerning the possible neurodevelopmental effects of low dose IR exposure; 2) the setting up and conduct of a study on neurodevelopmental effects of low-to-moderate doses of radiation among CCSs treated for a tumour other than in the central nervous system. The study is ongoing and the protocol can be found in Chapter III.

CHAPTER II: Diagnostic X-ray and cancer



Manuscript I

Trends in estimated thyroid, salivary glands, brain and eye lens doses from intraoral dental radiography over seven decades (1940 to 2009)

R.C. Fontana, **E. Pasqual**, D.L. Miller, S.L. Simon, E. Cardis, I. Thierry Chef

Accepted in Health Physics (30 May 2019)

Fontana RC, Pasqual E, Miller DL, Simon SL, Cardis E, Thierry-Chef I. Trends in Estimated Thyroid, Salivary Gland, Brain, and Eye Lens Doses from Intraoral Dental Radiography over Seven Decades (1940 to 2009). Health Phys. 2020 Feb 1;118(2):136–48. DOI: 10.1097/HP.0000000000001138

Manuscript II

Association of ionizing radiation exposure from common medical diagnostic procedures and lymphoma risk in the Epilymph case-control study.

Elisa Pasqual, Michelle C Turner, Esther Gracia-Lavedan, Delphine Casabonne, Yolanda Benavente, Isabelle Thierry Chef, Marc Maynadié, Pierluigi Cocco, Anthony Staines, Lenka Foretova, Alexandra Nieters, Paolo Boffetta, Paul Brennan, Elisabeth Cardis, Silvia de Sanjose.

Under review in PLOS ONE (submitted on 1 March 2019)

Pasqual E, Turne MC, Gracia-Lavedan E, Casabonne D, Benavente Y, Chef IT, et al. Association of ionizing radiation dose from common medical diagnostic procedures and lymphoma risk in the Epilymph case-control study. PLoS One. 2020 Jul 1;15(7 July 2020). DOI: 10.1371/journal.pone.0235658

Manuscript III

Exposure to medical radiation during fetal life, childhood and adolescence and risk of brain tumor in young age: results from the MOBI-kids study

Elisa Pasqual, Gemma Castaño-Vinyals, Isabelle Thierry-Chef, Noriko Kojimahara, Malcolm R Sim, Michael Kundi, Daniel Krewski, Franco Momoli, Brigitte Lacour, Thomas Remen, Katja Radon, Tobias Weinmann, Eleni Petridou, Maria Moschovi, Rajesh Dikshit, Siegal Sadetski, Milena Maule, Mariangela Farinotti, Mina Ha, Andrea 't Mannetje, Juan Alguacil, Nuria Aragonés, Roel Vermeulen, Hans Kromhout, Elisabeth Cardis

Under review in Neuroepidemiology

Pasqual E, Castanõ-Vinyals G, Thierry-Chef I, Kojimahara N, Sim MR, Kundi M, et al. Exposure to Medical Radiation during Fetal Life, Childhood and Adolescence and Risk of Brain Tumor in Young Age: Results from the MOBI-Kids Case-Control Study. Neuroepidemiology. 2020;54(4). DOI: 10.1159/000506131

Manuscript IV

The neurodevelopmental effects of low dose ionizing radiation exposure: a systematic review

Elisa Pasqual; Magda Bosch de Basea, Mónica López-Vicente, Isabelle Thierry-Chef, Elisabeth Cardis

Under review in Environment International

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Pasqual E, Bosch de Basea M, López-Vicente M, Thierry-Chef I, Cardis E. Neurodevelopmental effects of low dose ionizing radiation exposure: A systematic review of the epidemiological evidence. Environ Int. 2020 Mar;136:105371. DOI: 10.1016/j.envint.2019.105371

Research Protocol I

COGNITO study protocol: Evaluation of cognitive effect in a population of Childhood Cancer Survivors

Elisa Pasqual, Lourdes Arjona, Anna Saló-Rovira, Laura Mangado-Aloy, Luís Gros Subias, Soledad Gallego Melcón, Ofelia Cruz Martinez, Elisabeth Cardis

COGNITO Study Protocol:

Evaluation of cognitive effect in a population of Childhood Cancer Survivors

I. Summary

Introduction
It is well known that cranial radiotherapy is a risk factor for late neurocognitive impairment (Ki Moore, Hockenberry, and Krull 2013; Ullrich and Embry 2012). Neurocognitive effects of non-cranial radiotherapy have been not well studied, however the prevalence of cognitive impairment in non brain cancer survivors is estimated to be around 12-82% (Williams, Janelsins, and van Wijngaarden 2016).
Among radiation protection expert, the potential effect of low-to-moderate ionizing radiation dose on cognitive function is underdebate (Abayomi 2002; Kadan-Lottick et al. 2010; MELODI 2015). Such levels of dose might be absorbed in the context of a non-cranial irradiation therapy.
Methodos
We plan a cognitive evaluation in a group of childhood cancer survivors. Inclusion criteria are: a) Having received a dose below 500 mGy; b) Having survived at least 5 years from the primary cancer; c) brain childhood cancer survivors are excluded.
Global cognition, memory, executive functions, attention will be evaluated. Results from the tests will be correlated with the dose received in different brain anatomical structure. The dose will be estimated from the treatment planning records.
Objectives
Primary objectives:
a) Assess global intelligence, memory, executive functions, and attention in non-brain childhood cancer survivors
b) Estimate the association between different domains of the cognitive functions and the dose absorbed in different anatomical structure

II. Introduction

Childhood cancer survivors are at higher risk of a wide range of different health effects(Armstrong et al. 2014), including cognitive dysfunction (Mulhern et al. 2004).
Studies in survivors of brain tumor and leukaemia have identified the following risk factors for a cognitive deficit: cranial radiotherapy, intratecal chemotherapy, age at the time of the treatment, and clinical complication related to the cancer (hydrocephalus) (Ki Moore, Hockenberry, and Krull 2013; Ullrich and Embry 2012; Wolfe, Madan-Swain, and Kana 2012).
There is a paucity of literature among cognitive sequaele in survivors of solid tumors (non brain), however there is evidence that this population is at risk of late cognitive sequelae (Sleurs et al. 2016; Kadan-Lottick et al. 2010; Abayomi 2002).
Very few studies have specifically evaluated the association between the IR dose received in different anatomical parts of the brain and the score of different cognitive tests (Packer et al. 2003; Armstrong et al. 2010; Doger de Speville et al. 2017), none evaluating low-to-moderate IR doses.

III. Hypothesis

We hypothetize that radiotherapy at low-to-moderate dose level could have an impact on cognitive function.

IV. Objetives

Primary objectives	a) Assess global intelligence, memory, executive functions, and attention in non-brain childhood cancer survivors b) Estimate the association between different domains of the cognitive functions and the dose absorbed in different anatomical structure
Secundary Objectives	f) Evaluate the impact of variable related to the cancer itself (clinical complications) or of other treatment variables on the cognitive functions h) Evaluate the association between cognitive function and quality of life in CCCS.

V. Organization

ISGlobal_ Epidemiology and Statistics. Dr. Elisabeth Cardis is the Principal Investigator (PI) and coordination of the study will be carried out by Elisa Pasqual. Lourdes Arjona will coordinate all the field work.

Hospital Vall Hebron: Contact, recruitment of patients treated in Vall Hebron. Conduction of the neuropsychological evaluation. Collection of medical records. Participatns department are: Oncohematología pediátrica, Radioterapia y Física medica

Hospital Sant Joan de Deu: Contact, recruitment of patients treated in Vall Hebron. Conduction of the neuropsychological evaluation. Collection of medical records. Participants department are: Oncohematología pediátrica
Istitute Gustave Roussy: Dosimetry

VI. Study design

Design: Cross-sectional observational study

Inclusion criteria:
- Childhood cancer survivors (at least 5 year from the first cancer diagnosis)
- Brain tumor survivors will be excluded
- Free of baseline neurological diseases

VII. Procedures

Selection
Subjects are selected among the patients that have been treated in the Paediatric Haemato-oncology department of Hospital Vall Hebron and Hospital Sant Joan de Deu between 1980 and 2012.
- The study will be presented by the nurse/ medical doctor in charge of the long-term follow-up of the patient. A Brochure explaining the study will be printed.
- All patients wishing to participate will sign an appropriate consent form (see annex). Parents of patients should sign the consent form (in case the child is less the 18 years old). From 12 years old the signature of the child is also required.
- Consent form will be stored in each participating hospitals and access limited to the investigator of the study.

Details

i. Cognitive evaluation

Cognitive evaluation is composed in two parts: a) Administration of neuropsychological tests, b) Assessment of psychological well being with self-reported questionnaire.

a) Neuropsychological test

	TEST (time)
IQ (Global cognition)	PMA-R (6 minutes) *
MEMORY	Test de Aprendizaje Verbal España-Complutense, Infantil. http://bi.cibersam.es/busqueda-de-instrumentos/ficha?Id=76 (Similar to the California Verbal Learning test)
EXECUTIVE FUNCTION	
Working memory	*N-back test* (10 minutos) *

Cognitive flexibility	*Trail making test part B* (5 minutos) *
Processing speed	*Trail making test part A* (3 min) *
	Flankers(15 min) *
ATTENTION	Ejemplo: *Flankers (10 minutos)* *

*Computerized Test Battery developed in IsGlobal within INMA (Infancia y medioambiente, http://www.proyectoinma.org) and BREATHE project (Forns et al. 2014)

b) Self-reported questionnaire

Psychiatric screening ***From 12 years of age***	*BSI scale (shorten version of SCL-90 family)* (Carlson and Bultz 2003) *(7 minutes)*
Stress related to traumatic event ***From 12 years of age***	**Impact of Event Scale (Version en Español)** ("Children's Revised Impact of Event Scale | Children and War" 2017) (10 minutes)

ii. Dosimetry

Radiotherapy treatment planning will be collected for each of the included patients. After having anonimized them, they will be sent to Institut Gustave Rousssy for the dosimetry. Dose to the whole brain, frontal, occipital, temporal and parietal lobe and hippocampus will be estimated.

VIII. Data Protection, Data Managment and Statistical analysis

Data Protection

For the purpose of this study, a database containing personal data (name of the patient, identification number within the health system) needs to be created. This database will be stored within the hospital and access strictly restricted to the investigators of the study. This data are needed for the collection of the treatment data and contact with patients.

Personal data will be protected according to the Spanish Law 15/1999 (Protección de datos de carácter personal). Note, from May 2018, we will take into account the changes according to the new EU directive (EU 2016/680).

If sata are needed to be transferred to other centres, data will be anonimized using a study identification code wich can be further linked to the personal data database.

Data management

The following databases will be created:

a) "*Basic clinical*":

This database contains personal data. This is the only database that stores the link between personal data and study identification number. This database must not be sent to othe collaborators centers.

b) *"Detailed clinical*"

Anonimized: Contain information on the clinical history and treatment.

c) "Follow up"

Contain information related to the participation in the study

d) *"Radiotherapy"*.

Contains the anonimized copies of the treatment planning.

e) "*Cognitive test*"

Contains results from the cognitive testing

Statistical analysis

Association between the cognitive outcomes and the absorbed brain dose will be evaluated using a multivariate linear regression model.

Challenges in this study include:

- Presence of multifactorial risk factors
- Multicollinearity of the treatment and cáncer related variables.
- Potential for selection bias
- Quality of medical records.

IX. Bibliografia

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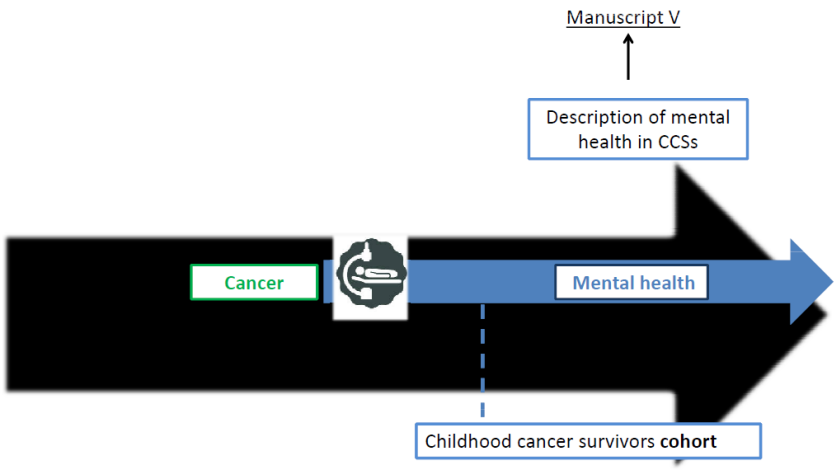
CHAPTER IV: Childhood cancer survivor cohort



Research Infrastructure

Manuscript V

Mental health in long term childhood cancer survivors in Spain: results from a hospital based cohort study

Elisa Pasqual; …..Isabelle Thierry-Chef, Elisabeth Cardis

In preparation

Aspects of mental health in childhood cancer survivors: results from a hospital-based cohort in Spain.

Author list:

Elisa Pasqual (ISGLOBAL), Agnes Dumas (INSERM), Lourdes Arjona (ISGLOBAL), Isabelle Thierry-Chef (ISGLOBAL), Laura Mangado (neuropsychologist HSJDD), Hector Salvador-Hernandez (MD, HSJDD), Miguel Angel Flores Taico (MD, HSJDD) , Genoveva Correa-Llano (MD, HSJDD). Ofelia Cruz-Martinez (HSJDD), Elisabeth Cardis (ISGLOBAL)

Target journal: As audience we want to target Spanish paediatric oncologists (or perhaps the wider European paediatric oncology audience… clinical audience anyways)

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Abbreviation list

CCSs	Childhood Cancer Survivor's
HSJDD	Hospital San Joan de Deu
MCS	Mental Component Score
MH	Mental Health
QoL	Quality of Life
RE	Role Emotional
SF	Social Functioning
VT	Vitality
GH	General Health
RP	Role Physical
PF	Physical Functioning
BP	Bodily Pain

Abstract

The advances in treatment and care of childhood cancer have resulted in an increased cancer survival rate. The growing number of childhood cancer survivors (CCS) in Europe requires appropriate long term follow-up, as they are at higher risk of different adverse health outcomes compared to the general population. Mental health is an important concern in this population and we aim here to describe the mental health status of a cohort of childhood cancer survivors set-up in Hospital San Joan De Deu in Barcelona, one of the major paediatric oncology centres in Spain.

All patients treated between 1980 and 2000 were contacted and invited to participate in a cohort study being set-up to study the long-term consequences of the cancer and its treatment in this population. Participation included, in particular, answering a questionnaire on quality of life (QOL), health status and socio-demographic factors. 500 questionnaires are included in the present analysis. Mental health (Mental Component Score) and the sub-component scales (Vitality, Mental Health, Role Emotional, Social Functioning) were measured using the SF-36 scale and the standardized z-score was chosen as the main outcome of interest.

Overall, the mean (interquartile range) of the Mental Component Score was 54.46 (48.21, 58.05) and is comparable with recent similar statistic of the US CCS study (CCSS). Brain tumour and nephroblastoma survivors tended to have a statistically significantly lower score (reference: leukaemia survivors). Taking any psychiatric or pain relief medication and reporting a worsening of physical health were all also associated with a lower score.

Adequate clinical and epidemiological follow up as well as targeted interventions are needed to improve the mental health of this population.

Introduction

Survival rates of childhood cancer survivors (CCS) are considerably improving thanks to the enormous advances in treatment (Allemani et al. 2018). For all childhood cancers, the survival rate in high income countries, is estimated to be around 80% (Gatta et al. 2014). In Europe, it has been estimated that the number of childhood cancer survivors currently alive is between 300,000 and 500,000 (Winther et al. 2015; Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board 2003). It has been shown that this population is at higher risk of developing late adverse health effect (Armenian and Robison 2013; Armstrong et al. 2014) and may require lifetime medical follow-up (Haupt et al. 2018; Jankovic et al. 2018; Tonorezos et al. 2018).

The World Health Organization defines health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1948). Mental health is an important component of well-being and the impact of mental health consequences in CCS is of clinical and public health concern. Poor mental health may be the result of the cancer related factors, the treatment received, or the current health and socioeconomic situation of the survivor (Zhang et al. 2018; Zeltzer et al. 2008). A recent systematic review (Friend et al. 2018) described the prevalence and the spectrum of mental health in cancer survivors and concluded that CCS are at risk of mental health problems late in adulthood. However, the exact prevalence and the risk factors related to poor mental health need further research (Friend et al. 2018). In addition, studies on mental health were mainly published from the US (34/67 found in (Friend et al. 2018)). 23 studies were found for European populations, mainly from Nordic countries. No study has yet been reported for Spain survivors, though around 900-1000 children are diagnosed with cancer, before the age of 15, each year in Spain (Peris-Bonet et al. 2010; Ferlay et al. 2013).

In the current paper we aimed to describe the aspects of mental health component and its four dimensions ("Vitality", "Social functioning", "Role emotional", "Mental health"), measured using the SF36 questionnaire (Ware 2000) in a Spanish hospital-based CCS cohort**.**

We also aimed to explore the association between demographic variables, first cancer diagnosis type and age, chronic diseases, socio-demographic factors and mental health in childhood cancer survivors.

Methods

The present analysis was conducted within the SPAIN-CCSS cohort study which currently includes a hospital based-cohort of long-term childhood cancer in one hospital only. Recruitment of survivors for the cohort study was performed between 2015 and 2017 at Hospital San Joan de Deu Hospital, in Barcelona, which has one of the largest paediatric oncology departments in Spain.

All patients treated for a cancer in the hospital between 1980 and 2010 (age at treatment < 20 years of age) having survived at least 5 years were invited to be enrolled in the cohort study. A letter was sent to all eligible patients by the oncologists and haematologists of the hospital informing them that a cohort study of cancer survivors was being set-up and asking them whether they were willing to be included. Mail address and personal identifier were obtained from the hospital database of treated patients, which also included information on the cancer diagnosis, the date of diagnosis and basic demographic characteristics (date of birth, sex).

Eligible patients were asked to give their consent to be enrolled in the cohort, including consent for access to their medical data, linkage of these data with population-based registries, abstraction of treatment data (including radiotherapy records and treatment planning charts) and other health data from their primary care physician, specialists and other hospitals. They were also asked whether they agreed to be further contacted for later, periodic follow ups. Along with the consent form and study information letter, a questionnaire on socio-demographic variables, health status, lifestyle factors and quality of life (SF-36) was sent and eligible and consenting patients were invited to complete it and return it to the hospital.

For the present analysis, we included all cohort members who completed the quality of life section of the questionnaire, that is, those who accepted to participate in the study and were alive at the time of the survey (2015-2017). The questionnaire could be completed by a next of kin, in particular in the case of younger children. Thus, among the very first questions of the questionnaire, we asked information about who completed the questionnaire and their relationship with the patient.

Assessment of the health status, education and employment status

Health related variables included in the current analysis were all extracted from the questionnaire.

The questionnaire included questions directed to the assessment of the health status. These questions were similar to the ones used in the UK ('BCCSS Study Documents - University of Birmingham' Web), French ('Study Methodology | FCCSS' Web) and US cohort studies ('Questionnaires US CCCs Study' Web).

Reporting "suffering from any chronic condition" was included as a general indicator of the overall health status. As an indicator of presence of psychiatric diseases, we used the information coming from three questions exploring if the participants was taking any of the main group of psychiatric drugs (antidepressant drugs, and depressant drugs, tranquilizers and drugs for sleeping). Common names of most common prescribed drugs in each group were also included in the question as examples. An additional free text question, asking the name of any drugs the participants were currently taking was also asked and free text was scanned for the present analysis. Additional psychiatric drugs were identified from the free text (mainly for ADHD treatment, or for one of the previous classes).

Reporting "taking any pain relief medication" was also asked in the questionnaire and the variable included in the analysis. Additional patients taking pain relief medication were identified thought the scanning of the free text questions on any other drugs treatment.

Average number of hours slept in the week previous to the completion of the questionnaire was also asked. Hearing impairment was also added as a variable of interest in the present analysis.

Questions on education and employment were asked at the end of the questionnaire. Participants were asked to indicate their level of education or their employment status, choosing an option from a list of possible situations. An additional cell for free text was also included and free text was scanned and information extracted.

Outcome: Mental health dimension of the Quality of Life

Quality of life (QoL) was measured using the SF-36 scale (Ware 2000), as done in other similar childhood cancer cohort studies (Fidler et al. 2015; Zeltzer et al. 2008). The SF-36 is considered a valid instruments to measure quality of life in childhood cancer survivors (Reulen et al. 2006). In this scale, 36 items were asked to explore the a) physical and b) mental dimensions of quality of life. In this article we aim to explore the mental health dimension.

The mental health component of QoL includes 14 items exploring four domains: Vitality (VT, 4 items), Mental health (MH, 5 items), Role emotional (RE, 3 items), and Social functioning (SF, 2 items). Vitality refers to the level of energy of the person (items are reported below in the example of the score calculation); the Mental Health domain gives a measure of a psychological wellbeing; the Role emotional domain measures the impact of the emotional health on daily activity, whereas the Social Functioning domain measure the overall impact of physical and mental health on the social life. All of these domains can also be combined into one score, the Mental Component Score (MCS).

As outcome, in the present analysis, we used the standardized z-score of the MCS and of each one of the above mentioned domains. We outline below all the steps of the calculations of the scores (Ware 1994).

First a *Transformed score* ranging from 0 to 100 for each domain (VT, MH, RE, SF) was derived using the following formula:

- a *raw score* for each domain was calculated by summing over the score in each item of each domain;
- From the *raw score* a transformed score was calculated as following:

$$Transformed\ score = \frac{Raw\ score - Minimum\ possible\ raw\ score}{Raw\ score\ range} * 100$$

The above score was calculated for subjects who answered at least 50% of the questions for each dimension. Among these, the value of missing questions was imputed by assigning to them the mean value of the non-missing questions (in each dimension) for the particular participant. As an example, the VT domain was explored with 4 items, specifically the participant was asked if they were feeling: i) Full of life; ii) having a lot of energy; iii) worn out; or iv) tired. Each items had six possible responses referring to the time frequency of that feeling ranging between "Never" and "Always". A score from 1 to 6 was derived, where the higher score always indicated better health. If one or two of the four outcomes were missing, we imputed to that outcome the overall mean calculated over the non-missing outcomes. Then we calculate the Transformed score for the VT domain as explained above:

$$Transformed\ score\ (VT) = \frac{Raw\ score - 4}{24 - 4} * 100$$

As an additional step we calculated a z-score standardization of the "Transformed Score" for each domain. We used the actual study population mean and standard deviation for the standardizations, as population mean for Spanish paediatric population is not currently available ('BiblioPRO - BiblioPRO' 2019).

$$Domain\_z\_Score = \frac{Transformed\ score - Mean\ of\ the\ Transformed\ score}{Standard\ Deviation\ of\ the\ Transformed\ score}$$

Once the z-score was obtained for each domain of quality of life (including the physical domains), we calculated the MCS with the following formula,:

$$\begin{aligned} Aggregate\ Score \\ &= ((PFz * -0.22999) + (RPz * -0.12329) + (BPz * -0.09731) \\ &+ (GHz * -0.01571) + (VTz * 0.23534) + (SFz * 0.26876) \\ &+ (REz * 0.43407) + (MHz * 0.48581)) \end{aligned}$$

where VTz, MHz, SFz and REz represent the z score of the above mention domains of the Mental Component, whereas PFz, RPz, BPz, GHz are z score of the domain of the Physical Health Component (Physical Functioning, Role Physical, Bodily Pain and General Health respectively). The last step consisted in transforming the aggregate score by normalising it to a score with mean 50 and standard deviation 10 (MSC= 50 + (Aggregate Score*10)). The score of each sub-domain (Vitality, Mental Health, Role Emotional, Social Functioning) was also normalized to a score with mean 50 and SD 10. The following outcomes were then analysed in this paper: Normalised score of the Mental Component Score and of each mental health domain: Vitality, Mental health, Role emotional and Social functioning.

The R code of all the calculations steps are provided in the supplementary material.

Statistical analysis

We explored the association between demographic, lifestyle and clinical related variables and mental health on a continuous scale using a linear regression. All analyses were performed in R (R Core Team 2016).

The variables tested for association with the outcomes were: (i) demographic variables: sex, age at survey completion; (ii) clinical baseline variables: age at diagnosis and type of first cancer diagnosed (Leukaemia, Central Nervous system, Lymphoma, Nephroblastoma, Neuroblastoma, Retinoblastoma, Sarcoma and an additional category including all other the cancer types). As clinical variables at follow-up we used: (i) Having at least one chronic disease; (ii) Having hearing impairment; (iii) Taking psychiatric medication; (iv) Taking any pain relief medication. The "health transition question" of the SF-36 (How is your health compared to one year ago?) was also tested for association. This item of the SF-36 has five possible answers: (i) Much better; (ii) Better; (iii) Same; (iv) Worst; (v) Much worst. We derived a categorical variable with three levels (No change, improving and worsening health). As a lifestyle variable, the sleep quality, measured as average number of hours of sleep per day, was also added to the model. As a socio-demographic variable the occupational status of the index subject at follow up was tested. Occupational status was defined as follow: studying or employed, unemployed, unemployed because of poor health status. Educational level was not included, in the regression model, because the wide age range of participants challenges the interpretation of this variable; however a descriptive analysis of this important variable is provided, stratified by age group.

RESULTS

Participation rate

2023 patients were identified within the hospital database. Of these, 1478 were diagnosed with a first cancer 5 year before the survey date and were contacted by the hospital. Of these, 475 could not be reached, 338 did not answer and 104 refused to participate.

We received 540 completed questionnaires. Of these, we excluded 32 as we did not received a completed consent form, 4 because found to be duplicated, 2 because follow up was found to be shorter than 5 years, one because the subject was not alive at the moment of the survey (questionnaire filled by next of kin). One more questionnaire was excluded because of missing in date of birth. Thus, we analyzed a total of 500 questionnaires.

Table 1 details the characteristic of the study population. Overall there were slightly more males (53.2%) then females. The most common first cancer diagnosis was Central nervous system cancer (24%) followed by Leukemia (22%). Median (inter-quartile range) age at diagnosis was 5 years (2-10). Median (min max) follow up was 22 years (5-50). Thus, mental health was assed mostly in young adult (inter-quartile range of age at follow up 15-29 years). 28% of participants reported suffering from at least from one chronic disease and 9% reported taking psychiatric medication at the moment of the questionnaire: in particular 5.8% were taking depressant drugs and 3.2%

antidepressants. Five participants reported hearing impairment. On average, participants reported 8 hours of sleep. 21(4%) perceived a worsening of their health status during the past year.

Educational attainment and occupational status is reported in Table 2, stratified according to age at follow up. In particular we reported educational attainment and occupational status for the subset of participants who were over 16 years old (age when compulsory education ends in Spain) and over 22 (age when university degree is usually obtained). At 16 years of age, the majority had completed compulsory education (9.5% reported a lower level of education). At 22 years of age, around 20% of the sample reported being unemployed, of these, 46% reported that this was related to some health conditions.

Table 1: table of study participants characteristics

	Overall N (%) or median [IQR]	**Number of missings**
n	500	
Sex = Male	266 (53.2)	
Age at diagnosis	5.00 [2.00, 10.00]	
Age at follow-up	22.00 [15.00, 29.00]	
Decade of diagnosis		
1980-1989	91 (18.2)	
1990-1999	120 (24.0)	
2000-2009	289 (57.7)	
Duration follow up (Years)	13.00 [9.00, 22.00]	
First cancer diagnosis		7 (1.4)
Leukaemia	112 (22.4)	
Central nervous system tumors	121 (24.2)	
Lymphoma	52 (10.4)	
Nephroblastoma	26 (5.2)	
Neuroblastoma	31 (6.2)	
Retinoblastoma	14 (2.8)	
Sarcoma	52 (10.4)	
Other	86 (17.2)	
Any chronic disease	142 (28.3)	35 (7.0)
Taking any psychiatric medication	46 (9.2)	17 (3.4)
Taking any depressant drug	29 (5.8)	18 (3.6)

	Overall N (%) or median [IQR]	**Number of missings**
Taking any anti-depressant drug	16 (3.2)	18 (3.6)
Taking pain relief medication	186 (37.1)	17 (3.4)
Average hours of sleeping/day	8.00 [7.00, 9.00]	
Hearing impairment	5 (1.0)	18 (3.6)
Health status respect previous year		8 (1.6)
Unchanged	376 (75.2)	
Improved	95 (19.0)	
Worsened	21 (4.2)	
Education		43 (8.6)
Pre_primary	5 (1.0)	
Primary	78 (15.6)	
lower_secondary	99 (19.8)	
upper_secondary	180 (35.9)	
university degree or above	56 (11.2)	
others	39 (7.8)	
Employment		54 (10.8)
Employed/studying	383 (76.6)	
Unemployed due to medical condition	27 (9.7)	
unemployed	36 (7.2)	
Questionnaire filled by mother/father	139 (27.8%)	
when participants < 15 years old	102 (73%)	
>15 years old	37(26%)	

Table 2: Education and employment by attained age

	≥ 16 years of age N (%)	**≥ 22 years old N (%)**
n	369	257
Education		
Pre_primary	4 (1.1)	2 (0.8)

	≥ 16 years of age N (%)	≥ 22 years old N (%)
Primary	31 (8.4)	21 (8.2)
Secondary (compulsory)	85 (23.0)	45 (17.5)
High schools	178 (48.2)	130 (50.6)
University degree or plus	56 (15.2)	53 (20.6)
Others	10 (2.7)	3 (1.2)
Missing	5 (1.4)	3 (1.2)
Employment		
Employed/studying	292 (79.1)	193 (75.1)
Unemployed due to medical condition	26 (7.0)	25 (9.7)
Unemployed	36 (9.8)	29 (11.3)
Missing	15 (4.1)	10 (3.9)

Median (inter-quartile range) of the Mental Component score was 54.46 (48.21, 58.05). Median for each domain of the mental aspect of the QoL were 52.26 (43.28, 56.75) for Mental health, 51.95 (44.83, 56.70) for Vitality, 54.61 (54.61, 54.61) for Role emotional and 55.38 (48.17, 55.38) for Social Functioning. These scores are comparable or slightly higher than those estimated within the large US cohort of CCS and in the US general population (Table 3). Comparison with the Spanish general population was not possible because of lack of data ('BiblioPRO - BiblioPRO' 2019). Figure 1 shows the distribution of scores, which is very skewed to the right, in each of the domains under study. Most of the participants achieved good scores in the domains of Role Emotional and Social Functioning, and these domains present very little variability.

We checked correlations between each component of the QoL and the two component score (Physical and Mental health) in Fig 2. Physical Functioning, Role Physical and Bodily Pain were strongly correlated with the Physical Component Score and less with the Mental Component Score. In contrast, Mental Health, Role Emotional, Social Functioning were strongly correlated with the Mental Component Score. Vitality and General Health were moderately correlated with both Mental and Physical Component. Physical Component Score and Mental Component Score were very poorly correlated (0.04).

Table 3: Median and IQ range of the mental health component of QoL, measured using the SF-36 questionnaire

	Overall median [IQR]	**Number of missings**
Mental Component - this study	54.46 [48.21, 58.05]	23
- US CCSS study (mean (95% CI)	49.43 (49.14; 49.72)	Ref: (Zeltzer et al. 2008)
- US general population (mean (95% CI)	48.79 (48.06; 49.51)	
Mental Health subdomain - this study	52.26 [43.28, 56.75]	15
- US CCSS study (mean (95% CI)	55.20 (54.96; 55.44)	Ref: (Zeltzer et al. 2008)
- US general population (mean (95% CI)	48.86 (48.13; 49.58)	
Vitality subdomain - this study	51.95 [44.83, 56.70]	12
- US CCSS study (mean (95% CI)	44.43 (44.16; 44.70)	Ref: (Zeltzer et al. 2008)
- US general population (mean (95% CI)	49.32 (48.63; 50.01)	
Role Emotion subdomain - this study	54.61 [54.61, 54.61]	15
- US CCSS study (mean (95% CI)	47.22 (46.85; 47.59)	Ref: (Zeltzer et al. 2008)
- US general population (mean (95% CI)	50.87 (50.21; 51.53)	
Social functioning subdomain - this study	55.38 [48.17, 55.38]	9
- US CCSS study (mean (95% CI)	49.42 (49.18; 49.66)	Ref: (Zeltzer et al. 2008)
- US general population (mean (95% CI)	50.41 (49.73; 51.09)	

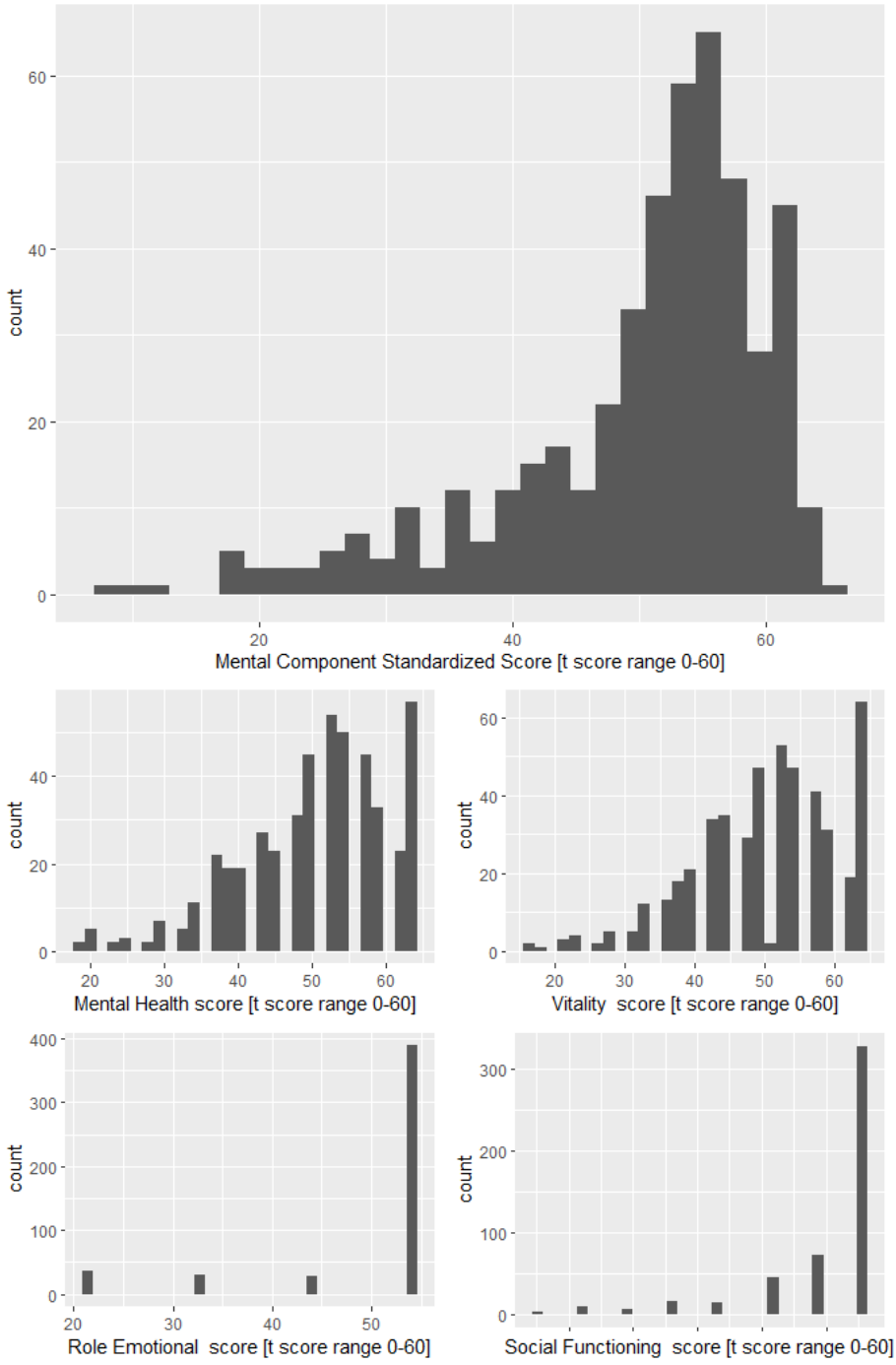

Figure 1: Distribution of Mental Component Score and each sub-domain: Vitality, Mental Health, Role of Emotion, and Social Functioning.

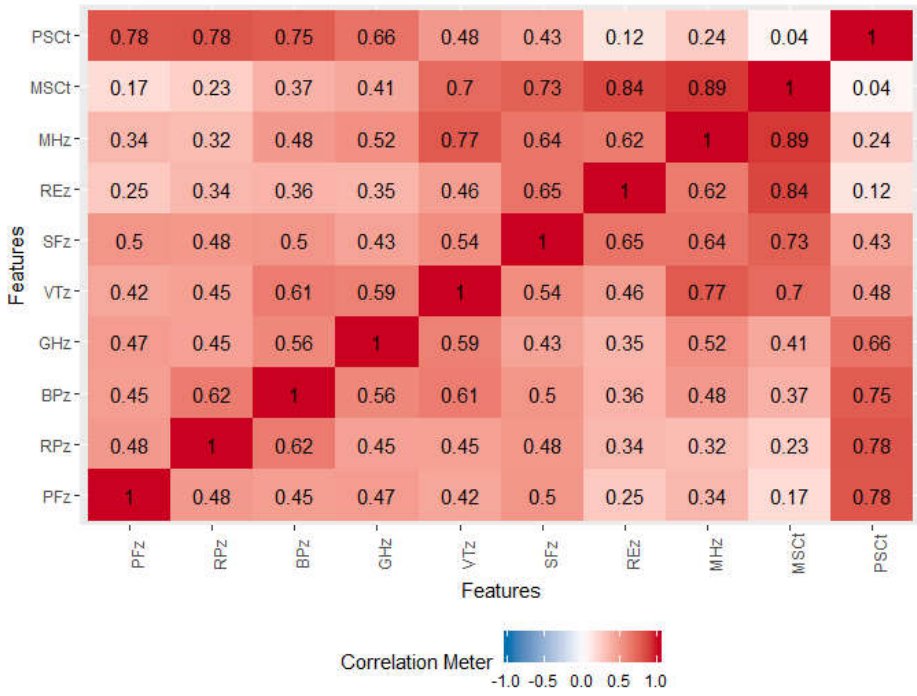

Figure 2: Correlation matrix for each component for the QoL scale
Legend:
Physical health: **PFz** Physical Functioning z score; **RPz** Role Physical zeta score; **BPz** Bodily Pain z score; **GHz** General Health z score;
Mental Health: **VTz** Vitality z score, **SFz** Social Functioning z score, **REz** Role Emotional z score; **MHz** Mental Health z score;
Component Scores: **MSCt** Standardized Mental Component Score; **PSCt** Standardized Physical Component Score.

Table 4 and Figure 3 show the beta coefficients for two linear regression model using MSC as outcome. The first, basic model uses only basic demographic characteristics and baseline clinical variable as predictors. Follow up variables (clinical and socio-demographic) are added in the second, fully adjusted model. In the basic model, increasing attained age (i.e. age at the time the questionnaire was completed), central nervous system cancer, neuroblastoma and other cancers were statistically significantly associated with a worst MSC score. Similar results were observed in the fully adjusted model (Figure 3) though only the associations with central nervous system cancer and neuroblastoma, remained statistically significant after adjustment for follow-up variables.

In the fully adjusted model, reporting a worse the health status than the previous year, taking any psychiatric medication, and being unemployed (not due to a medical condition) were negatively associated with the MSC component score, while sleeping more hours was associated with a better MSC score.

Similar results were obtained when using MH and VT as outcomes (Table 5, Figures 4 and 5). Models using RE and SF as outcomes was not run as there was little variability in the scores of these variables (Figure 2). Having been diagnosed with a CNS tumor or a neuroblastoma was associated with worst MH and VT scores. Better VT score was found among the participants with a diagnosis of retinoblastoma. Having reported any chronic disease or a worsening of the health status was associated with lower VT and MH score. Reporting taking any psychiatric or pain relief medication was also associated with worst MH and VT score. Hearing impairment was also statistically significant associated with lower VT score. Being unemployed was associated with lower VT and MH score, but not when unemployment was related to medical condition. Better VT and MH score was found among participants reporting sleeping higher numbers of hours.

Table 4: Association between Mental Component Score and cancer related and follow up variables. Beta coefficients of two linear regression model (basic and full) adjusted for the listed variables are reported

	N	Basic model[1] β [95% CI]	N	Full model[2] β [95% CI]
N	470		382[3]	
Females	222	Ref	187	Ref
Males	248	0.71 [-1.15, 2.57]	195	0.64 [-1.35, 2.63]
Attained age < 15	97	Ref	61	Ref
Attained age 15-29	**251**	**-5.18 *** [-7.81, -2.54]**	212	-1.93 [-5.59, 1.73]
Attained age >29	**122**	**-6.54 *** [-9.53, -3.56]**	109	-2.57 [-6.61, 1.46]
Age at diagnosis < 5	213	Ref	163	Ref
Age at diagnosis 5-15	215	0.14 [-2.15, 2.43]	180	-1.14 [-3.57, 1.28]
Age diagnosis >15	42	1.14 [-2.60, 4.88]	39	1.43 [-2.33, 5.19]
Leukemia	107	Ref	94	Ref
CNS	**116**	**-3.93 ** [-6.64, -1.23]**	**42**	**-2.87 * [-5.67, -0.07]**
Lymphoma	50	-2.49 [-6.09, 1.11]	44	-0.84 [-4.44, 2.77]
Nephroblastoma	25	-0.40 [-4.89, 4.08]	20	-2.00 [-6.67, 2.67]
Neuroblastoma	**28**	**-5.88 ** [-10.18, -1.58]**	**24**	**-4.97 * [-9.34, -0.60]**
Retinoblastoma	14	3.25 [-2.61, 9.11]	6	4.51 [-3.47, 12.49]
Sarcoma	50	-0.61 [-4.13, 2.92]	42	1.55 [-2.08, 5.18]
Other cancers	**80**	**-3.08 * [-6.07, -0.08]**	60	-2.40 [-5.53, 0.73]
Any chronic disease			118	-1.79 [-3.98, 0.39]
Better health compared to 1 year before			**73**	1.67 [-0.80, 4.14]
Worst health compared to 1 year before			**17**	**-9.81 *** [-14.86, -4.76]**
Taking any psychiatric medication			**34**	**-9.17 *** [-12.70, -5.64]**
Taking any pain relief				-1.68

	N	Basic model[1] β [95% CI]	N	Full model[2] β [95% CI]
Auditive impairment			154	[-3.71, 0.35]
			3	-0.43 [-11.54, 10.69]
Average 6-8 hours of sleep/day			146	5.73 [-0.00, 11.46]
Average >8 hours of sleep/day			**224**	**7.15 * [1.46, 12.83]**
Unemployed			**27**	**-5.93 ** [-9.74, -2.13]**
Unemployed with subsidy (medical)			23	3.30 [-1.05, 7.65]
Questionnaire filled by a next of kin			75	2.42 [-0.86, 5.71]

*** p < 0.001; ** p < 0.01; * p < 0.05.

1 Model adjusted for Sex, age at diagnosis, age at follow up, cancer diagnosis type

2 Model adjusted for Sex, age at diagnosis, age at follow up, cancer diagnosis type, suffering any chronic condition, self-perceived health status (compared to one year ago), taking psychiatric medication, taking pain medication, number of hours of sleeping/day, employment status, and a dummy variable that identify if the questionnaire was filled by the patient or a next of kin.

3 88 cases were excluded because of missing information on one or more of the adjustment variables

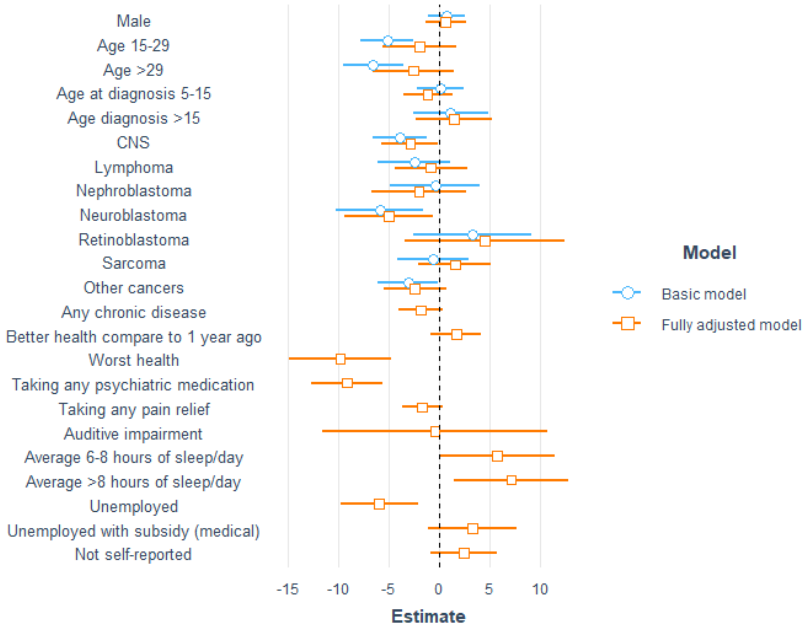

Figure 3: Association between Mental Component Score and cancer related and follow up variables

Table 5: Association between Mental Health and Vitality domains and cancer related and follow up variables. Beta coefficients of two linear regression model (basic and full) adjusted for the listed variables are reported

	Mental Health		Vitality	
	Basic model β [95% CI]	Full model β [95% CI]	Basic model β [95% CI]	Full model β [95% CI]
N	478	385	481	386
Male	1.09 [-0.64, 2.82]	0.92 [-0.86, 2.70]	0.66 [-1.05, 2.37]	0.94 [-0.79, 2.67]
Age <15	Ref	Ref	Ref	Ref
Age 15-29	**-5.38 *** [-7.79, -2.96]**	-2.35 [-5.57, 0.87]	**-6.05 *** [-8.44, -3.66]**	-3.62 * [-6.75, -0.49]
Age >29	**-6.10 *** [-8.86, -3.35]**	-2.30 [-5.87, 1.26]	**-6.64 *** [-9.37, -3.92]**	-3.19 [-6.66, 0.27]
Age at diagnosis < 5	Ref	Ref	Ref	Ref
Age at diagnosis 5-15	0.13 [-2.00, 2.25]	-1.31 [-3.46, 0.85]	0.71 [-1.40, 2.81]	-0.62 [-2.72, 1.48]
Age diagnosis >15	0.58 [-2.92, 4.08]	-0.11 [-3.48, 3.26]	0.72 [-2.76, 4.19]	1.00 [-2.28, 4.27]
Leukaemia	Ref	Ref	Ref	Ref
CNS	**-3.91 ** [-6.40, -1.42]**	**-2.64 * [-5.15, -0.14]**	**-3.93 ** [-6.41, -1.46]**	**-3.07 * [-5.51, -0.64]**
Lymphoma	-1.78 [-5.14, 1.58]	-0.09 [-3.32, 3.14]	-1.63 [-4.95, 1.68]	-0.65 [-3.79, 2.50]
Nephroblastoma	-0.96 [-5.14, 3.22]	-3.01 [-7.20, 1.19]	0.68 [-3.48, 4.84]	-0.68 [-4.76, 3.40]
Neuroblastoma	**-6.09 ** [-10.10, -2.07]**	**-5.20 ** [-9.13, -1.28]**	**-5.06 * [-9.05, -1.07]**	**-4.31 * [-8.13, -0.50]**
Retinoblastoma	2.71 [-2.75, 8.17]	5.14 [-2.03, 12.31]	6.61 * [1.18, 12.03]	7.35 * [0.38, 14.33]
Sarcoma	-2.22 [-5.51, 1.06]	0.11 [-3.15, 3.36]	-2.61 [-5.88, 0.65]	-0.22 [-3.39, 2.95]
Other cancers	-2.19 [-4.95, 0.57]	-1.17 [-3.95, 1.61]	-0.97 [-3.71, 1.76]	-0.13 [-2.82, 2.56]
Any chronic disease		**-2.63 ** [-4.59, -0.68]**		**-3.59 *** [-5.49, -1.68]**

Same health compare to 1 year ago	Ref	Ref
Better health	2.08	**3.30 ****
	[-0.11, 4.27]	**[1.17, 5.43]**
Worst health	**-7.08 ****	**-6.47 ****
	[-11.62, -2.54]	**[-10.89, -2.06]**
Taking any psychiatric medication	**-8.06 *****	**-5.35 *****
	[-11.23, -4.88]	**[-8.43, -2.26]**
Taking any pain relief	**-2.44 ****	**-3.26 *****
	[-4.26, -0.62]	**[-5.03, -1.49]**
Auditive impairment	-4.48	**-11.80 ***
	[-14.47, 5.51]	**[-21.52, -2.07]**
Average 6-8 hours of sleep/day	**6.34 ***	**8.14 ****
	[1.19, 11.50]	**[3.13, 13.15]**
Average >8 hours of sleep/day	**6.96 ****	**9.89 *****
	[1.85, 12.07]	**[4.92, 14.87]**
Unemployed	**-4.11 ***	**-5.04 ****
	[-7.46, -0.76]	**[-8.30, -1.77]**
Unemployed with subsidy (medical)	2.11	1.72
	[-1.80, 6.02]	[-2.09, 5.53]
Not self-reported	1.71	0.52
	[-1.21, 4.64]	[-2.33, 3.37]

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

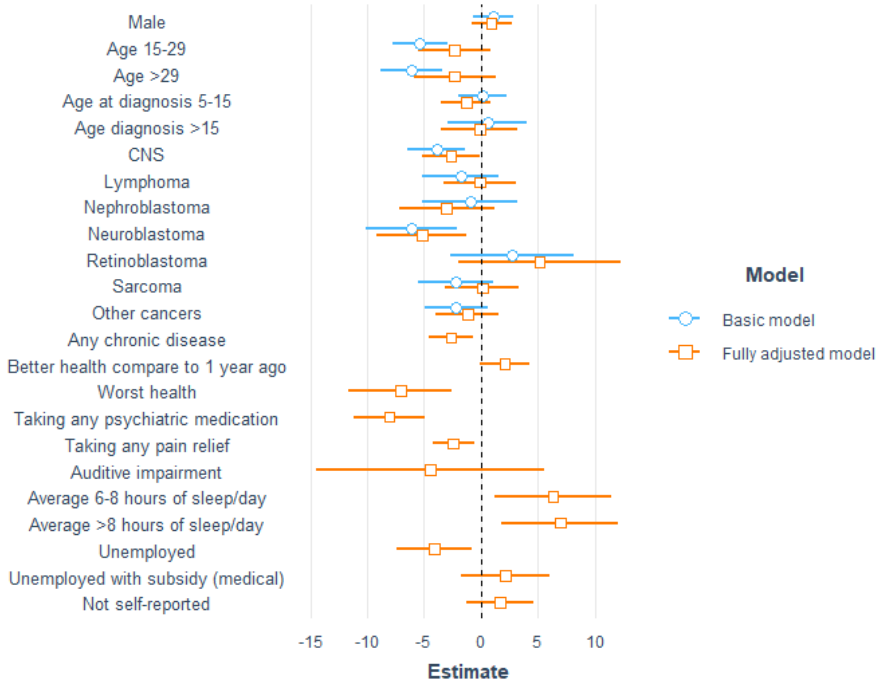

Figure 4: Association between Mental Health domain and cancer related and follow up variables

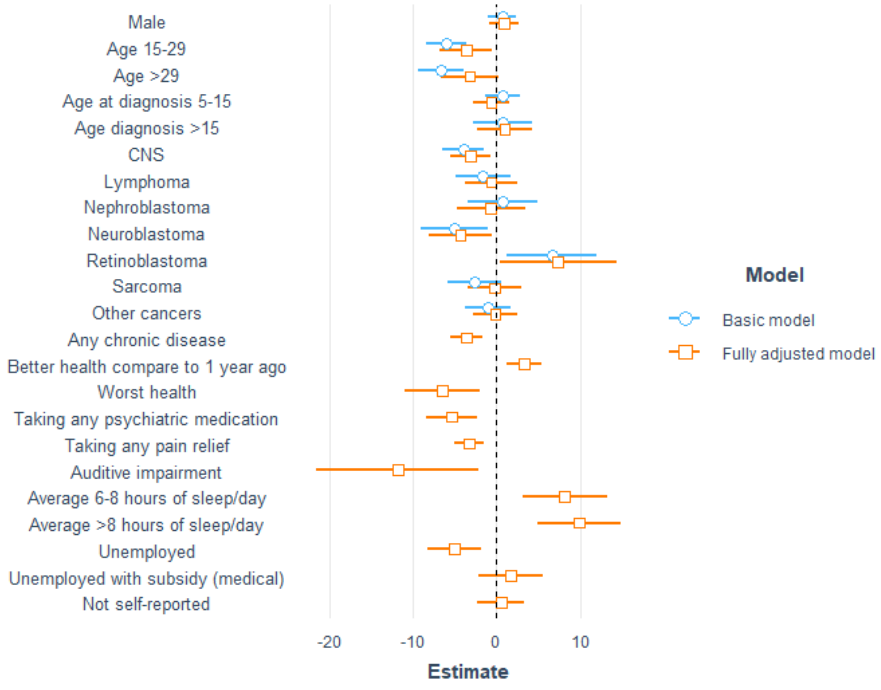

Figure 5: Association between Vitality domain and cancer related and follow up variables

DISCUSSION

We presented a first description of the mental health status of childhood and adolescent cancer survivors in Spain. The overall mental health scores (component and the sub-domains) are comparable with those in the US-CCSS (Zeltzer et al. 2008), with slightly higher scores in some domains that in the US.

Overall, we found that survivors of Central Nervous system tumours had a lower mental health score with respect to leukaemia survivors, in line with reports from other childhood cancer survivors cohort studies (Fidler et al. 2015; Friend et al. 2018; Ashford et al. 2014).

We also found that the physical health status (suffering any chronic condition, being under medications) may have an impact on the mental health in this population, though Physical and Mental Component were poorly correlated. Indeed, survivors reporting any chronic diseases or a worsening of their health status in the past year also scored lower in mental health, as did those who reported taking pain relief medication. These findings are not surprising and have also been reported in other similar studies (Friend et al. 2018). Taking any type of psychiatric medication was also associated with poorer mental health. Reporting higher number of hours of sleep, however, was associated with better mental health.

Being unemployed also seemed to negatively affect mental health in this population, however not when such unemployment status was due to any current medical conditions.

Strength and limitations

Despite the relatively low sample size, this is the first report of mental health in childhood cancer survivors in a Spanish population. It is also one of the few studies of CCS who used the SF-36 instrument (Fidler et al. 2015; Zeltzer et al. 2008), although this instrument has been shown to be valid for use in this population (Reulen et al. 2006). Due to the lack of Spanish normalised data for the SF-36 scores we were not able to compare the mental health scores of the patients in the cohort with those of the general Spanish population. However, comparison with other similar populations (US childhood cancer survivors) showed generally similar scores, slightly higher in our cohort for some sub-domains. In the absence of general population scores, a control group, for example siblings of the participants, or another group comparable to the cohort in terms of age at questionnaire completion, residence and socioeconomic status would have been useful.

Our ability of contacting patients to be enrolled in the cohort study was low, in particular due to the difficulty of reaching patients treated in earlier decades for whom address details were scant or out of date. Efforts to increase participation rate should be made, in particular for this population, by finding means, through the health service, of tracing the survivors' or their families' current addresses (Wakefield et al. 2017). The cohort is now being extended prospectively, with presentation of the study during follow-up visits, with much better participation rates.

The low participation rate and the low sample size may have influenced the representativeness of our cohort with respect to the population of childhood cancer survivors as a whole. We recruited patients from a very large paediatric oncology centre, which receives both public and private funding. The chance of being treated there does not, therefore, depend on the family's socioeconomic status as, even if it a partially private hospital, it functions as a public hospital and care is guaranteed to everybody, independently of income.

The low sample size has also prevented us to make internal comparisons between patients with different characteristics. Indeed, even when comparing subjects by type of first cancer, the groups became smaller, and hence the statistical power to detect differences was lower.

Our results are cross sectional in nature, thus it is hard to conclude regarding causal relationship. The vast majority of participants have accepted to be re-contacted in the future, however, and we will therefore have the opportunity to evaluate changes, if any, over time.

Research recommendations

It is undoubtedly of public health and clinical importance to better understand the health status in such population. A nationwide childhood cancer survivor's cohort would likely improve our understanding and would likely guide policy makers for a correct allocation of resources to improve the health of this population, including specialised interventions in mental health (Tonorezos et al. 2018; Haupt et al. 2018). In addition to follow-up for specific diseases we recommend that quality of life of the survivors be assessed, as part of the health surveillance of this population.

It is possible, as suggested in this research, that the health status of the subject (in particular the presence of chronic condition, of a physical pain require medication or a mental health illness require medication) may influence his/her quality of life, thus a better control of such late effects would likely improve the mental health status of CCS.

It is of note that, as expected, unemployment appears to influence mental health score and QoL, though not when unemployment is related to a medical condition. Working towards better inclusion of cancer survivors in the working environment is also recommended, in particular for those who do not have serious health conditions preventing them from being employed.

Conclusion

This is the first report of mental health status of childhood cancer survivors from a hospital-based cohort on CCSs in Spain. Overall QoL appears to be god, as reported also in similar populations in other countries. However, some subgroups appear to have lower mental health scores, depending on the type of tumour, their age and their health condition. These findings justify larger studies and possible interventions to improve the QoL of childhood cancer survivors.

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CHAPTER V: General Discussion

The present doctoral thesis contributed to a better understanding of the health effects of low-to-moderate doses of IR from medical radiological procedures. A specific discussion of the results and issues in each manuscript is written up within each individual manuscript.

In the General discussion chapter, I first summarize the main findings and then I detail the main methodological issues of the present thesis. A section discussing research and public health implications closes the chapter.

1 CONTRIBUTION TO CURRENT KNOWLEDGE

The present work, overall, contributed to the following:

1) Understanding risk of cancer after exposure to medical diagnostic procedures by:
    a) Providing estimation of radiation dose, by time period and age group, for diagnostic examination involving the head (including dental examination);
    b) Analyzing lymphoma and brain cancer risk in two large international case-control studies that collected self-reported information on history of medical diagnostic procedures.
2) Characterizing the current evidence around neurodevelopmental effects of low-to-moderate IR dose.
3) Building a cohort of Childhood Cancer Survivors, in which mental health was described and which served as a basis for the study of neurodevelopmental effects related to low-to-moderate doses of IR.

Main findings for each objective are detailed in Table 12

Table 12: Main findings of the thesis

Manuscript	Objective	Main finding/ results
Objective I: Estimating cancer risk from diagnostic radiological history		
I	Provide dose estimation for epidemiological study for adult intraoral dental X-ray across time period.	- Brain, eye lens, salivary glands and thyroid doses were very low (well below 1 mGy) of the order of 10^{-1} to 10^{-4} depending on the organ. - Decreasing trend over time in doses to the brain, salivary, thyroid and lens of the eyes dose;
II	Lymphoma risk in adults induced by lifetime cumulative IR bone marrow dose from common diagnostic procedures	- Overall very low doses, with a highly skewed distribution; - No increased risk (most ORs below 1); - No evidence for a confounding effect by medical radiation; - Overall negative association may be due to bias or chance though it has not been possible to identify the source (unlikely to be recall bias given the reduced risk estimates)
III	Brain tumour risk in children/young adult induced by lifetime cumulative IR brain dose from common diagnostic procedures	- Overall very low doses, with a highly skewed distribution (median 0.02 mGy, max 217 mGy) - Most ORs below 1. Increase ORs for the highest dose category for prenatal (OR for 5 mGy = 1.55 95% CI: 0.57; 4.23) and postnatal exposure (OR for 100 mGy=1.63 95%CI: 0.44; 6), based on very small numbers of subjects Little evidence of confounding by medical conditions

Manuscript	Objective	Main finding/ results
Objective II: Exploring radiation induced neurodevelopmental effects		
IV	Provide a synthesis of epidemiological evidence around neurodevelopment effect of low-to-moderate IR dose	- Heterogeneity across studies in term of effect estimated, instrument used and dosimetry prevented a quantitative synthesis, thus a qualitative synthesis was conducted - Limited evidence for an effect of low-to moderate dose to General cognition, Language abilities. Limited evidence for a decrease in school performance (school grade, education achievement) and increase risk for mental disease with low-to-moderate IR exposure. - Inadequate evidence of an effect of low-to moderate dose IR on the following domains: Attention, Memory, Visual-spatial abilities, Executive function, Emotional and Social competence, Fine motor developments. - Inadequate evidence of higher effect when exposure happened in uterus. - Need for further larger studies with better dosimetry and using a complete neuropsychological battery of tests.
Research protocol I	Neurodevelopment effect after exposure to low-to-moderate IR dose from non cranial radiotherapy	-Cognitive tests developed for birth cohort studies can be also applied in cancer survivor follow up context. - Recruitment and participation of patients in such follow up study has been possible because it was integrated with the clinical follow up. - Recruitment and dose reconstruction currently ongoing

Manuscript	Objective	Main finding/ results
Objective III: Setting up a cohort of Childhood Cancer Survivors:		
V	Building of a CCS cohort	- Recruitment of patient 1980-2000. Start of a prospective recruitment in HSJDD - Protocol for a nationwide cohort - Nested study of neurodevelopmental effects (COGNITO)
	Describe mental health in a CCSs cohort	- Overall mental health comparable to general population and other CCSs cohort (US-CCSs cohort) - Lower mental health score for brain cancer and neuroblastoma survivors - Variables related to long term health outcome (suffering any chronic disease, taking pain/psychiatric medication) are associated with lower mental health status - Unemployment status is also associated with lower mental health status.

1.1 Estimating cancer risk from diagnostic radiological history

1.1.1 Summary of findings

Overall we found no evidence that low medical IR doses from common medical radiological examination increase lymphoma risk in adults. Rather, we found an inverse association, possibly related to chance or, given the consistency of the results in sensitivity analyses, to a non-identified source of bias.

There was little evidence of an increase in brain tumour risk in young people after exposure to common medical radiological examinations, though non-significant increases were seen in the highest dose category both for pre- and post-natal exposures, based on very small numbers of subjects.

1.1.2 Certainty in the evidence

Overall, the low statistical power of the two studies did not allow us to reach a conclusion. This low statistical power is primarily due to the overall very low level of doses related to the diagnostic procedures reported by the study subjects. In addition to statistical power, other biases related to the case-control design may contribute to lowering the confidence in such risk estimates.

1.1.3 Original aspects

We contributed in advancing the methodology of case-control studies addressing medical diagnostic radiation exposure by estimating individual radiation doses to the tissue of interest (bone marrow for lymphoma and brain for brain tumours) based on typical values of organ doses by age and time period, as previously

performed in a few medical radiation studies (Preston-Martin and Pogoda, 2003).

Indeed, generally, previous similar case-controls studies addressing lymphoma or brain cancer risk after medical diagnostic exposure used categories of number of examination as the dose metric (Boice et al., 1991; Claus et al., 2012; Hammer et al., 2011; Preston-Martin et al., 1989; Rodvall et al., 1990; Tettamanti et al., 2017). Considering the wide range of doses delivered across different examinations, and how these change over time and by age group, this approach (by number of examination) leads to less precise exposure assessment and exposure misclassification (Linet et al., 2012).

To estimate organ doses from diagnostic procedures, a somewhat extensive dosimetry work is needed to provide organ doses for each examination type, age and time period. Such dosimetry work is of particular interest, as demonstrated by the growing number of similar dosimetry publications (Melo et al., 2015; Thierry-Chef et al., 2012; Villoing et al., 2017). We also contributed to this research line by providing organ doses for adult dental X-rays and skull and neck paediatric X-rays in different time periods. We provided look-up tables that can be used in further studies of this type, as well as for risk projections studies.

Another original characteristic of the two case-control studies is the exploration of the potential confounding effect of variables related to the subjects' medical history in the risk analysis. Actually, interpretation of recent findings from CT studies has been criticized for lack of taking into account possible medical predisposing condition which can be both related to the IR dose and to the cancer risk. We found that some of the medical conditions tested were indeed associated with higher cumulative radiation doses.

There was, however, little evidence for a confounding effect of medical conditions, as adjustment for these conditions did not modify risk estimates.

1.2 Radiation induced neurodevelopmental effects

1.2.1 Findings

There was limited evidence for a decrease in general cognition and language abilities after low-to-moderate doses of IR, while for other specific domains the evidence was inadequate, due to the very limited number of studies found. There was also inadequate evidence of a stronger effect on neurodevelopment when IR exposure occurred early in life, in particular, during the foetal period.

Based on these findings, we proposed a framework for future study in the field of neurodevelopment effect of radiation, by setting priorities and identifying main research gaps, which we then took into account in the development of the protocol for the COGNITO Study.

1.2.2 Certainty in the evidence

The small number of studies and their overall heterogeneity (in terms of study population characteristics, outcome, instruments used, dosimetry, and statistical methodology) prevented us from conducting a quantitative synthesis.

We therefore used qualitative synthesis methods as described in the Cochrane handbook (The Cochrane Collaboration, 2011) and by Popay et al. (Popay et al., 2006) and an adaptation of the GRADE methodology (Guyatt et al., 2011; Johnson et al., 2014;

Morgan et al., 2016) to rate the quality of evidence. These methods are possibly less informative than quantitative methods because they do not provide a summary of the magnitude of the effect estimates, however they can provide evidence based conclusion which can be used to guide policy makers future research.

1.2.3 Original aspects

This is the first systematic review on neurodevelopmental effects of low-to-moderate levels of IR and we have synthesized the current evidence around such effects.

Another original point, within the field of radiation epidemiology, is the implementation of a risk of bias assessment, methods for qualitative synthesis and for evaluation of certainty of the evidence.

We based our protocol on the most recent advancement in Systematic Review methodology for observational studies and qualitative synthesis methodology (Guyatt et al., 2011; IARC, 2014; Johnson et al., 2014; Morgan et al., 2016; Popay et al., 2006; Savitz et al., 2019; The Cochrane Collaboration, 2011). The SR is currently under review in Environment International were high standards for SR has been adopted (Whaley et al., 2016). The editor considered the submitted manuscript promising and fulfilling criteria for SR journal expectation and, together with reviewers, suggested a better characterization of the application of the above mentioned methods for qualitative synthesis, which are incorporated in the version of the manuscript included in this thesis. This protocol may be of benefit for raising the standard of SRs in the field of radiation epidemiology (and epidemiology in general) to better inform policy makers and research policy and identify research gaps.

1.3 Setting up a CCSs cohort

1.3.1 Findings

We provided a first description of mental health in a retrospective cohort of Childhood Cancer Survivors in Spain, based on data from the hospital-based cohort (the first of its kind to be set-up in Spain) constructed during the current PhD studies. The cohort was the basis for a number of analyses (Annex II) presented at meetings of the Spanish Society for Paediatric Haematology and Oncology (SEHOP), as well as for the study of neurodevelopmental effects of low-to-moderate doses of IR among CCSs (*Study Protocol I*).

In *Manuscript V*, we found that the mental health status of the cohort was comparable overall to that of the general US population and of the large US cohort of CCSs. However, lower mental health was found for those who reported suffering from any chronic medical conditions, pointing to the importance of a clinical and epidemiological follow up of this population.

1.3.2 Certainty in the evidence

Much effort should be devoted to enlarge the cohort in order to ensure adequate representativeness of this population. The overall low participation rate of cancer survivors in our cohort and the consequently risk for a selection bias, hampered us to generalize our conclusion. The cohort is now being enlarged prospectively in the same hospital, which should reduce the risk of selection bias, as the study is presented by the medical doctor in charge of the clinical follow up of the patient.

Enlarging the cohort to other large paediatric haematology and oncology departments in Spain will provide more statistical power, as larger number of individuals may be recruited, particularly those

treated in most recent decades, minimizing the challenges in contacting those treated in the past. This would also ensure that Spain can contribute to International and European efforts in evaluating the health and quality of life in this sensitive population affected by their cancer and the associated treatments.

1.3.3 Original aspects

The collection of the data and the establishment of a cohort require substantial effort and resources. Within the present thesis, we started building a cohort of CCSs, which can be used to study effect of radiotherapy, and in general define long term risk in such a vulnerable population.

Much effort has been required to adapt well know CCSs cohort protocols (including those of the French, UK, and US CCSS) to the clinical practice and clinical follow-up structure of the hospital.

1.4 Other findings: vulnerable exposure period

The question around vulnerable exposure period is a key question in radiation protection. By identifying populations at higher risk from radiation exposure, adequate radio protection measure can be effectively addressed.

Cancer: We attempted to study variation in brain tumour risk across age at exposure in the MOBI-kids study (*Manuscript III*), however the lack of power precluded any clear conclusion. We, however, found a increased risk of prenatal medical radiation even at a very low dose (5 mGy), however based on small numbers. We also saw a increased risk in the highest dose category for exposures in early life, based on small numbers. Thus, we have some suggestions of a higher effect when exposure occurs early in

life, consistent with the literature on radiation induced cancer (UNSCEAR, 2013).

Neurodevelopment: in reviewing epidemiological studies (*Manuscript IV*), there was too little evidence to evaluate a possible difference in risk for exposure *in utero* compared to in childhood.

Evidence from biology is indicating a susceptibility of the *in utero* period (Kempf et al., 2013; Moore and Persaud, 2015; Verreet et al., 2015). Findings related to other environmental neurodevelopment-toxic agents seems to affect the developing brain mostly *in utero* (Graignic-Philippe et al., 2014; Suades-González et al., 2015; Van den Bergh et al., 2017). Thus, the hypothesis of stronger effect in utero is plausible and should be further explored in epidemiological studies.

2 METHODOLOGICAL CONSIDERATIONS

In the present dissertation, a number of methodological issues have been identified (Table 13) and are discussed below.

2.1 Study design: Was the study well suited/planned?

To answer epidemiological questions, two main types of observational analytical studies are distinguished: case-control and cohort studies. Within the present doctoral thesis, the two types of epidemiological study designs have been used: the case-control design (*Manuscript II and III*) and the cohort design (*Manuscript V*).

In case-control studies, the epidemiologist proceeds by first identifying cases (i.e. subjects with the outcome of interest) and selecting adequate controls (subjects without the outcome of interest who are as close as possible to the cases in terms of age, sex, region and other important parameters) and then retrospectively collects their exposure history. Risk estimates are calculated by comparing the exposure history of cases to that of controls.

In a cohort study, people are recruited at exposure, when they are in principle free of the disease of interest. They are then followed up over time. History of exposure can be collected prospectively and/or retrospectively. At a particular follow-up point, all cases of the disease of interest are identified (through registries or screening) and risk estimated.

Table 13: Methodological consideration of the thesis work

Methodological consideration	Discussion point in brief
Study design: - Was the study well suited/planned to answer the specific questions?	Selection bias may be an issue in the two case-control study (*Manuscript II and III*) and in the cohort study.
	The two case-control studies (*Manuscript II and III*) were not well suited to provide an answer to the question of cancer risk after IR from medical diagnostic exposure. However, case-control study they might be still informative for radiation protection, if they overcome the issue of low study power due to the dose distribution.
	The CCSs cohort (*Manuscript V*) is an adequate study design to inform both radiation protection relevant questions, but also important clinical question. The setting up of the full database (baseline variables, treatment variables, and follow-up variables) requires a planning adequate to each hospital practice and national/regional availability of medical data (health registry).
Statistical power: - Were the data adequate to answer the specific questions?	Case-control studies were under powered in retrospect, considering the overall very low estimated doses for most subjects. Although head CTs can deliver rather substantial brain doses, the number of subjects with multiple head CTs was quite small.
	The low number of studies and overall high heterogeneity has prevented us to make more confident conclusion in the SR, at least for some specific neurodevelopmental domains.

	The CCSs study will benefit from an enlargement of the cohort at national level, to ensure adequate representativeness of different cancer type population and to join international effort to pool together such data
Sources of error - Are the data on which findings are based accurate and precise?	-The two case-control studies (*Manuscript II and III*) and the CCSs cohort study (*Manuscript V*, for the follow-up questionnaire) relied on self-reported information and they might be affected by a recall bias. - In the cohort study we also faced the issue of obtaining information as abstracted from medical records. Medical records, in particular the oldest, are possibly incomplete. - Dose estimation performed using typical value for time-age period may be imprecise. - Berkson error may be an issue as a group mean is used to assign individual doses - The incorrect choice of the target organ is a source of systematic error, and it is likely when the biological mechanism is still unclear (such as for neurodevelopmental outcomes).
Interpretation of findings -are confounding or other biases preventing a causal interpretation of the association?	- When evaluating radiation risk in medically exposed population, proper assessment of the potential effects of medical history should be conducted to better control for potential confounding by indication and reverse causation bias. In the two case-control studies (*Manuscript II and III*) medical conditions were taken into account. - In CCCs studies disentangling the effect of patient related characteristic, cancer effect and treatment effect may be particularly challenging, as such variable are highly correlated.

In both study type (cohort and case-control), it is key to obtain a sample which is representative of the population under study to minimize the selection bias (Paragraph 2.1.1 “Selection bias”).

Usually case-control studies, compared to cohort studies, require less time, effort and resources to be carried out and such advantage may be exploited also to answer specific questions in radiation protection (Paragraph 2.1.2 “Suitability of case-control studies”).

As reviewed in the introduction, most of the evidence in radiation epidemiology comes from large cohort studies (Cardis et al., 2007; Hamra et al., 2015; Ozasa et al., 2012; Pearce et al., 2012a), which, however, require more efforts to be set-up, higher costs and long follow-up periods to achieve the same number of cases as a case-control study. The practical issues faced in the setting up of the CCSs cohort are outlined below (Paragraph 2.1.3 “Planning of the cohort studies”).

2.1.1 Selection bias

The studies included here require obtaining informed consent and if the likelihood of participation is related to the exposure or the health status, a selection bias may threaten the validity of the study results.

In both case-control studies (*Manuscript II and III*) we found a higher level of dose in controls than cases. In both studies we speculated that some form of selection bias could have explained the higher number of examination reported in controls. Cases are generally interested in participating because of their case status; control participation rates tend to be lower in case-control studies, in general. It is possible that the controls who participated suffered from a chronic condition or a major disease (Wrensch et al., 2000),

and they might perceive some sort of benefit by participating in health research. Thus, we might end up selecting controls with some chronic condition, or who are in general more worried about their health status. It is, therefore, possible that such controls might also be more prone to consults doctors, which could eventually lead to higher medical radiation exposure (Wrensch et al., 2000).

In the EPILYMPH study (*Manuscript II*) we found a suggestion of the presence of this bias, as a higher prevalence of chronic diseases was found in the controls recruited than in the general population. Indeed, the prevalence of chronic medical conditions among population based and hospital based controls was higher than that of the cases.

In the hospital based CCSs cohort study analysed here, selection bias might also be an important issue, in particular considering the low participation rate. It is, therefore, possible that the likelihood of participation may be determined by the actual health status (i.e. survivors who are currently suffering from a chronic disease might be more likely to participate as they might perceive a sort of benefit) or mental health status (survivors with depression or lower mental health might not be motivated to participate in a study). Thus, results of external comparison must be taken with caution.

2.1.2 Suitability of case-control studies

Case-control studies have generally the advantage of ensuring adequate study power more efficiently and at lower cost than cohort studies for rare disease outcomes (such as for example cancer in childhood/young adulthood). However, the issue here (*Manuscript II and III*) is that we deal with a relatively low frequency of exposure in the general population. Thus, the case-control

studies included in this thesis, even though they are based on large numbers of cases, have low statistical power.

However, the advantage of a case-control study is the relatively easier and more efficient way to collect information about other potential risk factors for the disease and other factors of potential interest; therefore, we had also detailed information on medical history which was taken in to account in the analysis, and association between cumulative IR and different chronic disease was explored, as a contribution to the ongoing debate around possible confounding by indication in radiation medical diagnostic risk studies.

2.1.3 Planning of the cohort studies

Cohort studies require a large effort to be set up, long term funding and commitment of people.

In the present doctoral thesis, we set up the first retrospective Childhood Cancer Survivor's cohort study in Spain, which has now started recruiting prospectively. The cohort, at the moment, is hospital based, though we are working with the SEHOP to expand it. To set it up, we faced three main types of issues: establishing an efficient patient recruitment system, ensuring a high quality, secure and efficient data collection, and ensuring adequate infrastructure to complete the task required.

2.1.3.1 Patient recruitment

Because of the current patient data protection laws in Catalonia, it was not possible, as done in most European CCSs cohort, to set-up a cohort based on the records of the hospital for passive follow-up for cancer and mortality, without patients informed consent.

For our cohort study, we were therefore required to contact all former patients in order to present the cohort study to them, ask

whether they were willing to be included in the study and obtain appropriate informed consent forms from patients wishing to participate.

For the first recruitment campaign (2015-2016), funded by the European PROCARDIO project (PROCARDIO study group, 2015), the oncologists of the hospital contacted their former patients by mail to present the study and ask them if they wished to be included. However most of the addresses stored in the hospital administrative database were not updated, hence, many former patients could not be contacted. The mechanism was therefore not highly efficient. The data used for the mental health description article (*Manuscript V*) are based on this recruitment campaign.

A more efficient option, for patients still followed-up in the hospital is to establish a recruitment system within the follow up clinic, where patients usually come once a year (or more often) for a medical check-up. This option is more efficient but required a long time to be planned, and allocation of resources from the hospital (medical doctors or nurses should take care of the recruitment on a daily basis). A clinical follow up system is in place in Hospital San Joan de Deu for paediatric patients, however when they become adults, follow-up is continued outside the hospital, usually by the general practitioner. We therefore started a recruitment campaign (ongoing) for patients who still come to the follow up-clinic; this work was funded within the FIS KID-MED-RAD.

2.1.3.2 Data collection

Data collection requires appropriate planning. In the CCSs project three main types of databases were required, and for each one a different methodology of collection had to be planned. Table 14

details the main characteristics and the collection methods for each one of these databases.

2.1.3.1 Infrastructure issues

Building a cohort requires effort and different expertise should be involved. Adequate funding should be allocated for each task. Clinicians should be involved and a plan needs to be in place to guarantee that the time allocated for the additional work required does not compromise their clinical work. The role of research technicians is also important, as they ensure high quality collection of data. Epidemiologists have a key role in setting up the protocol to avoid possible biases, data collection, and validation of data and in analysing the results of different studies based on the cohort.

Table 14: Data collection issue in a cohort of Childhood Cancer Survivors

Database	Definition and description of variables included	Data collection methodology	Potential issues
Baseline database	Includes personal identifier information, information on cancer diagnosis, age at diagnosis and the information needed to check for inclusion criteria. Vital status at each follow-up campaign should also be included.	This database can be derived from the hospital database including all the patients treated.	It is important to know if and how hospitals have kept records of people they treated historically. Since the SEHOP runs a national childhood cancer registry, paediatric hospitals are asked to send this information annually to the registry. The completeness of the registry varies, however, based on time period and autonomous community. Though data on their patients was requested by Hospital Sant Joan de Deu (where the cohort was set up) from the National Registry, the information received was incomplete and access to historical paper archives was necessary.

Treatment database	Contains information on the type of treatment received by the patients and all the variables that detailed the clinical course during the cancer treatment (weight, adverse reactions, concomitant non-cancer treatment...)	The level of details required for this database is very high: for each chemotherapeutic agent the cumulative dose should be calculated, and for radiotherapy treatment the whole treatment planning must be collected.	Especially for the earliest patients, treatment may be not electronically recorded and this required an extensive revision of paper records. Information can be partially missing on not intelligible. For early periods, radiotherapy of Sant Joan de Deu patients was performed in other Barcelona hospitals, one of which has closed and all information destroyed.
Follow up database	Contains information of the health status at the moment of the follow up.	1. Obtaining self-reported information via contacting patients (mail questionnaire). This information may further confirmed with a medical record revision.	Possible low participation rate Patients may be difficult to trace if they have stopped follow-up in the hospital many years in the past
		2. Linkage with available health registry (mortality, cancer)	Depend on the availability (and quality) of registry. Fine for mortality (available at national level though cause of death is only available at the autonomous community level); more complicated for cancer registration as population based registries

(Continued) **Follow up database**			is available only in some autonomous communities and provinces. Public Hospital discharge registries are available at the autonomous community level in recent years and these, and the introduction of the shared medical history, are important sources of data for following patients for cancer and other outcomes can be important follow-up tools though revision and validation of the data are needed.
		3. Asking patients to come back for a follow up visit in which medical doctors (or another health professional) can assess their health. This approach was used for the assessment of neurodevelopmental function (Research protocol).	It works well if the hospital has such system in place already for long term clinical follow up. However, it extend the recruitment phase of the study for at least one year (usually patients are required to come once a year).

2.2 Statistical power: were the data adequate?

Studying the effect of low doses of radiation requires large sample size to detect an effect (Land, 1980), as power is a function of the number of subjects and of the magnitude of effect. An important determinant of power is also the dose distribution. Thus, if a population receives low doses and the magnitude of effect is anticipated to be small, very large population sizes are required.

2.2.1 Epilymph and MOBI-kids case-control studies

Both of these studies are among the largest case-control studies of the aetiology of these cancer types conducted to date.

In both studies, however, the distribution of dose was very skewed, with most of the subjects receiving extremely low doses from medical diagnostic procedures. Such dose distribution likely reflects the cumulative dose distribution in the general population (Fazel et al., 2009). Indeed, CT-scans, which entail higher radiation dose compared to other diagnostic examinations, are not the most frequent examination performed (Dose DataMed II, 2015; UNSCEAR, 2008b). The rate of CT-scans in the general paediatric population is low; it was estimated be around 8.5/1000 individuals in the UK in 2015 (Journy et al., 2017) and 10.9/1000 individuals in Spain in 2013 (Bosch de Basea et al., 2018). Consequently, if cases and controls are sampled from the general population, only a small proportion of them is expected to have received dose levels high enough to allow detection of a possible radiation induced risk, if any.

As a consequence, we did not have a sufficiently wide range of doses and sufficient number of subjects in the moderate and higher dose categories to ensure sufficient power to detect a risk, if any.

To increase the efficiency to study the effects of rare exposure, cases and controls should be sampled from a population with a wide distribution of doses (thus, different from that expected in the general population), to ensure a sizeable number of cases and controls in the highest dose categories. For example, nesting case-control studies into cohorts of subjects with medical diagnostic (i.e. CT-scans) or therapeutic (i.e. Childhood Cancer Survivors) exposure would ensure a broad range of doses with sizeable number of individuals in all dose categories.

2.2.2 Childhood Cancer Survivors study

Childhood cancer is a rare disease overall, composed by several heterogeneous histological and topographical cancer types, with possible different aetiologies. Assessing the long term risk of treatment in such a context is, therefore, particularly challenging as there is high heterogeneity of doses, and rapid evolution in type of treatment. Thus, to ensure adequate statistical power to appropriately assess the effects of the cancers and of their treatments on the health and welfare of the survivors and compare the long-term effects of different treatment modalities, very large international consortia are required to ensure enough number of cases for each specific diagnostic type (Bhatia et al., 2015).

2.2.3 Studies included in the systematic review

For some of the neurodevelopmental domains, the low number of studies and the small sample size reduced the level of confidence in the finding.

Currently, for neurodevelopment, evidence suggests that, at low dose levels, the effect can be a decrease in a few IQ points. To be able to estimate such a small effect, studies must include large enough number of subjects to ensure adequate statistical power. In

addition, the instrument used to measure the neurodevelopmental function should be sufficiently precise to detect even a small variation. Also, it is necessary to increase the precision in dose estimation, as analyses by category of exposed/unexposed may not be fully adequate to detect such changes and to determine a possible dose-response, and also are under-powered compared to analyses by level of dose. Indeed, increasing precision both at the level of outcome and dose assessment will allow a better evaluation of a possible dose effect and increase the study power, reducing uncertainty in risk estimates.

2.3 Sources of Error: are the data on which findings are based accurate and precise?

The ultimate goal for an epidemiologist is to provide unbiased and precise risk estimates, that is, provide risk estimates that are as close as possible to the truth, with minimal uncertainty. For this, not only do studies need to have adequate statistical power, but data, on which findings are based, should be accurate and precise. Thus, systematic and random errors in assessment of dose, outcome and possible confounders should be reduced as much as possible.

2.3.1 Recall bias

In the present thesis we dealt mainly with medical information as both the exposure and the main possible confounders are part of the medical history. These data were obtained using self-reported information in the two case-control studies (*Manuscript II and III*) as well as in the cohort study for the follow-up of health related information (*Manuscript V*). From the use of self-reported information, systematic error (recall bias) may arise if the reporting

error is associated with a particular health status (including the case-control status).

2.3.1.1 Recall bias in case-control studies

In both case-control studies included here (*Manuscript II and III*), the collection of medical information was done by means of a structured interview to the subject (or to the next of kin), and reporting error is likely (Berrington de Gonzalez et al., 2003). The possibility of validating response with a medical record review was not planned in the Epilymph and MOBI-kids studies, because it would have been extremely challenging to organize it, given the very large number of hospitals and clinics that would have needed to be contacted. Also, regarding exposure information, diagnostic examination are not generally registered in a centralized registry, and, depending on the country, they can often be performed in private care facilities, thus any discrepancy between self-reported and the medical review information would be difficult to interpret (Berrington de Gonzalez et al., 2003).

The impact on risk estimates of recall bias may depend on the characteristic of such recall bias: if the bias is differential between cases and control, risk estimates will be biased in one direction or another, depending on whether the cases report more or less examinations than the controls: in general, overreporting by cases compared to controls is often seen in epidemiological studies – leading to artificially high ORs – as the cases are ill and are trying to find reasons for their illness, while controls, who are generally healthy, might spend less time thinking about the examinations they received. The fact that most of the estimates in our analyses were below one, suggests that results are unlikely to be much affected by such differential recall bias. If, instead, recall bias is not

differential between cases and controls, the slope of the dose response may be increase or decrease, depending on whether the subjects under or over report their exposure.

Other studies have attempted to estimate the magnitude of the uncertainty and the existence and possible direction of systematic error arising from self-reported information. They have observed a tendency of under-reporting with increasing number of examinations (Berrington de Gonzalez et al., 2003). This systematic misclassification would result in an overall under-estimation of the dose. However, CT-scans are much less frequent than conventional X-rays, with most subjects reporting 0 or 1; thus, the frequency of this type of examination, which results in the higher levels of organ dose, is unlikely to be systematically over- or under-estimated and the uncertainty in number of such procedures should be low, except if it misreported because of confusion with Magnetic Resonance, as has been reported in the literature (Dreger et al., 2015). If this misreporting is random, the effect on risk estimates would likely be a bias of the dose-response towards the null and an increase in the uncertainty of the risk estimates.

2.3.1.2 Recall bias in the CCSs cohort study

In the mental health analysis within the CCSs cohort (*Manuscript V*), we may face some type of recall bias as follow-up information was self-reported. The follow-up questionnaire included a part on health status, which might also not be correctly reported by subjects. Actually, even if reporting the actual health status does not require the subject to remember the past (thus the recall bias is minimized), subjects might not report correctly the type of medication they take or the type of disease they are suffering from, in particular if the self-reported information was not obtained in a

structured in-person interview. If such misreporting is associated with health status (i.e. a subject with depression more likely to over-report any other medical diseases) our results might be biased.

2.3.2 Random error

Random classical (independent between subjects) errors are particularly frequent when subjects are asked to recall events; this results in exposure misclassification which tends to bias risk estimates toward the null.

Medical record abstraction may also be affected by sources of random error as some records may not be systematically collected or may have been lost. In the CCSs cohort study, information on treatment was abstracted from paper based medical records in archives. To minimize this source of error a high level of expertise and medical knowledge is required for this type of data extraction, and appropriate training is required. Thus, adequate resources should be allocated to such task, in the case of setting up a CCSs cohort, to avoid any abstracting error which may lead to random errors.

2.3.3 Dose estimation

Once information is collected, error may arise from incorrect assignment and imprecise cumulative dose estimates, expressed in absorbed dose to the target organ, for each participant. Even if the true number of procedures undergone by a subject is known exactly, the true absorbed dose is hard to evaluate retrospectively without detailed information about the machine types and settings and size and position of the patient.

The magnitude of such uncertainty, relatively to the true level of dose, is lower for very complex procedures (such as radiotherapy),

because the treatment planning history allows a quite precise reconstruction of the absorbed dose (Vũ Bezin et al., 2017). Medical physics departments are able to reconstruct in field-dose with an uncertainty of around 5%, and some department have tools to reconstruct out of field doses with about 20% of uncertainty (Vũ Bezin et al., 2017). In medical radiation epidemiology, more precise dosimetric algorithms are used to estimate the out of field dose, with a level of uncertainty of the order of 7-10% (Benadjaoud et al., 2012; Bezin et al., 2015), if all patient and treatment parameters are known.

When it comes to more common and less complex procedures, the magnitude of uncertainty can be higher as less information useful for dose reconstruction is available, particularly historically, before the introduction of the Picture Archiving System (PACS), which records, in the heading of images, the machine type and all technical parameters of the examination. However, the impact on risk estimates of such uncertainty will depend on the level of dose delivered in each single examination. As an example, in Table 5 of *Manuscript I* (dental X-ray dosimetry) we provided the median organ dose and the range across all the simulations run for each decade. This range gives a measure of uncertainty. In the earliest (1940-49) and more recent decades (2000, 2009), the magnitude of the range is 0.0225 mGy and 0.0026 mGy respectively (for the brain dose, Table 5 of *Paper I*), which correspond to almost three times the median value reported. However as doses are very close to 0, such relatively large magnitude of uncertainty will not likely have a major impact on the risk estimates. Lee et al. (Lee et al., 2018) reported that the median brain dose (across 500 simulations) for a head CT scan in a 15 years old child in 2000 was 29 and the 2.5% and 97.5% percentile were 9 and 98 respectively (10 fold

difference). The difference is larger still for some organs, such as the thyroid, which may or not be in the field during a chest CT for example. Such wide ranges might imply dose misclassification for individual patients.

Further, as standard protocols has been used to assign doses to individual organs on the basis of the body part scanned, the age of the patient, the time period and the scanner (when known), dose assessment might have resulted in Berkson error (Berkson J., 1950), rather than classical random error, as a group mean is used to assign individual doses. While this generally does not affect the slope of the dose-response if it is linear, it does, however affect the precision of the estimate (width of the confidence intervals). Thus, effort to reduce uncertainty in dose reconstruction should be devoted to individual dose assessment for the more complex and high dose examinations (taking advantage of relatively recently introduced PACS systems), as reduction of dosimetric error would likely result in more precise risk estimates.

It should be noted, however, that even if the dose estimation step comes with a certain degree of uncertainty, the inclusion of dose estimation, rather than number of procedures, in risk analysis is likely to improve the precision of the results.

This observation opens the possibility that the studies on medically exposed population included in the Systematic Review (van der Geest et al., 2013; Krull et al., 2012; Nordenskjöld et al., 2015; Ron et al., 1982; Salonen et al., 2018; Zeltzer et al., 2008) failed to detect a true association because of the lack of dosimetry. While these studies generally had very good exposure assessment because exposure was based on good quality medical record review, no attempt was made to estimate the actual dose, which could be quite variable, hence leading to dose misclassification.

2.3.3.1 Choice of the target organ

In the introduction, we defined the concept of target organ, which is the organ for which the absorbed dose is estimated. As radiation from medical radiation is not uniformly distributed across the body, dose across organs may vary considerably, thus the correct choice of the organ or anatomical tissue of interest for a particular study is important to reduce dose misclassification.

To make this choice we rely on the knowledge of the biological basis of the effect under study.

For example, it is known that one of the main mechanisms of radiation induced carcinogenic effect is related to a mutation at the DNA level of a particular cell. Thus, in studies of cancer risk, the organ (or a specific anatomical part of the organ) from which a cancer arises should be chosen as the target for dose estimation. Thus, in the MOBI-kids study (brain cancer as outcome) the brain was the chosen target organ. For the Epilymph study we chose bone marrow as the target organ for lymphoid neoplasms, as generally done in previous studies, including the atomic bomb survivors study (Hsu et al., 2013). However, debates exists about whether it may not be more adequate to use dose to lymph nodes (Berrington de Gonzalez et al., 2017). Actually, malignant transformation of lymphoid cells can occur at different stage of cell maturation, which only partially happens in the bone marrow (Jiang et al., 2017a, 2017b; Morton et al., 2014a; Swerdlow et al., 2016).

For neurodevelopment effects, the biological mechanisms or radiation are still not clear. The brain is a good target organ candidate, if it is assumed that the radiation induced cognitive effect is due to a direct effect on the neurons or other brain cells (Padovani et al., 2012); dose to specific anatomical regions of the brain, for example the hippocampus or frontal lobe may also be

more appropriate for specific types of outcomes. The vascular system (including heart and large arteries), however, may also be the relevant target organ as radiation induced cognitive impairment may also result from a cardiovascular impairment (Krull et al., 2012; Padovani et al., 2012).

2.4 Interpretation of results: are confounding or other biases preventing a causal interpretation of the association?

2.4.1 Medical conditions in medical radiation studies

In the recent CT-scan cohort studies, the issue of confounding by clinical indication has been raised: an underlining medical condition may be both related to a higher probability of undergoing CT scans (or a higher number of scans) as well to the risk of the outcome (i.e. cancer) (Boice, 2015; Pearce et al., 2012b). Also, the issue of reverse causation was raised, that is, the possibility that the observed increased risk may be overestimated by including CT-scans performed in the presence of early symptoms of the tumour.

Medical conditions that have been pointed out as potential confounder are “genetic-predisposing medical conditions and syndromes”, which are known to cause cancer (Lindor et al., 2008) and the impact of such conditions on CT-scan risk estimates has been studied (Berrington de Gonzalez et al., 2016; Journy et al., 2016).

In the two case-controls studies included in the present dissertation, we attempted to address confounding by indication and reverse causation more broadly. We hypothesized that, not only cancer predisposing genetic conditions should be taken into account, but also other medical conditions which may increase the

chance of getting an examination, and may also be somehow related to the cancer risk (causally or not) (Fig. 12). For example, some medical conditions may represent early cancer symptoms (i.e. epilepsy for brain cancer), thus, failing to take this condition into account may lead to a bias due to reverse causation (Panel C of Fig.12)

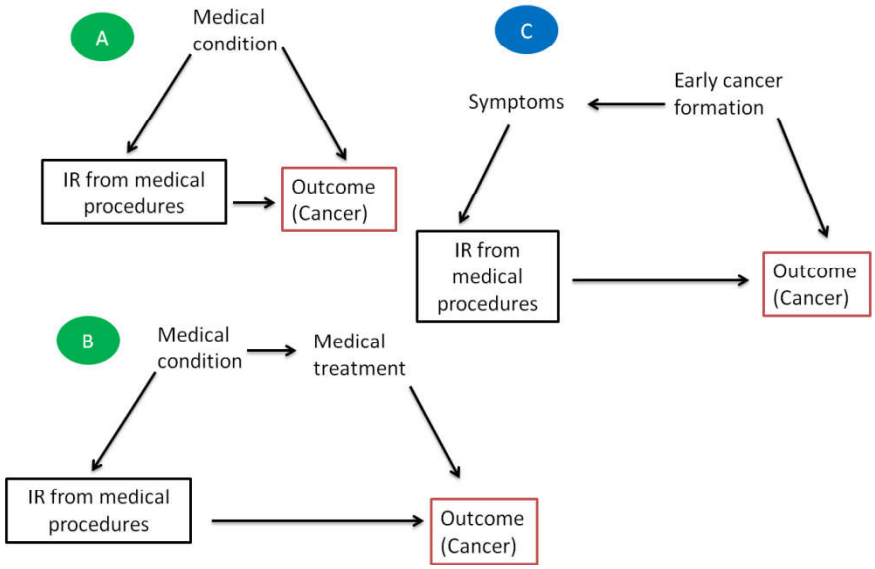

Figure 12: Direct Acyclic Graph representing confounding of indication (A, B) and reverse causality (C) in medical radiation effect studies

We found that, indeed, some medical conditions were associated with higher radiation cumulative exposure. For some of these conditions, the association was quite obvious, such as the higher cumulative brain radiation dose among subject who reported neurological conditions in the MOBI-Kids study. For others, like the association between higher cumulative bone marrow dose and atopic disease reported in the Epilymph paper, the association was less obvious as radiological follow up is not required for atopic

disease. However, an association could arise because of the fact that subjects with this disease and other conditions may tend to receive more medical attention, possibly leading to higher number of radiological examinations.

To test for confounding, we adjusted the final analysis by medical history variables. We found little variation of the risk estimates, suggesting that these medical conditions are not strong confounders of the association.

2.4.2 Complex exposure scenario in Childhood Cancer Survivors

Childhood Cancer may require a complex treatment including radiotherapy, surgery and chemotherapy. In the introduction we briefly summarized the current knowledge around the effect of specific treatments on specific health outcome. The cancer itself can also cause some of these. Thus CCSs studies are challenged by a multiple exposure context which should be taken into account. Consequently, the effort in obtaining detailed treatment information as much as possible is well justified.

3 RESEARCH RECOMMENDATION

The study of risk from medical IR exposure may be framed within five main research lines: a) Radiation Epidemiology, b) Clinical research, c) Radiation Biology and d) Dosimetry as shown in Figure 13.

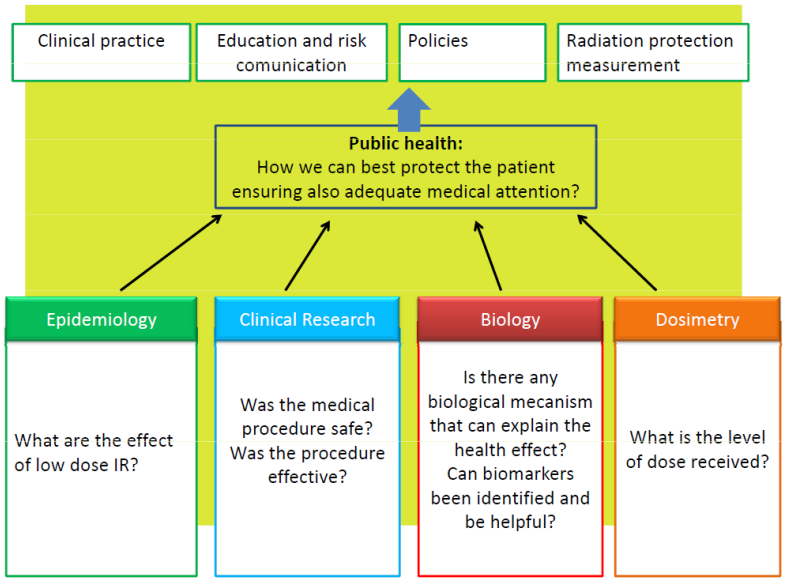

Figure 13: Main research lines devoted to the study of medical IR effect

In this sense it is of fundamental importance to build research infrastructures that bring together all these aspects, with the final aim of making an impact in public health and radiation protection of the patients.

In the following paragraph we highlight the important questions and research infrastructure in radiation epidemiology.

3.1 Research questions of importance in radiation epidemiology

A better characterization of the dose-related health effects of low-to-moderate IR dose is of undoubted societal importance, considering the widespread exposure of the general population. The constant technological changes and improvements (i.e. the progressive decreasing trend in exposure from single diagnostic examinations, the increasing number and changing technologies for diagnostic procedures, the introduction of new radiotherapy techniques) are a challenge in epidemiological studies as exposures and doses are constantly changing with time.

The current radiation protection system is based on extrapolation of risk from moderate and high dose studies to low dose situations using a linear non-threshold dose-response model, thought to be conservative and ensure protection of the population. However, the debate regarding the existence and magnitude of an effect at low doses (and the potential cost of the current radiation-protection model) is currently under discussion in the US (Milbank, 2018; US EPA, 2018), Europe (MELODI), and many other high income countries including Japan. This is the reason why the European High Level and Expert Group (HLEG, 2009), followed by the various European Radiation Protection Research Platforms (MELODI, EURADOS, EURAMED) continuously review new evidence and develop research priorities and roadmaps to challenge the basis of the current radiation protection system and, through the conduct of clinical, epidemiological and biological research and their integration, develop a stronger scientific evidence base for radiological protection.

A better description of medical radiation exposure in the population is also needed. In particular, a better characterization of the relationship between chronic disease and IR dose from medical procedures would help to interpret the findings from studies on diagnostic examination and long term health outcomes. Identifying diseases that entails higher IR exposure from medical radiation may be also informative in radiation protection, to optimize examination protocols.

While much work has been conducted and is underway on cancer risk and several non-cancer outcomes including vascular diseases and cataracts, neurodevelopment has been under-studied. Further careful studies of neurodevelopmental outcomes are therefore strongly recommended as this is an important effect with many quality of life and societal implications, particularly among cancer survivors. Epidemiological research should also be combined with biological research in order to understand the biological mechanisms behind the effects, if any. A better understanding of the biological mechanism would also help design more appropriate and informative epidemiological studies. These studies would also benefit considerably from experience from outside the radiation research world, in particular from epidemiologists and biologists with extensive experience with the study of neurodevelopmental outcomes related to other environmental exposure (Alemany et al., 2018; Sunyer et al., 2015).

3.2 Methodology and research infrastructure

3.2.1 Medical data collection and patient dose repository

Research devoted to provide appropriate methodology to better collect medical history data (including medical radiological data) is recommended.

Appropriate questionnaires should be designed to collect relevant medical history variables and a system for validation of the questionnaire information from medical records should be set-up in order to minimize biases and uncertainty due to self-reported information. This would be an asset in possible future studies, though we have found many difficulties in our cohort studies in obtaining the necessary medical information from General Practiconer and hospital records to validate the questionnaire data.

Currently, the process of medical record revision is extremely laborious and time consuming. Medical records are stored for clinical or insurance reimbursement purpose mainly, and research on a very large scale (such as the studies required for the estimation of low-to-moderate doses from medical exposures) currently requires allocating a large part of resources on medical data collection and can be impracticable. Innovation in the medical sector is required also to foster and improve the actual mechanism of medical record storing to promote epidemiological research. This would require research advances in:

- Storing patient medical history electronically in an harmonized way across hospitals in a country;
- Facilitating extraction of relevant information from different medical files to be used for research purpose;
- Developing high standard ethical and data protection guidelines to protect the privacy of the patients while allowing the conduct of surveillance studies aimed at evaluating the potential health impact of medical exposures from new and evolving medical technologies.

In addition to adequately stored medical data, patient dose should be routinely recorded and stored. There is an ongoing debate regarding the usefulness of a treatment passport (including

radiation treatment dose) among cancer survivors (Haupt et al., 2018) and some mobile applications have been developed to inform and educate patients (Baerlocher et al., 2010). However, an additional important objective of storing patient dose should go beyond the individual clinical usefulness: data should also be made available, with all necessary security and confidentiality guarantees, for epidemiological and radiation protection surveillance.

3.2.2 Systematic review and qualitative synthesis

We recommend a more standard use of the Systematic Review methodology to address different topics in radiation health effects and better inform researchers, clinicians, patients and policy makers. SR should follows high standards in qualitative and quantitative methods for synthesis (Guyatt et al., 2011; Morgan et al., 2016; The Cochrane Collaboration, 2011) to provide evidence-based conclusions.

3.2.3 CCSs cohort study

Childhood Cancer Survivors represents an important study population. However, the building of such cohorts needs innovative methodology in radiation protection research. In term of funding and resource allocation, much effort and reflection should be given to the design of the cohorts, the field work and data collection. In the design phase, it is important to involve epidemiologists, clinicians, medical physicists, psychologists and other related experts for optimal design and usefulness of a cohort. This process may take a lot of time but is essential and will lead to long term collaborations and important results.

Research technicians should have a key role in the field work, as they ensure quality data collection. They also may play a key role

in building long term collaboration between research centres and hospitals, as they take care of the practical work and are in charge of collaborating directly with clinicians and health professionals at the hospital level.

Table 15 discusses the main issues we have found in building and designing the cohort study and the solutions we have found.

Tabla 15: Solutions proposed when building a cohort Childhood Cancer Survivors study

Issue	**Solution and key role person**
Design of the study	Clinicians, epidemiologists, research technician and all professional involved in the childhood cancer care. Frequent meeting are important. Also it is important to show the importance of survivorship research.
Data collection	It is important to revise and have clear, since the protocol phase, the quality of data and decide how data collection and validation will be done.
Organization of the database	Research technician. Database should be easy to understand and use. Applications to insert data may also be considered.
Data quality control assurance	Well trained and motivated research technicians
Establish a collaboration	We need a structure that connects the research centers with the hospitals. It is also important to regularly present results to clinicians, even in descriptive data in the early phase of an investigation as this motivates them and strengthens the collaboration.
Data management and transfer	Decide where personal data should be stored, ensuring data security and protection of patient information. Personal data should be dissociated and kept in a secure restricted environment. No personal data should be transferred for the purpose of analyses of data
Recruitment	Plan a recruitment of patients according to the follow up scheme in place. If patients are coming back for a check up, the most efficient strategy would be for them to be recruited by the doctor or nurse at the time of the visit. Otherwise other systems (letter from the hospital) should be put in place and validated.

4 IMPLICATION FOR PUBLIC HEALTH AND RADIOLOGICAL PROTECTION

The current radiological protection system is based on the linear non-threshold dose-response model for stochastic diseases such as cancer, that is, a little increase risk is assumed even at the lowest doses. In medical radiology, the principle used for dose delivery and patient protection is the acronym “As Low As Reasonably Achievable” (ALARA), meaning that all necessary efforts to keep the dose low should be put in place, without compromising adequate patient care (IAEA and WHO, 2012).

In our studies, we found very little evidence of increased risk of brain tumour in young people and no evidence of an effect on lymphoma risk in adults after exposure to common diagnostic examinations; we also found limited evidence of neurodevelopmental impairment after exposure to low-to-moderate IR exposure, in particular for the general cognition and the language domain.

Such results do not contradict the current radiological protection system, which should be therefore kept, as ensure appropriate clinical evaluation togheter with adequate patient protection.

A system to record and store patients’ IR dose, even for common diagnostic procedures, should be put in place as a basis for radiation protection and epidemiological surveillance (trend and risk analysis), with the final aim to optimize doses and better protect patients and reduced the burden of radiation related cancer or other health effects.

Conclusions

This dissertation explored the effects of medical Ionizing Radiation exposure. In summary, the thesis showed:

a) Very little evidence of increased risk of brain tumour in young people and no clear evidence of an effect of lymphoma in adults after exposure to common diagnostic examinations.

b) The brain absorbed dose from dental X-rays and paediatric skull and neck X-rays have decreased over time. The contribution to the cumulative dose of these procedures is very small, and consequently it is extremely difficult to detect any increased health risk.

c) The evidence for neurodevelopmental impairment after exposure to low-to-moderate IR exposure, especially for the general cognition and the language domain was limited.

d) There was inadequate evidence that exposure during foetal and early life might bear a higher risk of brain cancer and neurodevelopmental impairment compared to postnatal exposure.

e) Establishing and fostering a long term follow up for Childhood Cancer Survivors in Spain is feasible and is needed to contribute to this important research field.

f) The mental health status of the hospital-based Childhood Cancer Survivors cohort was comparable to that of the large US cohort of CCSs. Lower mental health was found for those reporting suffering from any chronic medical conditions, pointing to the importance of a clinical surveillance of this population.

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Annex I

SUPPLEMENTARY MATERIAL OF INCLUDED MANUSCRIPTS

Manuscript I: **Trends in estimated thyroid, salivary glands, brain and eye lens doses from intraoral dental radiography over seven decades (1940 to 2009)**

Fontana RC, Pasqual E, Miller DL, Simon SL, Cardis E, Thierry-Chef I. Trends in Estimated Thyroid, Salivary Gland, Brain, and Eye Lens Doses from Intraoral Dental Radiography over Seven Decades (1940 to 2009). Health Phys. 2020 Feb 1;118(2):136–48. DOI: 10.1097/HP.0000000000001138

Manuscript II: **Association of ionizing radiation exposure from common medical diagnostic procedures and lymphoma risk in the Epilymph case-control study.**

Pasqual E, Turne MC, Gracia-Lavedan E, Casabonne D, Benavente Y, Chef IT, et al. Association of ionizing radiation dose from common medical diagnostic procedures and lymphoma risk in the Epilymph case-control study. PLoS One. 2020 Jul 1;15(7 July 2020). DOI: 10.1371/journal.pone.0235658

Manuscript III: **Exposure to medical radiation during fetal life, childhood and adolescence and risk of brain tumor in young age: results from the MOBI-kids study**

Pasqual E, Castanõ-Vinyals G, Thierry-Chef I, Kojimahara N, Sim MR, Kundi M, et al. Exposure to Medical Radiation during Fetal Life, Childhood and Adolescence and Risk of Brain Tumor in Young Age: Results from the MOBI-Kids Case-Control Study. Neuroepidemiology. 2020;54(4). DOI: 10.1159/000506131

Manuscript IV: **The neurodevelopmental effects of low dose ionizing radiation exposure: a systematic review**

Pasqual E, Bosch de Basea M, López-Vicente M, Thierry-Chef I, Cardis E. Neurodevelopmental effects of low dose ionizing radiation exposure: A systematic review of the epidemiological evidence. Environ Int. 2020 Mar;136:105371. DOI: 10.1016/ j.envint.2019.105371

Annex II

COMMUNICATION PRESENTED AT THE SPANISH PAEDIATRIC ONCOLOGY SOCIETY MEETINGS

Seguimiento epidemiológico en supervivientes de cáncer infantil: experiencia de una cohorte hospitalaria en el hospital Sant Joan de Déu de Barcelona (Poster)
Elisa Pasqual, Lourdes Arjona (presenter), Genoveva Maria Correa Llano, Ofelia Cruz Martinez, Elisabeth Cardis.
30-31 May 2019, XI Congreso Nacional de la Sociedad Española de Hematología y Oncología Pediátricas, Jerez de la Frontera

Nivel de instrucción en supervivientes de cáncer infantil: resultados de una cohorte de base hospitalaria (Poster)
Elisa Pasqual, Miguel Angel Flores Taico, Hector Salvador Hernandez, OfeliaCruz Martinez, Elisabeth Cardis
19-21 May 2016, IX Congreso Nacional de la Sociedad Española de Hematología y Oncología Pediátricas, Santander

NIVEL DE INSTRUCCIÓN EN SUPERVIVIENTES DE CÁNCER INFANTIL: RESULTADOS DE UNA COHORTE DE BASE HOSPITALARIA

Elisa Pasqual[1], Miguel Angel Flores Taico [2], Hector Salvador Hernandez [2], OfeliaCruz Martinez [2], Elisabeth Cardis [1]

1_ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, España / Pompeu Fabra University (UPF), Barcelona, España / CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, España / 2_Hospital Sant Joan De Déu, Barcelona,

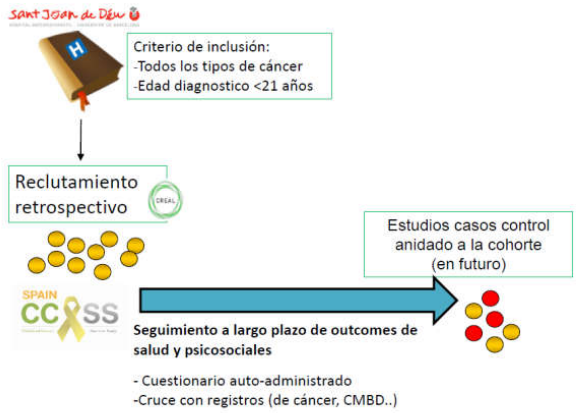
*Contact information: epasqual@creal.cat

ANTECEDENTES

Debido al incremento de supervivientes de cáncer infantil (SCI), hay un interés creciente acerca de los efectos a largo plazo del cáncer y de su tratamiento, incluyendo los efectos neurocognitivos. El nivel educativo alcanzado ha sido explorado como medida de la función cognitiva global en una cohorte hospitalaria de supervivientes de cáncer infantil.

METODOLOGÍA

Hemos ofrecido participar a todos los pacientes tratados entre 1980 y 2009 en la unidad de Onco-Hematología del Hospital Sant Joan De Déu (Barcelona). Los que han aceptado han enviado un consentimiento informado y rellenado un cuestionario sobre calidad de vida y datos socioeconómicos. El reclutamiento todavía está en marcha. Hemos descrito la finalización de la educación secundaria obligatoria (ESO) en participantes mayores de 16 años de edad y del grado universitario en mayores de 21 años. Por último, hemos estimado la influencia del tipo de cáncer en el nivel alcanzado de la ESO con un modelo de regresión logística multivariante ajustado por el sexo, edad en el momento de la encuesta así como del diagnóstico.



PERFIL DE LA COHORTE

Tabla 1. Resultados reclutamiento

	Número	%
TOTAL	**2021**	**100**
Participantes	**613**	**30.3**
- que rellenaron el cuestionario	**504**	**24,9**
No se pudieron contactar	229	11.3
Ninguna respuesta (todavía estamos reclutando)	694	34.3
Rechazaron participar	102	5
Fallecidos (rechazaron participar)	379	18.7

Tiempo de seguimiento

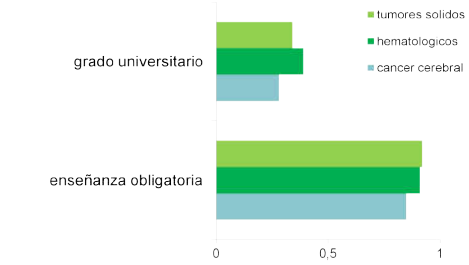
Mínimo	Mediana	Máximo
3	13	35

Tabla 2. Perfil de los participantes que enviaron el cuestionario

	Número / mediana	Porcentaje / Mínimo- Máximo
Género (varones)	268	53,2 %
Edad	22	6 - 50
Edad del diagnóstico (años)	5	0 - 19
Año del diagnóstico de cáncer		
1980-1989	91	18 %
1990-1999	122	24 %
2000-2009	290	17,6 %

RESULTADOS

Gráfico 1. Porcentaje de la cohorte que ha completado la educación obligatoria y que ha completado un grado universitario



De los 354 SCI que han completado la encuesta sobre el nivel de educación y que tienen más de 16 años en el momento de responderla, 167 (86%) varones y 152 (93%) mujeres completaron la ESO. Por grupos de cáncer infantil finalizaron la ESO 70 (85%) supervivientes de tumores de sistema nervioso central (SNC), 122 (91%) de neoplasias hematológicas y 127 (92%) de tumores sólidos (no incluyendo los del SNC). Entre los que, al momento de la encuesta tenían más de 21 años (N=271), 17 (29%) supervivientes de tumores de SNC , 40 (38%) de cáncer hematológicos y 35 (34%) de neoplasias sólidas, han conseguido un grado universitario.

No se han observado diferencias significativas en la consecución de ESO entre los supervivientes de neoplasia hematológicas y de tumores sólidos (referencia). En cambio, los supervivientes de tumores de SNC parecen tener menos probabilidades de completar la ESO (OR 0.45 IC 95% = 0,17 a 1,16; p = 0,09). En nuestro grupo de estudio, los hombres parecen tener menos probabilidades de completar la ESO (OR 0.40 IC 95% = 0,17 a 0,87; p = 0,025) respecto a las mujeres.

CONCLUSIONES

Entre los subtipos de cáncer, los supervivientes de tumores de SNC parece tener menor probabilidad de completar la ESO, pudiendo reflejar un efecto del tratamiento del cáncer o de la misma enfermedad. Estos resultados merecen ser confirmados en poblaciones más amplias.

Seguimiento epidemiológico en supervivientes de cáncer infantil: experiencia de una cohorte hospitalaria en el hospital Sant Joan de Déu de Barcelona

Elisa Pasqual [1,2,3], **Lourdes Arjona** [1,2,3,4], **Genoveva Maria Correa Llano**[5], **Ofelia Cruz Martinez** [5], **Elisabeth Cardis** [1,2,3].

1_ISGlobal, Barcelona, Spain / 2_Universitat Pompeu Fabra (UPF), Barcelona, Spain / 3_CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, España / 4_ IMIM (Hospital del Mar Medical Research Institute) , Barcelona, Spain / 5_Hospital Sant Joan De Déu, Barcelona.

***Persona de contacto: lourdes.arjona@isglobal.org**

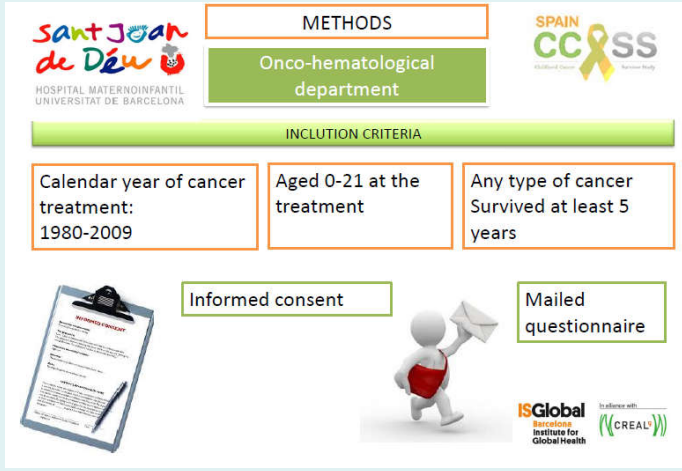
ANTECEDENTES

En las últimas décadas la tasa de supervivencia del cáncer infantil ha mejorado espectacularmente en la mayoría de los países desarrollados, y se encuentra actualmente alrededor del 75% en España.
Los sobrevivientes de cáncer infantil tienen un mayor riesgo de desarrollar efectos secundarios debido al tratamiento y al propio cáncer. En Europa (Francia, Inglaterra, Holanda) y en Estados Unidos se han desarrollado estudios epidemiológicos a nivel nacional de cohortes de supervivientes que han permitido describir de manera detallada estos efectos secundarios, identificando los factores de riesgo.

MÉTODOS

En el Hospital Sant Joan de Déu, en 2012 se empezó un reclutamiento de supervivientes de cáncer infantil, se creó una cohorte desde el año 1980 hasta el 2000. Se desarrolló un cuestionario de estado de salud y calidad de vida, similar a los que están en uso en las cohortes europeas. También se ha empezado el reclutamiento de sujetos de manera prospectiva, cuando son visitados en la consulta de seguimiento.

Figura 1. Metodologia del estudio



RESULTADOS

Tabla 1. Tasa de respuesta

respuesta	n	Porcentaje (%)
Participantes (CI)	536	34
Solo cuestionario	25	1,5
Rechazado	104	6
No contactados	480	30,5
No hay respuesta	340	21,6
Exitus	83	5,2

Tabla 2. Tasa de participación por año calendario de tratamiento.

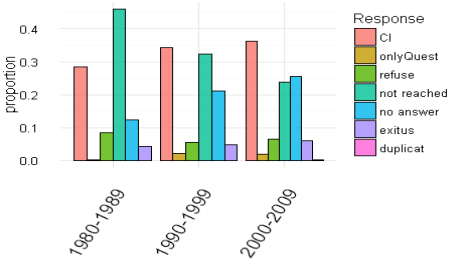


Tabla 3. Características de la cohorte

	Min	Media	Max
Seguimiento (años)	5	13	35
Edad participante	6	22	50
Año del tratamiento	0	5	19

Fueron identificados 1568 supervivientes a partir de 5 años, 536 (34%) participaron (509 rellenaron el cuestionario de calidad de vida), 83 (5%) no estaban vivos en el momento del reclutamiento, 480 (30%) no se pudieron contactar y 140 (6%) no aceptaron participar. La edad media de los participantes era de 23.87 (6.79 DS) y la máxima de 50 años. Entre los participantes 285 (53 %) eran hombres. El tiempo de seguimiento era de 13 años (rango 5-35). La edad media en el momento del diagnóstico era de 5 años (rango 0-19).
La mayoría de los participantes han sido tratados en las décadas más recientes (2000-2009).
Las neoplasias más prevalentes fueron los tumores del sistema nervioso central (N= 120, 22%) y las leucemias (N= 113, 21%).
En relación al estado de salud: 61 (13.1%) reportaron un cáncer secundario, 35 (7.54 %) una enfermedad tiroidea, 25 (5.3%) una deficiencia de hormona de crecimiento y 7 (1.5%) diabetes.
De las 14 preguntas sobre salud mental, 228 (44%) reportaron una disfunción al menos en 1 pregunta. Analizando separadamente por los 3 grandes tipos de cánceres (hematológicos, sistema nervioso central y otros tumores sólidos) el porcentaje de supervivientes que reportaban disfunciones en salud mental era más alto entre los supervivientes de tumores cerebrales, en cada una de los diferentes aspectos evaluados con el cuestionario.

CONCLUSIÓN

Un seguimiento a nivel nacional podría aumentar la potencia estadística necesaria para el análisis detallado de los efectos secundarios a largo plazo. Los resultados también permitirían desarrollar un programa de seguimiento adecuado para estos pacientes.

ISGlobal Barcelona Institute for Global Health

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Annex III

SCIENCE COMMUNICATION WORK

“Que sabem sobre la radiación? What we know about radiation?”
Elisa Pasqual and Elisabeth Cardis
Elipse June 2016

“Nothing has to be feared, only to be understood”
Elisa Pasqual
Public Health Association of South Africa newsletter,
October 2018, Edition 3

CIÈNCIA AL DESCOBERT / SCIENCE UNCOVERED

Què sabem sobre les radiacions?

Elisa Pasqual / Elisabeth Cardis

Enguany és el 30è aniversari de l'accident a la central nuclear de Txernòbil, i el 5è del de Fukushima, accidents que van causar una contaminació radioactiva generalitzada.

La radiació no és una cosa nova. Els humans hem evolucionat en un mar de radiació natural provinent de la terra i de l'espai. La radiació és energia transferida en forma d'ones o partícules. S'anomena ionitzant si té prou energia per canviar l'estructura d'un àtom (fer que guanyi o perdi electrons), i si no en té suficient, s'anomena no ionitzant. En la nostra vida quotidiana estem envoltats de radiació. Les fonts naturals de radiació ionitzant inclouen alguns minerals, com l'urani, i l'espai (raigs còsmics). La radiació ultraviolada (UV) del sol i el camp electromagnètic de la Terra són exemples de radiació natural no ionitzant. La radiació ionitzant s'utilitza per a la producció d'energia, o per al diagnòstic i tractament de malalties. Els telèfons mòbils, el Wi-Fi, els microones i les cuines d'inducció funcionen gràcies a les radiacions no ionitzants.

És dolenta la radiació per a la salut humana? Està demostrat que l'exposició a les radiacions ionitzants provoca càncer, cataractes i, en altes dosis, malalties cardiovasculars. La magnitud del risc, però, és una qüestió de quantitat: l'ús de radiació ionitzant està estrictament regulat per tal de minimitzar la dosi i, per tant, els efectes sobre la salut. En medicina, els beneficis dels exàmens de raigs X i la radioteràpia són enormes, encara que l'optimització de les dosis és molt important per minimitzar els efectes en la salut a llarg termini. L'exposició als raigs UV és també clarament cancerígena, tot i que l'exposició solar és important per a la producció de vitamina D. Els efectes adversos potencials per a la salut d'altres tipus de radiació no ionitzant són encara incerts. L'exposició tant a camps electromagnètics de baixa freqüència (ELF) com a radiofreqüència (RF), respectivament relacionats amb les tecnologies de distribució d'electricitat i les de comunicacions, ha estat classificada com a possible carcinogen per l'Agència Internacional de Recerca del Càncer (IARC) de l'OMS. La investigació continua, en particular al CREAL, per aclarir si existeixen aquests efectes.

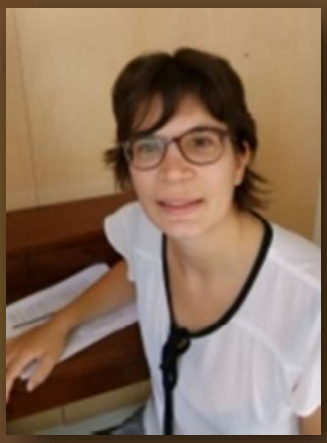
Monument and the fourth reactor (Wikipedia)

What do we know about radiation?

2016 marks the 30th anniversary of the accident at the Chernobyl nuclear power plant, and the 5th of the Fukushima accident. Both of them resulted in widespread radioactive contamination.

Radiation is nothing new. The human race evolved in a sea of natural radiation from the Earth and outer space. Radiation is energy transferred in the form of waves or particles. It is said to be ionising if it has sufficient energy to change the structure of an atom (make it gain or lose electrons), and non-ionising otherwise. In our daily lives we are surrounded by radiation, both from human and natural sources. Natural sources of ionising radiation include certain elements (e.g., uranium) and space (cosmic rays). Ultraviolet radiation (UV) from the sun, and the Earth's electromagnetic field, are examples of natural non-ionising radiation. Ionising radiation is used in industry for producing energy, and in medicine for diagnosing and treating disease. Your mobile phone, Wi-Fi, micro-wave and induction cooker work thanks to non-ionising radiation.

Is radiation bad for human health? It has been demonstrated that exposure to ionising radiation causes cancer, cataracts and, at high doses, cardiovascular diseases. The magnitude of the risk, however, is a matter of quantity: the use of ionising radiation is strictly regulated in order to minimise doses and thus health effects. In medicine, the benefits of X-ray examinations and radiotherapy are enormous, though optimising doses is very important to minimise any long-term health effects. UV radiation is also clearly carcinogenic, though solar exposure is important for vitamin D production. The potential adverse health effects of other types of non-ionising radiation are still uncertain. Both exposure to extremely low frequency (ELF) and radiofrequency (RF) electromagnetic fields (related to electricity distribution and communication technologies, respectively) have been classified as possibly carcinogenic by the WHO International Agency for Research on Cancer. Research continues, in particular at the CREAL, to clarify whether such effects exist ■



NOTHING IN LIFE IS TO BE FEARED, IT IS ONLY TO BE UNDERSTOOD.

Dr Elisa Pasqual
Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain
Universitat Pompeu Fabra (UPF), Barcelona, Spain

Radiation, as many major scientific findings, was discovered almost by chance. In all probability, early radiation scientists weren't imaging how such a discovery would shaped history. Today, as public health experts, we may be interested in this story as an opportunity to reflect upon the role of epidemiology in public health.

Radiation was discovered at the beginning of the 20th century. Soon, many industries became interested, foreseeing a high applicability in society. Cosmeticians and clock makers were interested in luminescence, a property of radioactive materials. Cosmetic products enriched with radium were sold promising a bright and ever-young skin. A special paint, enriched with radium was patented in 1903 and used to produce "radio-luminescent clocks". At that time, radiation was not suspected to be harmful; instead, it was thought to be a sort of lifelong elixir. The pharmaceutical industry started to sell radioactive products as the "panacea" of many diseases. At the same time, first observations that radiation could also kill cancer cells pushed Marie Curie to promote cancer treatment with radium (called "Curie-therapy"). During the same period the first x-ray diagnostic equipment started to be used.

As radiation was used by different industries, workers began to raise concerns regarding the potential adverse effects of radiation. One of the first groups that questioned radiation safety was a group of young women. They were employed at the United States Radium Corporation in New Jersey as radium dial painters. Because precision was required, they were taught to lick the paint-brush. A few became ill, suffering from mandible necrosis, dental infection, bone fractures, anemia (radium tends to accumulate in bone) and some died very young. The radium contained in the paint was suspected to be the cause of such diseases; however a proper public health approach was delayed because of conflicts of interest and the economic crisis. Marie Curie was asked to provide her opinion but she was initially reluctant to consider the radium, her invention, as the cause of such conditions. In parallel, dermatitis, cases of skin carcinoma and hematological lesions were documented among healthcare workers working with x-ray equipment. The same scientists that were experimenting with radiation also started to suffer skin and hematological lesions. In 1934 Marie Curie died of aplastic anemia.

Society started to change its attitude towards radiation. Throughout the century major events occurred that contributed to the spread fear and concerns about radiation. In 1945, the atomic bombs were dropped in Hiroshima and Nagasaki, causing unprecedented devastation and radiation related health effects that are still being observed today. Major environmental radiation disasters (Chernobyl, Techa-River and Fukushim) also occurred and impacted on the life of millions of people.

Meanwhile, the question of whether radiation can cause adverse health effects started to be properly scientifically addressed. Large studies were set up in different exposure settings: occupational (radiologists, miners, nuclear workers, atomic veterans), medical (patients treated with radiotherapy, exposed to diagnostic x-rays) and environmental (atomic bomb survivors, nuclear-weapons fallout, Techa-Rive and Chernobyl). A joint effort between epidemiologists, dosimetrists, statisticians and biologists resulted in advancing the methodology towards providing radiation risk estimates and defining dose-response relationships. In parallel to advances in epidemiology, awareness related to radiation safety grew and it was finally translated into radiation protection protocols and guidelines.

Today, the use of radiation is much more widespread than in the early 1900s but there are still many public health related questions that need to be answered and new challenges that need to be tackled. The use of radiation in medicine is one of these. Thanks to the introduction of radiation, diagnostic and therapeutic approaches have improved dramatically, resulting in major improvements in patient care. However, medical radiation has become the largest man-made source of exposure to ionising radiation for the general population. Such a growing source of exposure represents a double challenge for radiation epidemiology.

The first is a scientific challenge: risk estimation at very low doses (such as that typically delivered in medical settings) requires large epidemiological studies (of the order of 1 million individuals) to ensure sufficient statistical power. To date, direct risk estimates at this low dose level have not been well characterised. The second challenge is a public health matter: from an individual point of view, undergoing an examination represents a benefit (improved clinical care) and a minimal risk, because the dose levels are low. However, from a population point of view, even a small risk can result in an increased number of cancer cases (or other chronic diseases) if the exposed population is large. Thus, we should promote actions that aim to reduce population exposure without compromising individual clinical benefits.

The ultimate challenge for radiation epidemiology is the challenge of any science: promoting culture to contrast irrational attitudes by inspiring confidence in the knowledge. Marie Curie said: “Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”