CT scans in children and young adults and cancer risk: the Spanish EPI-CT cohort

Magda Bosch de Basea i Gómez

TESI DOCTORAL UPF / ANY 2016

Director de la tesi   Dr. Elisabeth Cardis
Tutor de la tesi   Dr. Josep Mª Antó

DEPARTMENT OF EXPERIMENTAL AND HEALTH SCIENCES

upf. **Universitat Pompeu Fabra** *Barcelona*

ISGlobal
Barcelona
Institute for
Global Health

In alliance with
CREAL

Acknowledgements

I would like to start by conveying my gratefulness for her generous support and scientific guidance to my thesis director, Dr. Elisabeth Cardis, who honoured me with her trust from the very first day. It has been a truly enriching journey at her side, and I will treasure all the acquired skills and knowledge for years to come.

I am also deeply grateful to my thesis supervisor, Dr. Josep Mª Antó, for his valuable advice and the efforts he has ensued to help bring forward the EPI-CT study.

I would also express my gratitude to the all the collaborating radiologists and IT professionals for their generous involvement in this study. Your help, talent and expertise is greatly acknowledged.

I consider it an honor to have worked with the EU EPI-CT Consortium members and had them as role models in my formation as a researcher. Thanks for all the reposed confidence in me.

A special thank you to the EPI-CT team (Jordi Figuerola, Ana Espinosa, David Moriña, Mariona Gil, Sam Reyes, Lourdes Arjona, Montse Plazas, Laura Argenté and Àlex Albert) who has been key in the development of the study and have demonstrated outstanding commitment, professionalism and perseverance during all this time. I am truly indebted to you all and I would not be presenting this compendium of work without your outstanding contribution.

Heartfelt thanks also, to the rest of the Radiation group and to all my CREAL / ISGlobal friends and colleagues, for the shared enthusiasm regarding this thesis, all the happy times, great memories and vibrant atmosphere of knowledge. Also, special thanks to all of those with whom I have crossed paths in this academic/professional road and departed later on as friends (among them Kyriaki, Eileen, Elena, Tom, Ane, James, Chelsea, Nina, Ana and so many more..). Thanks to Judith Garcia-Aymerich for generously sharing her passion (and knowledge) for epidemiology.

Thanks to my dearest friends from Escola Pia (Bofill), for (after 20 years) being such a solid base in my life, for all the happiness that revolves around this group of amazing individuals, for their support

throughout my life and for the deep sense of belonging that provides thriving through the times together, as family. Your unbreakable friendship is one of the winds that help me sail in life. To my University friends, a big thank you for seeking always new ways to support each other, for celebrating the highs and lifting each other's heads in the lows of our careers, for pushing me further that I thought I could go. Thank you to the rest of my good friends (Sara, Gato..), with whom I keep blissful memories, from IES-Abroad (colleagues and students/roommates alike) and URECMC to my beachvolley mates: thanks for being in my life.

M'agradaria agrair a la meva família el seu suport imbatible i amor incondicional, per ser-hi sempre, per creure en mi i acompanyar-me en cada decisió que he pres en aquesta vida. Gràcies al meu pare per infusionar la meva vida amb esperit d'aventura, per les fotografies familiars dalt dels arbres, per la seva entrega i dolça estima. A la meva mare, gràcies per aquest cor tan generós i bo, per convertir-nos sempre en prioritaris a la seva vida, per definir l'amor en majúscules. A les meves germanes per ser grans amigues a qui admiro obertament, per la camaraderia i perquè sempre és festa quan us tinc aprop. A la meva àvia per ensenyar-me què vol dir tenir capacitat de lluita, per ser font inesgotable d'energia i per centrar la família en l'eix que ens arrela a tots plegats. Gràcies per aquesta lliçó de vida.

I would also like to thank my extended family (cousins, aunts, uncles and brothers-in-law) for their encouragement during all this time.

To my Puerto Rican family, thanks from the bottom of my heart, for sending all the love and support across the ocean, for making me feel part of your family and for the warm embrace that comes with being one of yours.

And the most genuine thanks to the love of my life, for showing his deepest levels of commitment by moving to Barcelona for me, for his endless love, unbreakable faith in me and willingness to help with this thesis. Per omplir-me els ulls de flors i la vida d'intensitat. For being a true inspiration.

Barcelona, September 2016

Summary

Computed tomographic scanning is an extremely informative diagnostic technique, with a wide range of clinical applications. Since its introduction in the 1970 the use of CT scans and, more recently, the concerns about the potential deleterious health effects of ionising radiation exposure have grown in parallel. However, as of today, the potential increase in cancer risk related to the radiation exposure from CT scan is still under debate. Recently, some studies assessing the radiogenic cancer risks of CT scans have been criticised due possible dosimetric and epidemiological flaws. The present thesis assesses the main epidemiological factors that could bias the cancer risk estimates in these studies and introduces the EPI-CT cohort study, a European collaborative effort specifically designed to address these factors. This thesis also focuses on the Spanish part of the EPI-CT cohort, which includes 177,034 patients and is the 2nd largest cohort in EPI-CT. This thesis confirms an increase in the CT scan usage among patients aged less than 21 years in Catalonia (Spain) during the period 1991-2013, similar to what has been observed in other industrialised countries. Of importance is that, based on the results obtained within the Spanish branch of the EPI-CT study, the number of CT scans per person does not seem to significantly differ among the socioeconomic spectrum, suggesting a similar health care access and usage among all the cohort members. This thesis also includes a health risk assessment of the 2013 Spanish CT imaging practice in young population, which projects 0.2% additional cancer cases (over the spontaneously arising cancer cases) to occur in the expected lifespan of the CT scan exposed individuals. Finally, a very initial analysis quantifying the association between the cumulative organ-doses and leukaemia and brain cancer mortality among the Spanish EPI-CT cohort members is included, suggesting a dose-related increase in the risk of brain tumours and leukaemia mortality (non-significantly elevated for the later), consistent with what was seen in the studies of atomic bombs survivors. Although further research is required to elucidate the health effects associated to low-dose ionising radiation exposure, the increasing use of CT imaging in young people and the current level of knowledge warrants efforts to ensure the appropriate use of CT imaging and its dose optimisation.

Resum

La tomografia computaritzada (TC) és una tècnica de diagnòstic extremadament informativa, amb una àmplia gamma d'aplicacions clíniques. Des de la seva aparició en la dècada dels 70, tant l'ús de la TC com la preocupació sobre els possibles efectes nocius en la salut associats a l'exposició a radiació ionitzant han incrementat en paral·lel. Tot i això, avui dia, el possible augment del risc de càncer relacionat amb l'exposició a la radiació de la TC segueix sent objecte de debat. Recentment, alguns estudis que avaluaven el risc de càncer a causa de les tomografies computaritzades han estat criticats a causa de possibles errors dosimètrics i epidemiològics. La present tesi analitza els principals factors epidemiològics que poden esbiaixar les estimacions de risc de càncer en estudis d'aquest tipus i presenta l'estudi de cohorts EPI-CT, el qual és un esforç de col·laboració europea específicament dissenyat per fer front a aquests factors. Aquesta tesi també es centra en la part espanyola de la cohort EPI-CT, que inclou 177,034 pacients i és la segona cohort més gran de l'estudi EPI-CT. La tesi confirma un augment en l'ús de la TC en pacients menors de 21 anys a Catalunya (Espanya) durant el període 1991-2013, tal com s'ha observat en altres països industrialitzats. A partir dels resultats obtinguts a la part espanyola de l'estudi EPI-CT, no sembla que el nombre de TC per persona difereixi de forma significativa segons l'espectre socioeconòmic de l'individu, la qual cosa suggereix un accés i ús similar dels serveis d'atenció sanitària entre els membres de la cohort. Aquesta tesi també inclou una avaluació del risc per a la salut de la pràctica radiològica de l'any 2013 en població jove espanyola, la qual cosa projecta un 0,2% de casos de càncer addicionals (als que s'esperen que ocorrin de forma espontània) durant la resta de la vida d'aquells individus exposats a la radiació d'una TC. Finalment, també s'inclou una anàlisi molt inicial quantificant l'associació entre les dosis acumulades a nivell d'òrgan i el risc de mortalitat per leucèmia i càncer cerebral en els membres de la cohort espanyola EPI-CT. Els resultats suggereixen un augment en funció de la dosi del risc de mortalitat per tumor cerebral i leucèmia (no estadísticament significatiu per a leucèmia), d'acord amb l'observat en els estudis de supervivents de les bombes atòmiques. Encara que es necessiten més estudis per poder dilucidar els efectes en la salut associats a l'exposició a dosis baixes de radiació ionitzant, el creixent ús de la

TC en els joves i el nivell actual de coneixements justifiquen qualsevol esforç per assegurar l'ús apropiat de la TC així com l'optimització de les dosis.

Resumen

La tomografía computarizada (TC) es una técnica de diagnóstico extremadamente informativa, con una amplia gama de aplicaciones clínicas. Desde su aparición en la década de los 70, tanto el uso de la TC como la preocupación acerca de los posibles efectos nocivos en la salud asociados a la exposición a la radiación ionizante han incrementado en paralelo. Aún así, en la actualidad, el posible aumento del riesgo de cáncer relacionado con la exposición a la radiación de la TC sigue siendo objeto de debate. Recientemente, algunos estudios que evaluaban el riesgo de cáncer debido a las tomografías computarizadas han sido criticados debido a posibles errores dosimétricos y epidemiológicos. La presente tesis analiza los principales factores epidemiológicos que pueden sesgar las estimaciones de riesgo de cáncer en estudios similares y presenta el estudio de cohortes EPI-CT, un esfuerzo de colaboración internacional específicamente diseñado para hacer frente a estos factores. Esta tesis también se centra en la parte española de la cohorte EPI-CT, que incluye 177,034 pacientes y es la segunda cohorte más grande del estudio EPI-CT. La tesis confirma un aumento en el uso de la TC en pacientes menores de 21 años en Cataluña (España) durante el periodo 1991-2013, tal y como se ha observado en otros países industrializados. A partir de los resultados obtenidos dentro de la parte española del estudio EPI-CT, no parece que el número de TC por persona difiera de forma significativa a lo largo del espectro socioeconómico, lo que sugiere un acceso y uso similar de los servicios de atención sanitaria entre los miembros de la cohorte. Esta tesis también incluye una evaluación del riesgo para la salud de la práctica radiológica del año 2013 en población joven española, lo cual proyecta un 0,2 % de casos de cáncer adicional (a los que se espera que ocurran de forma espontánea) durante el resto de la vida de aquellos individuos expuestos a la radiación de una TC. Por último, también se incluye un análisis muy inicial en el que se cuantifica la asociación entre las dosis acumuladas a nivel de órgano y el riesgo de mortalidad por leucemia y cáncer cerebral en los miembros de la cohorte española EPI-CT. Los resultados sugieren un aumento en función de la dosis del riesgo de mortalidad por tumor cerebral y leucemia (no estadísticamente significativo para leucemia), en consonancia con lo observado en los estudios de supervivientes de las bombas atómicas. Aunque se necesitan más

estudios para poder dilucidar los efectos en la salud asociados a la exposición a dosis bajas de radiación ionizante, el creciente uso de la TC en los jóvenes y el nivel actual de conocimientos justifican cualquier esfuerzo para asegurar el uso apropiado de la TC así como la optimización de las dosis.

Preface

Since the introduction of computed tomography (CT) scanning early in the 70's, the use of this non-invasive procedure for detailed imagery of human anatomical inner structures has experienced a rapid growth, resulting in a broad positive impact on patient management and the follow-up of their conditions. In parallel, the significant doses involved in CT imaging coupled with the existing knowledge of the higher life-time risk of radiation-induced cancer in the young population compared to exposures during adulthood has led to increasing concerns.

Up to now, the assessment of the CT related risks, as well as the regulatory guidelines for population exposure, are based on the radioprotection model developed to linearly extrapolate the risks from high to low doses/dose rates. In the absence of direct low-dose risk measures, the linear non-threshold model (LNT) has received the endorsement of authoritative scientific agencies such as the United Nations Scientific Committee on the Effects of Ionizing Radiation (UNSCEAR), the National Council on Radiation Protection and Measurements and the U.S. Environmental Protection Agency. The use of the LNT model for assessing risks from ionising radiation is not free of its opposition share, which widely rely on the allegedly inconsistencies of biologic and experimental data at low doses. The validity of the LNT model and the shape of the dose–response curve for radiation-induced cancers at low doses is the subject of an ongoing debate, which highlights the existence of a research void and a unified opinion among the scientific community.

Due to the lack of direct measurements of radiation risks at low doses, in 2006 the US National Academy of Sciences expressed the need for well-designed cohort studies of individuals exposed to CT scan radiation (1).

Recently, several studies have attempted to directly assess the relationship between CT scan exposure during childhood and long-term cancer risk, although they have been largely criticised adducing significant dosimetric and epidemiological flaws.
It is in this context that the creation of a collaborative international cohort was gestated, and translated into the set-up of the EPI-CT

cohort in 2011. The EPI-CT cohort, an international collaborative cohort study coordinated by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) was carefully designed to exhaustively tackle all those issues that could lead to biased cancer risk estimates.

A critical related-work, which is the object of the present thesis, has been the setup and coordination of the Spanish branch of the EPI-CT cohort study, which includes 24 hospitals and more than 177,000 individuals. The Spanish cohort contributes 16% to the international cohort size, which, at present, surpasses the million of patients. The EPI-CT is one the largest cohort studies in the world, which provides a clear chance to obtain new evidence to clarify the controversy about the potential detrimental health effects of low-dose exposure.

Meanwhile, CT scans account for the largest contribution to the population dose from medical procedures (2) and an increasing number of reports describe their possible overutilization beyond the appropriate clinical justifications. Given the extensive use of imaging medicine, the CT scan related radiation exposure is, at present, considered a public health issue and efforts are devoted to optimise the protocols and uses. At the country level, monitoring the use of CT imaging is crucial to understand its intensity of use, to provide supported evidence for comparison with usage in other countries and to foster the avoidance of unnecessary examinations, particularly in vulnerable population, such as children and young adults. In countries such in Spain the limited monitoring of the CT scan usage precludes any assessment regarding the proper application of indication guidelines and prevents the decrease of radiation exposure of its population.

Since the field of CT imaging is rapidly expanding, with new indications reported every year, it is desired that the contents of this thesis may be useful for physicists who are involved in studies of radiation hazards and radiation protection, radiology physicians who may question themselves regarding the potential detrimental effects of the imparted doses and radiation epidemiologists working in the low-dose range. CT scan is, undeniably, a life saving medical tool and its use should be decided upon a balanced risk-benefit perspective. The contents of this thesis may provide some helpful

evidence, that together with the existing body of knowledge about the health risks at low doses, may contribute towards an informed decision-making process.

This thesis represents a collaborative effort by multidisciplinary professionals committed to contribute to the current knowledge in the field of radiation epidemiology and to the advocacy of the population health.

Thesis contents

Figure list

Table list

Abbreviation list

AEC	Automatic exposure control
ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
ATM	Ataxia telangiectasia mutated
BEIR	Biological Effects of Ionizing Radiation
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CNS	Central nervous system
CPS	Cancer predisposing syndromes
CT	Computerised tomography
DDR	DNA damage response
DDREF	dose and dose rate effectiveness factor
DNA	Deoxyribonucleic acid
DPCs	DNA-protein cross-links
DSBs	Double-strand breaks
EAR	Excess of absolute risk
EC	European Commission
ERR	Excess relative risk
EU	European Union
Gy	Gray
HR	Hazard ratio
HR	Homologous recombination
IARC	International Agency for Research on Cancer
ICD	International Code of Diseases
INE	Spanish National Statistics Institute
IRR	Incidence rate ratio
LAR	Lifetime attributable risks
LET	Linear energy transfer
LMDS	Locally multiple damaged sites
LNT	Linear non-threshold model
LSS	Life Span Study
MDS	Myelodysplastic syndromes
MPNST	Malignant peripheral nerve sheath tumours
NHEJ	Non-homologous end-joining
OSCC	Oxford Survey of Childhood Cancers

PACS	Picture archiving and communication system
RIS	Radiology Information System
ROS	Reactive oxygen species
RR	Relative risks
SES	Socioeconomic status
SI	International system of units
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
SSBs	Single-strand breaks
Sv	Sievert
TC	Tomografía computarizada
UNSCEAR	United Nations Scientific Committee on the Effects
US	United States
UV	ultraviolet radiation
WHO	World Health Organization

1. INTRODUCTION

1.1.   Ionising radiation

1.1.1. Concepts

Radiation is the emission or transfer of energy in the form of waves or particles. Ionising radiation is radiation with sufficient energy to knock tightly bound electrons out of the orbit of an atom or of a molecule, a process known as ionisation (3).

The two types of ionising radiation are particulate and electromagnetic radiation (4). Particulate ionising radiation consists of sub-atomic particles with mass and it includes:
-   alpha particles, which consist of two protons and two neutrons bound together into a positively charged particle;
-   beta particles, which are essentially high-energy, high-speed electrons and are negatively charged particles;
-   neutrons, small chargeless sub-atomic particles.

Electromagnetic ionising radiation entails the transference of energy by oscillating electrical and magnetic fields travelling through space at the speed of light; as bundles of energy wrapped up in photons (3). The frequency and wavelength of these oscillations determine the energy transferred by the electromagnetic radiation, and they also determine its properties (4). Typically, higher frequency and shorter wavelength will imply higher energy transference. Electromagnetic ionising radiation includes:
-   high-frequency ultraviolet radiation (UV) (below 121 nanometres of wavelength (3)) which has a high photon energy range;
-   x-rays, which are emitted from electron orbits, such as when an excited orbital electron "falls" back to a lower energy orbit;

-   γ-rays (gamma rays), which are photons emitted from the atomic nucleus, often as part of radioactive decay.

X-rays, which are at the upper end of electromagnetic spectrum, have very high frequencies (in the range of 10^{16} to 10^{20} hertz) and

very short wavelengths (10^{-8} to 10^{-12} metre) and, therefore, are high energy (5).

1.1.2. Sources and exposure to ionising radiation

Ionising radiation exposure is an inevitable effect of life on earth. Ionising radiation occurs naturally in the environment but it also can be artificially produced for energetic, research, medical, industrial and military purposes (6).

The main contributors to natural ionising radiation exposure are the very high-energy cosmic rays and the omnipresent radioactive nuclides on the earth surface that originated in the Big Bang. The concentration of both the cosmogenic and terrestrial isotopes varies according to the location, being the altitude and latitude of a site and its soil composition the main determinants of this concentration (7). Consequently, the doses received from natural ionising radiation vary from individual to individual according to his/her location (7). Additional sources of exposure for humans to natural ionising radiation include the naturally-occurring radioactive materials present in food and water, which contribute to internal exposure of the individual, and the exposure to radon gas which is produced by the decay of the uranium and thorium present of the soil (7). These external and internal doses of natural ionising radiation, known as background radiation, are on average higher than those from all man-made sources combined for most individuals (6).

Radiation quantities and units (8):

Absorbed dose is the energy absorbed per unit mass at a given point. In the SI system of units, the unit of measure is the joule per kilogram (J kg^{-1}) and is given the name gray (Gy). This measure is of fundamental relevance in radiological protection for calculating radiation dose but this physical quantification does not serve adequately to assess the effects of radiation in human health.

Organ dose is the absorbed dose averaged over an organ, i.e., the quotient of the total energy imparted to the organ and the total mass of the organ. The unit is the same as for absorbed dose, gray (1Gy = 1J kg^{-1}).

Equivalent dose to an organ or tissue is the average absorbed dose corrected by a radiation weighting factor that takes into account the quality of the radiation and its relative biological

effectiveness. This weighting factor is numerically 1 for 75 KV x-rays, considered to be the reference radiation. The unit is the joule per kilogram of tissue mass (J kg^{-1}) and is given the name sievert (Sv).

Effective dose is the weighted sum of equivalent doses to all relevant tissues and organs where the weighting factors represent a measure of the relative sensitivity of organs to radiation damage and their contribution to the overall determinant for stochastic effects. The unit is the joule per kilogram (J kg^{-1}) and is given the name sievert (Sv).

1 millisievert (mSv) = 1000 microsieverts (μSv); 1 μSv = 0.001 mSv
For X-rays, 1 mSv = 1 mGy

Background radiation doses are rarely measured at the individual level and instead are assessed using environmental data and exposure simulations. When quantifying the total background radiation doses, the doses from all ionising radiation sources incurred by different groups of people are summed and averaged in order to provide a worldwide average annual effective dose per person. The average individual effective dose per caput of the general population due to natural radiation is considered to be 2.4 mSv per year (6), and, in a large population, doses would be distributed as follows: 10% of the population would have annual effective doses greater than 3 mSv, 65% would have annual effective doses between 1 and 3 mSv, and the annual effective doses of about 25% of the population would be below 1 mSv (9).

Regarding man-made sources of radiation, the mining, milling and processing of mineral resources can lead to enhanced natural radioactivity exposure, due to the radioisotope content of the ore bodies and the mechanisms of the extraction process (10). Also, nuclear power production and the disposal of nuclear waste, the nuclear weapon production industry and specific research facilities are identified as potential sources of radioactivity for the general population (6). In all these cases, doses are estimated to be extremely low for the general population (in the microsieverts range), although for those involved in these occupational settings it could contribute to annual doses in the millisievert range (6).

Other sources of man-made ionising radiation include sites contaminated by military atomic weapon tests and nuclear accidents, as well as consumer products, including but not limited to some smoke alarms and tobacco, which contain measurable

quantities of radionuclides. Again, for the general population these sources contribute little to the estimates of the per capita exposure to ionising radiation, except for specific groups living in the immediate vicinity of these contaminated sites or for those who are occupationally involved with any of the named sources (9).

Over the last century, ionising radiation applications in medicine have increasingly become essential for the diagnosis, monitoring and therapy of different health conditions. As a result, nowadays, medical radiation has become the largest man-made source of ionising radiation exposure for human beings (6). These exposure sources, which include diagnostic radiology, radiotherapy and nuclear medicine, are estimated to be responsible for 0.66 mSv (20%) of the average annual per caput dose to the global population (11). In Europe, however, it has been estimated to account for up to 1.1 mSv (approximately 32% of the total annual per caput dose; 3.5 mSv). This represents about one-third of the corresponding medical radiation exposure in the United States (US) (12). Currently, it is estimated that the world average annual per caput dose from all the different radiation sources is on average 3.1 mSv. A summary of the global annual per caput effective dose of exposures to the various components of ionising radiation can be found in the Table 1.

Table 1. World average per caput dose by sources of ionising radiation
(UNSCEAR 1988, 1993, 2000 and 2008 reports).

Source	Per caput effective dose (mSv / year)			
	1988	1993	2000	2008
Natural background	2.4	2.4	2.4	2.4
Diagnostic medical radiology:				
• Diagnostic medical radiology	0.3	0.3	0.4	0.62
• Diagnostic dental radiology	-	0.003	0.002	0.0018
• Nuclear medicine	0.005	0.03	0.026	0.031
Nuclear test fallout	0.01	0.0037	0.005	0.005
Total	**2.72**	**2.74**	**2.83**	**3.06**

1.1.3. <u>Medical radiation procedures</u>

Among all the medical practices, diagnostic procedures entailing x-rays are the most common radiation application for countries with the highest levels of health-care[1]. It is in these countries where 75% of the world population resides (6). Given the topic of the present thesis the following sections will delve solely into x-ray radiation procedures, and, in particular, CT scans.

X-ray diagnostic radiation includes radiography, fluoroscopy, computed tomography (CT), interventional radiology, and bone densitometry. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has been monitoring the use of diagnostic medical examinations since 1955, and it has reported a steady increase in the annual frequency of radio-diagnostic procedures in high level health-care countries[1]. In particular, it was estimated that in these countries[1] the average annual frequency of diagnostic medical x-ray examinations per 1,000 population increased from 820 in the period of 1970-1979 to 1,332 in 2000-2007 (6), without taking into account dental x-ray. In Europe the total annual frequency of x-ray procedures (including dental and interventional radiology) is estimated to be 600 million procedures or 1,100 procedures per 1,000 population (11).

In Spain, according to the "European Commission 180 Radiation Protection Report" (11), the overall total frequency of x-ray procedures is 1,565 per 1,000 population (1435.7 conventional radiography and dental procedures, 24.7 fluoroscopy examinations, 100.2 CT scans and 4.2 interventional procedures), ranking 5th place among European countries in terms of number of radiation medical procedures (11). The annual ionising radiation per caput mean effective dose to the Spanish population in 2010 from diagnostic imaging and nuclear medicine was estimated to be 1.14 mSv and it was distributed as in the following Table 2:

---

[1] High level health care countries are defined in the UNSCEAR 2008 report as: health care level I in which there was at least one physician for every 1,000 people and health care level II, in which there was at least one physician for every 1,000 -2,999 people in the general population.

Table 2. The per caput mean effective doses (mSv) of the main groups of medical radiation procedures (conventional radiography and dental procedures, fluoroscopy, computed tomography, interventional radiology and nuclear medicine), according to the estimates of the Radiation protection 180 report.

	Per caput effective dose (mSv / year)				
	Conventional radiography*	Fluoroscopy	CT scan	Interventional radiology	Nuclear medicine
Spain (2010)	0.19 (16.7%)	0.09 (7.9%)	0.72 (63.2%)	0.074 (6.5 %)	0.065 (5.7%)
Total				**1.14 mSv**	

* including dental procedures

As observed in Table 2, in Spain computed tomography alone was responsible for more than half (63.2%) of the total population dose attributable to medical procedures. The remaining x-ray procedures were responsible for most of the residual population exposure, with nuclear medicine only contributing about 6% (11). Globally, the population exposure from medical radiation exposures is also dominated by CT, accounting for approximately 34% of the annual collective dose (6).

1.1.4. <u>CT scan frequency of use and related doses</u>

Frequency of use
Computed tomography is an x-ray imaging modality based on the measurement of x-ray attenuation from a multitude of angles around the patient (13). Since its introduction in the 70's, major progress has taken place and nowadays the most advanced clinical scanners are able to simultaneously acquire up to 320 slices per rotation in less than a second, with an isotropic spatial resolution of 0.3 millimetres, and reconstruct the image in a few seconds for a swift evaluation of the patient (14). Spain, is well endowed with CT equipment; the most up-to-date statistics estimate that in 2013 there were 744 CT scanners yielding fast and precise scan examinations for a wide range of age groups (15). As mentioned in the previous section, CT scanning is the most significant contributor to the radiation dose from diagnostic radiology (11). From 1996 to 2013 the annual rate of CT scan examinations in the Spanish population

almost tripled (from 34.89 to 92.52 CT scans per 1,000 population), and the annual number of CT scan examinations increased from 1.4 (16) to 4.3 million CT scans during the same time period (17). The upward trend in CT scanning frequency observed in Spain and some Western countries could be explained by the increasing number of CT scanners in use and the continuous enhancement of this diagnostic technique (2,18–21). In Spain, between 1996 and 2013 the equipment availability (scanners) raised from 0.88 to 1.6 per 1,000 population (22).

Although in Spain there is sparse data available on the age and sex distribution of the patients undergoing CT scans, in Western countries the largest increases in CT scan use have been seen in paediatric diagnosis (23) (with the exception of Australia (24)). The advent of the multi-slice spiral CT technique meant a decrease in image degradation from motion artefacts due to a more rapid image acquisition which, at the same time, avoided the controversial use of sedation in paediatric radiology (25,26). It also allowed for very detailed retrospective image reconstruction in an infinite number of planes (25,26).

It is important to note that in some Western countries such as the United States, the use of CT seems to have flattened out since 2007 (17, 24). Similarly, in Australia a decrease in the rates of CT scans has been observed among the youngest patients (5 to 10 year olds) and the growth has slowed among those above age 11 (24).

Using the typical averaged European age/sex distributions for CT scanned-patients established in the "European Guidance on Estimating Population Doses from Medical X-Ray Procedures - 154 report" by the European Commission, it is estimated that approximately 2% of all CT scan examinations are performed in patients under 15 years of age and 4% to 5% of all CT scans are performed in those that are below 21 years of age (28). UNSCEAR reported that in well-developed countries (health-care level I countries) 8%, 4%, 5% and 3% of all head, abdomen, thorax and spine CT scans respectively were performed in patients below 15 years of age (29) and over 10% of CT examinations worldwide are performed in patients under 18 years of age (6). In the scientific literature there is some uncertainty associated to the estimation of the pediatric CT scanning fraction and the relative frequency of

pediatric CT scanning is typically reported between 5 to 11% (23,30). According to the European 154 report, the proportion of CT scans undergone by the population increases with increasing age until they reach 74 years of age, when the proportion of examinations starts declining (28). The ratio of the number of examinations performed on male and female patients also differs, specifically for patients under 40 years of age, where male patients received a higher proportion of CT scans (28). The averaged European age/sex percentage of CT examinations by main types of CT scans for males and females below 25 years of age is summarised in the following Table 3:

Table 3. Averaged European age/sex percentage of CT examinations according to the estimates of the Radiation protection 180 report.

Scan type	Sex	Age bands				
		0 - 4	5 - 9	10 - 14	15 - 19	20 - 24
CT head	Female	0.53	0.46	0.7	1.24	1.55
	Male	0.75	0.76	0.84	1.29	1.62
CT neck	Female	0.29	0.2	0.26	0.71	1.09
	Male	0.25	0.49	0.34	1.08	1.43
CT chest	Female	0.16	0.21	0.21	0.47	0.75
	Male	0.32	0.28	0.22	0.75	1.13
CT spine	Female	0.06	0.16	0.3	0.9	1.49
	Male	0.1	0.22	0.3	1.15	1.76
CT abdomen	Female	0.07	0.08	0.18	0.5	0.83
	Male	0.09	0.12	0.21	0.63	0.82
CT pelvis	Female	0.16	0.19	0.75	1.59	1.71
	Male	0.1	0.28	0.67	1.67	1.75
CT trunk	Female	0.07	0.07	0.11	0.59	0.69
	Male	0.18	0.34	0.15	1	1.62
All CT	**Female**	0.17	0.25	0.41	0.88	1.15
	Male	0.24	0.37	0.54	0.99	1.32

The most frequent indications for paediatric and young adult CT scanning in the general population include trauma, especially of the head, abdomen, and chest, and suspicion and management of cancer (19,31). However, when all other investigations (e.g., ultrasound) are inconclusive, the following medical conditions are also diagnosed with CT imaging: cephalalgia with aggravated criteria,

sinusitis, general abdominal problems such as indigestion/dyspepsia and renal disease (19,31).

In the literature, head CT is consistently the most common scan procedure in paediatric and young adult patients (19,20,32–34), accounting for 65% (on average) of all CT scans performed. The second most prevalent CT type is abdomen and pelvis in some studies (20,33) and thorax/chest in others (19,32,34), accounting on average for 9% and 15%, respectively, of all CT scans performed. Spine CT, whole body CT, upper/lower extremities or a combination of anatomical areas round up the ionising radiation exposure received by children and young adults through this exploratory technique (19).

CT scan related doses
Table 4 summarises the typical effective doses from the most frequent examinations for the main groups of x-ray medical applications (conventional radiography, fluoroscopy, computed tomography and interventional radiology) for all ages/sexes based on the European Commission (EC) Radiation protection nº180 report (11). Doses delivered in one CT scan examination are significantly higher than those involved in most prevalent x-ray procedures, such as conventional radiography (11). As described in Table 4, effective doses from CT scanning are up to two orders of magnitude greater than those from corresponding conventional radiography, as can be observed when comparing an abdomen radiography (0.69 mSv) with an abdominal CT scan (10 mSv). CT scan effective doses are typically described to be around 10 mSv (averaging all ages), which is approximately in the range of doses involved in fluoroscopy and interventional radiology. However, as previously observed in Table 2, the less frequent use of the two latter techniques translates into a lower contribution in the annual per caput effective dose. As it can be observed, in Spain the average effective doses for most radiography, fluoroscopy and interventional procedures are slightly lower than the mean doses in Europe (average of 36 European countries) (28). On the contrary, the typical effective doses involved in head, spine, pelvis and trunk CT scans in Spain are marginally above the mean European doses (11).

To contextualise the typical patient doses, the occupational exposure reference levels to radiation for Europe have been limited to 20 mSv per year on average over 5 years (35).

The effective doses in Table 4 require a fair and careful judgement since they may fail to reflect all the variations in clinical practice that take place in Spain (as well as in the rest of the European countries included in the survey) along the age/sex spectrum, and should be considered as indicative of the effective dose range involved in these common x-ray procedures.

Table 4. Typical effective doses (mSv) for medical radiation applications (averaged for all sex/ages) according to the Radiation protection 180 report.

Conventional radiography

	Chest / Thorax	Cervical spine	Thoracic spine	Lumbar spine	Mammo-graphy	Abdomen	Pelvis & hip
Spain	0.06	0.09	0.23	0.89	0.28	0.69	0.55
Europe	0.10	0.19	0.64	1.23	0.27	0.90	0.71

Fluoroscopy and interventional radiology

	Ba meal	Ba enema	Ba follow-through	IVU	Cardiac angio-graphy	PTCA
Spain	4.9	8.3	7.7	2.5	4.9	19.0
Europe	6.16	8.48	7.25	2.90	7.71	15.2

Computed tomography

	CT head	CT neck	CT chest	CT spine	CT abdomen	CT pelvis	CT trunk
Spain	2.0	1.8	4.4	8.9	10.0	7.8	15.8
Europe	1.92	2.52	6.56	7.72	11.3	7.26	14.8

While 'effective dose' is a useful dosimetric concept when dealing with radiological protection, 'organ doses' is more directly relevant to the quantification of the risk of cancer in a specific organ or tissue, particularly in the case of partial body irradiation, as is typically the case for CT examinations. Table 5 describes the selected organ-doses for the three most common CT examinations. These were obtained using the Monte Carlo simulation of a Siemens Sensation 16 CT scanner, based on the CT scan parameters of clinical paediatric imaging protocols (36). In this analysis,

computational anatomic phantoms (computerised representations of the human anatomy for use in radiation transport simulations) from newborn to sex-specific 15-years old, were used.

Generally, it can be observed that for those organs entirely covered by the CT beam, the incident radiation to the internal organs experienced greater attenuation in the older anthropomorphic computational models (phantoms) than in the younger ones due to larger body diameters and higher shielding by overlying tissues. This resulted in lower organ-doses in the older phantoms compared to the younger ones. Additionally, in children, the smaller organ size and the thinner tissues increase the probability of being exposed to the scattered radiation from the primary x-ray beam (37). Typical organ-doses for the most common CT examinations are in the range of 0 mGy/100 mAs for the more distal organs to over 10 mGy/100 mAs for those included in the imaging field. It is worth mentioning that the recommended mAs settings for children weighting less than 15 kg are reduced to 25 mAs for abdomen and thorax scans (i.e. 15% of the adult settings) (38).

Table 5 also shows that in a head scan, the brain and the eye lens, two highly radiosensitive organs, received non-negligible doses. Using the same scanner and scanning protocol, the brain of the newborn is estimated to receive 1.5-fold the dose to the brain of the 15-year old male phantom. The heart wall in the newborn phantom is also estimated to receive a 1.5-fold higher dose than that of a 15-year old phantom (male or female).

Table 5. Organ absorbed doses (mGy/100 mAs) for newborn, 1, 5, 10 and 15 year (male and female) reference phantoms, calculated as for a Siemens SOMATOM Sensation 16 scanner model with a tube potential of 100 KVp (36).

CT type	Organ	Age reference phantoms					
		Newborn	1-year	5-year	10-year	15-year female	15-year male
CT head	Brain	11.1	9.3	8.3	8.1	7.8	7.4
	Pituitary gland	9.8	7.7	7.6	7.3	7.3	6.5
	Lens	11.5	10.3	10	9.5	10.7	10.1
	Eyeballs	11	10.6	9.7	9.4	9.8	9.7
	Salivary glands	5.9	5	7.8	6.9	7.7	7.9
	Oral cavity	4.1	7.6	7.4	7	5.2	5.1

CT	Organ	Age reference phantoms					
		Newborn	1-year	5-year	10-year	15-year female	15-year male
head	Spinal cord	0.5	0.6	0.7	0.3	1.2	1.4
	Thyroid	1.8	1.2	1	0.8	0.5	0.5
Chest CT	Oesophagus	10.2	8.5	7.4	6.2	5.2	4.9
	Trachea	10.6	9.7	9.2	7	6.4	5.9
	Thymus	11	10.1	9.9	7.8	7	6.3
	Lungs	11.8	11.1	9.7	8.4	7	6.7
	Breast	11.4	9	8.2	7.3	6.5	6.4
	Heart wall	12.2	11	9.9	8.5	7.5	7.3
Abdomen - pelvis CT	Stomach wall	11.8	9.8	9.3	8.1	7.6	6.4
	Liver	12.1	10.4	9.3	8	7.5	6.7
	Gall bladder	11.1	9.7	9.1	7.9	6.6	5.7
	Adrenals	10.6	8.8	8	6.7	5.9	5.3
	Spleen	12	10.7	9.5	8.6	7.8	6.8
	Pancreas	11.9	10.1	9.1	7.4	6.7	5.3
	Kidney	12.2	11.4	10.4	9.1	8.2	6.7
	Small intestine wall	12	10.1	9.7	8.1	7.5	5.8
	Colon wall	12.5	10.8	10.6	9.4	9.2	7
	Prostate	7.2	5.1	1.8	1.7	NA	0.8
	Uterus	9.9	7.8	7	5.9	4.3	NA
	Testes	1.6	1.8	1.1	0.7	NA	0.7
	Ovaries	10.4	9.4	8.3	6.7	5.4	NA

Although the doses associated with a single scan are low, it is important to bear in mind, that a non-negligible fraction of the CT scanned individuals will receive more than 1 scan during their follow-up visits, which will translate in a cumulative exposure of tens of mSv (19,24). In some instances, cumulative exposure may exceed the 100 mSv, the dose range in which dose-related increases in cancer risk have been demonstrated (1).

The increasing awareness of risks associated with radiation exposure has triggered a search for dose reduction in CT scanning, particularly in children, who for the same machine settings, receive higher doses than adults. Starting in 1990, a decline in the organ-doses of paediatric CT scans has been observed in countries like Great Britain and Germany (39). This reduction is mainly due to the

increasing knowledge about the potential risks, the European Commission's initiative to set guidelines for better practice in CT scans (40), and later on, from the Image Gently initiative (41).

The adequate adjustment of the CT scan parameters to the body weight and size of the child may significantly reduce radiation exposure (26,36). However, the use of adult protocols for pediatric and young population scanning is still common practice in some countries / hospitals (42,43).

Other ways to reduce the dose involved in pediatric CT scanning include:

- Using helical CT instead of conventional CT scanning reduces the number of repeat CT sections and therefore reduces radiation exposure due to a lower frequency of motion artefacts (26).
- Using in-plane bismuth shields for paediatric CT to avoid exposure of sensible areas such as gonads or breast tissue in girls, where the association between low-dose radiation exposure and the development of deleterious health effects has been well described (44).
- Enabling the following scanner integrated radiation saving tools:
  - Automatic exposure control (AEC), an x-ray termination device designed to adjust the CT tube current (the number of x-ray photons produced) to the patient attenuation of the x-ray beam, leading to a radiation dose reduction from 26 to 43%, depending on the child's anatomy without trading-off for image quality (25).
  - Adaptive section collimation, which is designed to reduce over-scanning or over-ranging in the longest axis of the patient (z-axis), reducing radiation up to 38% (25).
  - Bow-tie filters or wedge filters, which are CT filters designed to shape the x-ray beam and remove lower energy photons before the beam passes through the collimators, leading to a 50% reduction of the dose to the peripheral regions of the patient when

compared with the non-shaped filters (flat filters) (25).

Regardless of the previously mentioned radiation-saving mechanisms, the most effective way to decrease ionising radiation exposure from CT scan in paediatric and young patients is through an adequate justification of the procedure based on existing clinical referral criteria (40). In Sweden it is estimated that 30% of the annual CT examinations in patients ranging 0-20 years old were not justified (45). To my knowledge, there is no information available evaluating the proper justification of CT scans among young Spanish population. However, there are some indications about the lack of awareness of existing clinical referral criteria for radiological imaging among paediatric emergency medical staff of some public and private Spanish hospitals (46).

1.1.5. Conclusions

Diagnostic procedures entailing x-rays are the most common source of exposure to human-made radiation, and CT scanning is, among all the medical procedures, the most significant contributor to the effective annual dose per caput of the general population. Although CT scan effective doses are described to be around 10 mSv (averaging all ages), the use of repeated CT scans during the follow-up of specific diseases is not uncommon, leading to cumulative doses in the tens of mSv.

In the last two decades, Spain has witnessed a significant increase in the annual rate of CT scan examinations. However, the lack of available data precludes us from identifying which population groups have been more affected by this increment. In other Western countries the largest increase in CT scan frequency use has been seen in paediatric imaging, which despite the undeniable diagnostic benefits of CT scanning, justifies current concerns regarding the potential harm to young individuals.

1.2. Health effects of low-dose ionising radiation exposure

1.2.1. Biological mechanisms of radiation effects at low doses

When x-rays photons deposit their energy in the molecules and atoms of the cell, several energy-transfer processes occur. Depending on the energy of the photons and the absorbing material, these processes are the Compton scattering effect, the pair production or the photoelectric effect (1). In the range of diagnostic radiology, both the Compton and the photoelectric processes take place, displacing the orbiting electrons from an atom (47).

Along the primary electron track travelling through biological tissue, ionisation can occur anew, producing secondary electrons with lower energies and amplifying the electronic interactions in a localised area or cluster (1). These clusters of damage are a unique characteristic of ionising radiation, in contrast to other forms of radiation (48) or normal endogenous oxidative processes within the cell (1). At 10 mGy, a relevant dose to CT scanning, one cell nucleus is usually irradiated with approximately 10 electron tracks or fewer, typically at a distance above 1 μm. Therefore, it is considered unlikely that one remote electron track will interact together with other tracks to increase or decrease the cancer risk, which led scientists to conclude that at 10 mGy any significant event is due to one-track action (49).

When the interaction of primary electrons occur directly with a critical target such as deoxyribonucleic acid (DNA) molecules in the form of strand breaks or damaged bases, it is known as a *direct effect* (1). This is an event of fairly uncommon occurrence with x-rays due to the small size of the target; the diameter of the DNA helix is only about 2 nm in width (50). If, as introduced before, along with the primary electron, secondary ionisations occur in a very small volume close to the DNA molecule (within a few nanometres of the DNA molecule), there is a possibility of locally multiple damaged sites (LMDS) (1).

Alternatively, an x-ray photon may directly ionise a water molecule, which is the most prevalent chemical compound in the human body, representing up to 70% of the mass of all human tissue (1). The ejection of an electron (e^-) from the water molecule (H_2O) forms an ionised water molecule (H_2O^+), which may interact with another water molecule ($H_2O^+ + H_2O$) and produce a highly reactive hydroxyl radical (OH^-) (1). This and the following reactions produce hydrated electrons (e^-_{aq}), hydroxyl radicals (OH^-) and hydrogen free radicals (H^+), which may interact with DNA (among other critical cellular constituents); this is known as *indirect effects* of radiation (1). Indirect effects may also result from the interaction of photons with other cellular components (50). For instance, radiation-induced lipid peroxidation, another distinguishing property of ionising radiation, generates free radical intermediates or peroxyl radicals ($ROO^{\bullet}$) that significantly contribute to DNA base damage (1).

Figure 1. Illustration adapted from the figure in Morgan and Sowa (51) of a photon - atom interaction and the resulting effects of the ejected electron in a DNA molecule. Above: direct effect of the ejected electron over the DNA molecule. Below, photon - atom interaction, the subsequent radiolysis of a water molecule by the ejected electron, and the production of the reactive species (hydrogen radical, hydroxyl radical, and hydrated electron) causing indirect effects in a DNA molecule.
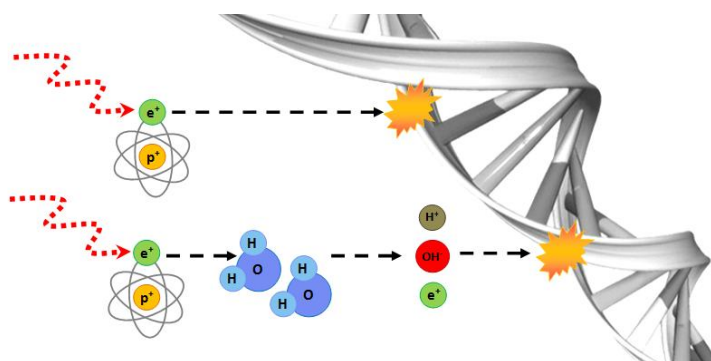
As introduced before, *indirect* action is the predominant process resulting from the interaction of low linear energy transfer (LET) radiation (such as x-rays) with biological material (50). The resulting reactive oxygen species (ROS) may generate over one hundred different oxidative LMDS when interacting with the DNA

molecules (1). Among this array of different lesions, those with a higher biological relevance are single-strand breaks (SSBs), double-strand breaks (DSBs), nucleotide base damage, DNA-DNA cross-links and DNA-protein cross-links (Table 6).

Table 6. Expected DNA lesions of biological significance per cell out of an absorbed dose of 1 Gray (deposition of 1 joule in 1 kg. of tissue) and their primary repair pathway.

DNA lesion	Frequency of events per Gray (52)	Primary repair pathway
DNA single strand breaks	1,000	Base excision repair
DNA double strand breaks	30-40	Non-homologous end joining and homologous recombination
Nucleotide base damage	10,000	Base excision repair
DNA-DNA cross-links	30	Unclear
DNA-protein cross-links	150	Unclear

The types of lesion produced by low-LET ionising radiation in DNA are, in general, chemically identical to those formed by endogenous ROS (53), and are mainly base damage and DNA single strand breaks (SSBs) (Table 6).

The DNA double helix structure is ideally built for repair because it is equipped with two complementary copies of all the genetic information. Therefore, when one strand is altered, the other strand retains an intact copy of the genetic material that could be used as a template for repair.

Nucleotide base damage, if left unrepaired, may affect physiological states and disease phenotype (54). However, they are efficiently corrected through the base excision repair pathway, a mechanism that exsects the mutagenic base lesion from the DNA and replaces it by an adequate one (55). The same repair pathway is activated when a DNA single-strand break (SSB) is produced by reactive oxygen species, which in general results in accurately repaired DNA (1). SSBs pose a serious threat to genetic stability and cell survival, and

this explains the extremely efficient mechanisms for their repair that cells have developed (56). DNA-DNA and DNA-protein cross-links (DPCs) may prevent the normal operations of the cellular nucleus, thus impeding DNA replication and transcription (57,58). However, the biological consequences of unrepaired cross-links and their repair mechanisms remain elusive.

Regarding double strand breaks, the number of DSBs induced by radiation represents only 6% of the radiation-induced SSBs (Table 6) (1,59). The induction of DSBs is considered the most harmful lesion produced by ionising radiation (29,60). When complex DSBs occur no intact DNA strand is left to be used as a guide for restoration. Fortunately, human cells are equipped with two major DSB repair processes, the error-prone non-homologous end-joining (NHEJ) pathway, which is the most prevalent repairing process, and the homologous recombination (HR) (1). The NHEJ rejoins the fragments of DNA near the break and fills in the ends, generally with the loss of one or more nucleotides at the site of joining (61). On the other hand, HR uses the homologous chromosome itself as a template to copy the nucleotide sequence in need of repair and, although it is a more demanding process, it is significantly more precise (62). While NHEJ can occur during all phases of the cell cycle, HR occurs only after replication (S phase) (63). The HR repair pathway is also activated when the replication fork collapses at unresolved single-stranded DNA lesions (64).

Because DNA contains the genetic information of a cell (the instructions required for the cell to perform its function and to replicate) it is essential to secure its integrity and stability. Lesions to the DNA may cause structural damage, altering or arresting critical cellular processes, such as DNA replication or transcription (65). Although the DNA insult is generally believed to be the most relevant biological damage leading to health effects, other endpoints such as the damage of the nuclear membrane, the DNA-membrane complex, and the outer cell membrane may also be of importance in terms of altering signal transduction pathways (1).

In order to ensure the integrity of the genome, cells have evolved a complex mechanism to identify and restore the various types of DNA damage (66). This repair machinery is also activated when DNA damage occurs due to endogenous processes, such as spontaneous hydrolysis, errors during replicative or DNA repair

events (65), base adduct formation, or when damage occurs by the ROS released during normal mitochondrial function or lipid peroxidation (1), among others. These DNA attacks of intrinsic origin occur at a higher frequency than those caused by exogenous agents (65), such as ionising radiation. It is estimated that billions of cells within the human body are subject to tens of thousands of spontaneous and metabolically generated DNA-damage processes on a daily basis (65), and in general, the vast majority are properly repaired through a highly coordinated cascade of events known as the DNA damage response (DDR)(1).

Both for endogenous and for exogenous DNA damage, the activation of the molecular mechanism responding to DNA-damage requires the recognition of the damage-induced chromatin alterations. It also requires the activation of a signal transducer, such as the kinase ataxia telangiectasia mutated (ATM), which will activate or inactivate the 'effectors' that will directly participate in the induction of cell cycle arrest, apoptosis, repair process or chromatin remodelling depending on the cell type and extent of the damage (55). The activation of regulatory mechanisms related to chromatin organization has been observed at doses as low as 5 mGy, and an increased expression of genes related to DNA damage response and p53 pathway has been observed from 25 mGy onwards (67).

As will be discussed further in section "1.3 Effect modification and confounding", dysfunctional ATM and other signalling proteins cause failure to sense DNA damage and intracellular signal transduction preventing the cascading repair mechanisms to initiate (68). This and other defects in DNA repair underlie a number of human congenital disorders that confer a predisposition to malignancy (69).

As previously mentioned, the restoration of DNA double-strand breaks is not exempt of errors, and clustered DNA damage can compromise the restoration process. Unrepaired or defectively repaired DSBs may lead to rearranged gene order, lose of both gene fragments or of entire chromosomes, deletions of chromosome segments, inverted reattachment of broken segments, attachment of segments of different chromosomes, or the exchange of segments between two broken chromosomes (70). In summary, if a break is

produced it can either be restituted or if the strand fails to be properly rejoined it could produce an aberration. If the aberration is small and not lethal to the cell (such as a small deletion or a symmetric translocation) it is passed on to the cell progeny and persists for many years (71). Importantly, dose and dose rate of ionising radiation seem to be determinants of the fraction of misrepaired events (1,71).

The formation of a tumour is considered a multistep clonal process of overlapping stages (1). Although it is possible that radiation acts at several stages in multistage carcinogenesis, evidence suggests that ionising radiation, through excessive production of reactive oxygen species, is primarily capable of kicking off the malignant transformation of normal cells through mutations in genes that control key regulatory pathways in the cell (*tumour initiation*)(60). In the case of solid tumours, mutations in gene and chromosomes that inactivate the control of cell proliferation (tumour suppressor genes) may be of importance in their initiation phase (1). On the other hand, proto-oncogene activation (mutations that increase the expression level or activity of genes normally involved in cell growth and division) by chromosomal translocation and gene loss events are often associated with early lymphoma and leukaemia (1). The mutations or damage may be erroneously repaired and if cell viability is achieved, the transformed genotype will be passed on and expressed in the cellular offspring of the initiated cells. Existing evidence suggest that the tissue microenvironment through cell to cell communication could be responsible of preventing the apoptosis of the damaged proliferating cells (72). A clonal expansion of these mutated offspring cells starts due to mitogenic stimuli in what is known as the *promotion phase*. The subsequent onset of genomic instability through further gene mutations and chromosomal aberrations in cell clones may be a critical event in the transformation from benign to malignant state (73). It is later on, in the *progression phase,* which may take many years, that the proliferated cells suffer an intense genetic and phenotypic modifying process that leads to the development of cell heterogeneity within the tumour, and to the acquisition of invasive and metastasic properties (74).

It has been suggested that, in addition to the genetic damage, ionising radiation may alter the production of soluble growth

factors, cytokines, reactive oxygen species (ROS) and extracellular matrix proteins affecting the cellular microenvironment and the signalling between cells (75). These alterations may create the necessary context for the promotion of cancer development (76).

Figure 2. Illustration of the radiation-induced process of tumorigenesis of a somatic cell at low doses of x-rays exposure.
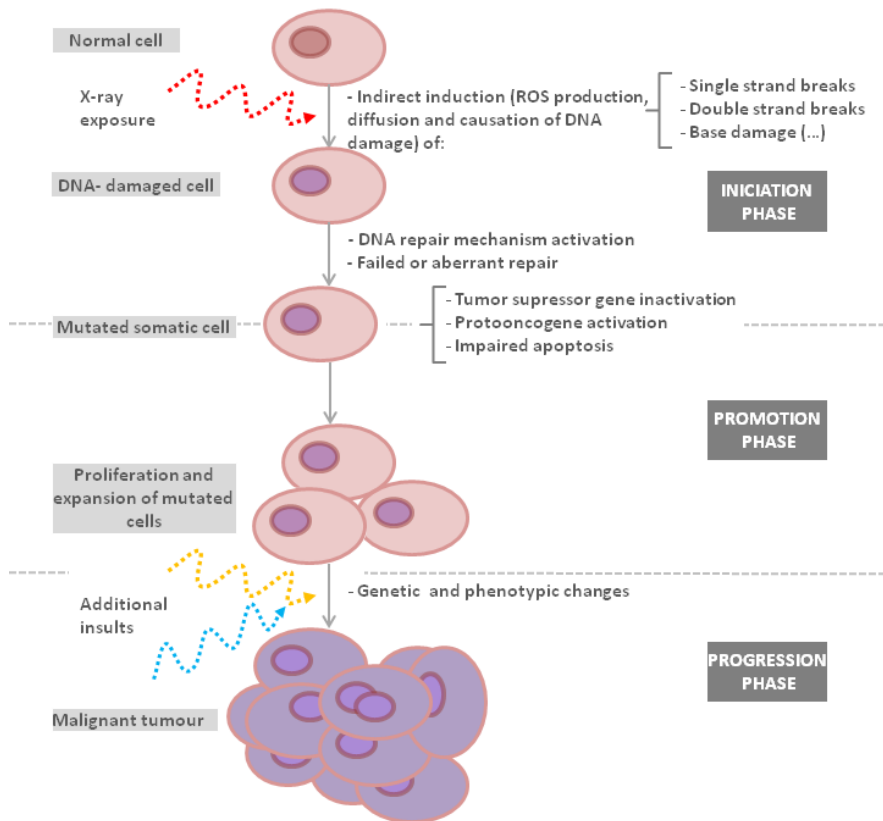
1.2.2. <u>Epidemiological evidence for ionising radiation induced cancer</u>

> The terminology used in the present thesis in terms of doses is aligned with the categories defined in ICRP publication 99 and used by the World Health Organization in radiation-related reports (77,78) . Therefore, for photon radiation, low doses are considered to be doses below 100 mSv.

This section aims to review the main epidemiologic evidence for ionising radiation exposure and cancer, and given the scope of the EPI-CT study and of this thesis, special consideration is given to the evidence regarding the risks of brain cancer and leukaemia in young people following low dose ionising radiation exposure. The deleterious health effects resulting from ionising radiation exposure are of "stochastic" nature: their probability of occurrence increases with the dose received (79). The magnitude (and even existence) of an effect following low-dose exposure is still the subject of an intense scientific debate.

Quantitative information on the long-term cancer risks typically following intermediate to high doses of ionising radiation has been provided by several studies (30). The magnitude of the carcinogenic risk from radiation exposure has been periodically reviewed by UNSCEAR, resulting in multinational recommendations for radiation limits. In 2000, the International Agency for Research on Cancer (IARC) evaluated ionising radiation as carcinogenic to humans (Group 1) (80). In 2004, x-rays appeared on the *Eleventh Report on Carcinogens* of the U.S. Department of Health and Human Services (81).

Epidemiologic evidence relies heavily on the results of the studies based on the survivors of the atomic bombs in Japan (the Life Span Study; LSS), which are complemented by studies of exposed population, either due to medical reasons (34,82–84), accidentally (85) or occupationally (86). All these epidemiological studies strongly suggest that the relationship between ionising radiation exposure and solid cancer induction is approximately linear in the moderate dose range from approximately 0.15 Gy to approximately 1.5 Gy (49,87). For radioprotection purposes, the International Commission on Radiological Protection (88) has based its

recommended limits on a linear extrapolation from high radiation doses and high dose rates to low radiation doses and low dose rates by applying a dose and dose rate effectiveness factor (DDREF) equal to 2 (88). The VII report of the National Academy of Sciences (NAS) Committee on the Biological Effects of Ionizing Radiation (BEIR) combined data from human and animal studies and proposed a DDREF of 1.5, with a wide uncertainty interval (1). Despite some dissenting voices, the linear non-threshold model (LNT model) is considered the most appropriate dose–response description for radiation protection purposes at low doses. The LNT model assumes, in agreement with mechanistic biophysical data, that any single electron track could produce an event such as one or more DNA double strand breaks (DSBs) with carcinogenic potential if repaired incorrectly (1). Given that track number is directly proportional to dose, it is considered that even the smallest doses may pose some risk and that at low-dose exposures the predicted level of excess cancer risk is infinitesimal although it is not zero (78). As a result of this, at low doses where a diminutive cancer risk would be expected, it is difficult to detect reliable risks against the normal fluctuations in the baseline cancer incidence rates.

At levels most relevant to medical diagnostics, epidemiologic studies would need large numbers of exposed individuals at low doses. Furthermore, current epidemiological data do not allow providing a definitive answer regarding the shape of the dose–response curve at these levels of exposure. The linear extrapolation assumption (LNT) is consistent with the excess cancer risks proportional to exposure predicted by the Life Span Study, as will be presented below (49,87). Additionally, there is direct evidence for risk in groups exposed to low and moderate doses compatible with the LNT model (30).

The hypothesised existence of a threshold level of exposure below which there is no biological response would imply that for a specific exposure range the repair processes were totally effective. Additionally the existence of a threshold would invalidate the theory that even a single track is able to produce a biological effect (87). Available data on biological mechanisms does not seem to indicate significant departures from linearity of the tumorigenic response at low doses in cellular endpoints (chromosome aberrations, gene mutation, and cell transformation) (49,87).

Complementarily, the rate of error in the DNA repair pathways activity has been well characterized and the existence of spontaneous DNA damage in mammalian cells support the absence of dose threshold or even "hormetic" (beneficial) effects of low doses of ionising radiation (49,73,87). However, contrary opinions consider that the immediate protections at cell level, and different processes such as the adaptive response, genomic instability and bystander effects in non-exposed cells are incompatible with the LNT model (89). As previously indicated, the carcinogenic risk induced by low doses of ionising radiation is controversial and the dominating mechanisms at low doses remain still elusive.

As mentioned earlier, the Life Span Study (LSS) is the cornerstone of radiation epidemiology. The LSS consists of a group of 120,000 people, 93,000 who were in Hiroshima and/or Nagasaki at the time of the bombings and 27,000 who were not in the cities. The LSS cohort has been followed-up since 1950 for haematopoietic and lymphatic cancers and since 1958 for the rest of malignant tumours. Extensive information regarding the initial radiation received at the time of the explosion and the factors influencing the individual doses (distance from the epicentre of the bombings, shielding, or posture, among others) was collected and has allowed for an accurate estimation of individual absorbed doses for 15 organs. Leukaemia was the first cancer to be associated to the radiation exposure delivered by the A-bombs just 3 years after the explosions (90). However, an association was observed only for acute and chronic myelocytic leukaemias and for acute lymphocytic leukaemia (91) but not, until very recently, for chronic lymphocytic leukaemia (a type of leukaemia extremely rare in Japan) (92).

The risk of leukaemia differed by age at the time of the exposure, being around 70-times higher in those who were 10 years of age at the time of the explosions compared to those exposed later in life, around 10-times higher in those 20 years of age compared to those exposed at older ages and almost non-existent for those 30 years or older at the time of the bombing (93). Leukaemia type is strongly related with age, and, therefore, acute lymphoblastic leukaemia (the most common among young people) dominated the absolute number of cases, because its relative risk was higher among the young (90,91,94). Chronic myelogenous leukaemia and acute myelogenous leukaemia are more common among elderly people

and since the radiation-related relative risks were lower they accounted for less cases (91).

A matter that remains unresolved is that no leukaemia cases were identified within individuals with intrauterine exposure to the A-bombs, or within the first 9 months of postnatal life. However, the size of the exposed population was very small and, consequently, the statistical power to identify any leukaemia increase was low (90,95). A hypothesis suggests also that the under-recording of cases and the exposure to such low doses are behind the unnoticed increments of incidence (90).

The excess relative risks of leukemia after the A-bombings were higher for females than males, in contrast with the naturally occurring acute lymphoblastic leukaemia which presents an approximate sex ratio of 1.2:1 for boys compared to girls (96,97). The leukaemia excess risk peaked within 6-10 years after the bombings, and decreased later on (91,93), and risks decreased faster among those exposed at younger ages compared to older individuals (98).

The LSS proved that the best fit to describe leukaemia mortality data is a linear quadratic dose–response model in the 0 to 2 Sv dose range with a linear component in the low doses, an upward curvature in the upper part of the dose range, and a downward curvature above the 2 Sv to describe the effect of dose sterilisation occurring at high doses (90). In the study, an increased cancer mortality risk of 1.4 (Confidence Interval (CI) 95%: 0.1-3.4) was associated with a mean dose to the bone marrow of 30.5 mGy (1,99).

The first indications of an excess risk for solid tumours arrived later on, approximately 10 years after the bombings (94). Most related studies are based on mortality data because solid cancer incidence data became available after 1990 (1). The results of the study indicated that the excess of absolute risk (EAR) for all solid tumours considered together increased throughout life for all ages whereas the excess relative risk (ERR) decreased with increasing attained age. An elevated risk was still observed at the end of follow-up. In general, the solid cancer incidence data described a significant linear no-threshold dose-response over the 0 to 1.5 Gy

range, slightly flattening at higher doses (100). The excess risk for non-gender-specific cancers was similar in both sexes (1). Similarly to leukaemia, significant radiation-associated increases in risk of site-specific cancers were observed for oral cavity, oesophagus, stomach, colon, liver, lung, non-melanoma skin, breast, ovary, bladder, nervous system and thyroid (100), exhibiting significant variation with attained age and age at the time of the exposure (100). Specifically, the brain and nervous system showed elevated risks of borderline statistical significance for glioma and meningioma (ERR/Sv: 0.56 (95% CI: -0.2-2.0) and 0.64 (95% CI: -0.01-1.8), respectively), while the risk for schwannoma was extremely high (100). For the LSS survivors that were younger than 20 years of age at the time of the exposure the ERR/Sv for brain and central nervous system tumours was 0.88 (95% CI: 0.28-1.78) (101).

As previously mentioned, leukaemia incidence and mortality (as well as non-melanoma skin and bone cancer incidence) (94) exhibited an upward curvature in the dose-response whereas most cancer sites incidences over the full dose range were best fitted using a linear model. The disparity in the dose–response relationship and onset patterns may be indicative of different pathogenesis between leukaemia and solid cancer.

Although much of the cases in the LSS were observed in survivors exposed to doses above 1 Gy, this group of highly exposed population comprises less than 3% of the cohort, whereas about 35,000 (75%) received moderate doses between 5 and 200 mGy (100). When analyses were limited to cohort members with doses of 0.15 Gy (150 mGy) or less, a statistically significant dose-response with all solid cancers as a group was observed (100). A marginally significant dose-response (p=0.08) for the same outcome was observed when the analysis was restricted to doses <100 mSv (100).

A significant finding of the late effects of radiation was an increased risk of solid cancer mortality sustained throughout life (102), which was significant in the range of 0 to 0.20 Gy or higher, with no evidence for a threshold below which no effects are expected, and an ERR/Gy of 0.56 (102). Similarly to what was observed with leukaemia both the excess relative risk and the excess absolute risk for solid cancer mortality were higher in the young at

the time of the bombings, reinforcing the idea of an accentuated radiosensitivity in the young ages (102).

The late activity onset of the cancer registry prevented the assessment of childhood cancer incidence. However, the observed high risks of adolescence and young adulthood tumours suggested that the risks for childhood cancer would have been extremely high (100).

Accidental large-scale releases of ionising radiation such as in the Chernobyl disaster, the nuclear reactor accident that occurred in 1986 in the city of Pripyat, provided conflicting results in terms of evidence for childhood cancer. On the one hand, the Chernobyl studies bolstered the evidence supporting the particular sensitivity of children to cancer induction, in this case to radiation-induced thyroid cancer, after exposure to estimated organ-doses of less than 1 Gy through radioactive isotopes of iodine (85). On the other hand, these studies did not find substantive evidence for an increased risk of childhood leukaemia (90), though the studies were limited in statistical power and had methodological limitations including absence of accurate individual dose estimates (103). It is worth mentioning that the fact that childhood leukaemia is a rare disease prevented the detection of small changes in its incidence among the exposed (104). Again, the best fit to the dose-response relation between exposure from the iodine radioisotope I-131 (the main contributor to the radiation dose to the thyroid) and thyroid cancer was a linear model up to 1.5-2 Gy on exposed children (85).

Other nuclear installations, mainly Sellafield and Dounreay in the United Kingdom, and Krümmel in Germany have been studied due to the suspected existence of clustered childhood leukaemia cases in their vicinity (105). The current methodological limitations of studies near nuclear installations (different study design and unspecificity of leukaemia type, among others) compromise the possibility of associating an elevated risk of leukaemia in children under 15 years of age with living near a nuclear power plant (97).
Recent results of studies based on young people (18 years old and under) exposed to the ionising fallout of the nuclear accident of Fukushima have detected an excess of thyroid cancer within 4 years of the release (106), although several methodological flaws may have impacted these precipitous estimations (107).

Of significance to radiation epidemiology are the studies based on population exposed to ionising radiation due to nuclear testing. The tests of more than 100 nuclear weapons at the Nevada test site performed between 1952 and 1958 shed light on the increase risk of childhood leukaemia from protracted, low dose and low dose-rate exposure to the nuclear fallout, confirming the predictions of models derived from the findings of moderate-to-high dose studies (108). In a published study, those who were younger than 20 years of age at the time of the exposure and received the highest doses showed the greatest risks of acute leukaemia (108).

The set of studies based on population irradiated due to therapeutic or diagnostic purposes complements extensively the LSS findings discussed previously, with the caveat that some of the medical irradiated groups may have had a different health status at the time of the exposure compared with the Japanese population before the Atomic bombs exposure (30,96). Comparatively, medical series (mainly radiotherapy) exhibit lower relative risks than the ones estimated in the studies of the bomb survivors. This is especially true for leukaemia patients who may have received radiotherapeutic doses (although more highly fractionated) that are well into the cell sterilization range. The elevated therapeutic doses prevent the viability and division of cells with the potential to be leukemogenically transformed and may explain the discrepancy observed in terms of risk estimates with the individuals in the LSS cohort (109).

In general, the population treated with significant doses for non-malignant diseases are valuable because they provide information on effects of ionising radiation exposure excluding the confounding effects due to the disease to be diagnosed or treated (1). Additionally, the epidemiological studies with large sample sizes that are based on a substantially higher dose range and where the signal-to-background ratio is more accentuated have the potential to detect the smaller increases in paediatric cancer incidence (110). The high-doses used in radiotherapy to treat these patients increase the risk of second cancer occurring later in life, particularly of brain, breast and thyroid cancer (30).

Adult patients treated with x-rays for ankylosing spondylitis (111,112) were studied for leukaemia mortality risk and cancer incidence. Although the mean total body doses of both studies are in the range of high acute doses (>1 Gy), they provided evidence of a linear dose-response model for all cancers except leukaemia (96). In the case of leukaemia mortality it was observed that a linear-exponential model, where the exponential term allowed for cell sterilization in heavily exposed parts of the bone marrow, described adequately the risk for all leukaemia types, excluding chronic lymphocytic leukaemia (CLL) (1). Importantly, the greatest leukaemia mortality rates were observed 1 - 5 years after the first irradiation session, supporting the evidence that leukaemia exhibits a short lag time from radiation exposure to onset of disease (111,112).

The treatment of *tinea capitis* (a superficial fungal infection of the skin of the scalp) and enlarged tonsils using radiation provided important information about radiation-induced childhood cancer risks. In the study of 20.000 *tinea capitis* patients irradiated at very young age, they received an average absorbed dose of 0.3 Gy and 1.5 Gy to the bone marrow and brain, respectively (1). Subsequently, an increased risk of leukaemia and brain tumours was observed in comparison with those that were not irradiated. Additionally, benign tumours, breast and thyroid cancer incidences were higher among the irradiated population (113). Age was a determinant of the risk and a higher thyroid cancer risk was observed among those below age 5 at the time of the exposure (113). Among those who received radiotherapy for enlarged tonsils and adenoids an increased risk of thyroid cancer, benign and malignant salivary gland tumours was observed (114). For that same group an increased risk of acoustic neuromas and schwannomas (115) was also observed. Infants treated with radiation due to enlarged thymic glands confirmed an increased risk of childhood leukaemia and thyroid cancer shortly after irradiation compared with their unexposed siblings (90).

Radiation exposures of the order of a tenth of a mGy from obstetric radiography (x-ray exposure) in the Oxford Survey of Childhood Cancers (OSCC) (116) and other studies of subjects exposed in utero (117) provided evidence that low-dose prenatal irradiation (fetal doses of approximately 10 mSv) might increase the risk of

childhood cancer and leukaemia mortality (90,116,117). The OSCC study was severely criticised due to possible selection and recall biases (mothers of children with cancer might remember exposures during pregnancy better than mothers of cancer-free children) that could have influenced the homogenous increase of approximately 40% risk between all different childhood tumour groups and also of leukaemia, without any specificity in the risk estimates (94). A later review of all the evidence regarding childhood cancer after intrauterine irradiation concluded that doses to the fetus in utero of the order of 10 mSv discernibly increase the risk of childhood cancer in approximately a 6% per Gy (118).

The carcinogenic potential of postnatal exposures to diagnostic radiation used to be less studied than in utero exposures. Lately, however, the number of studies addressing this subject has increased. Several studies have assessed the long-term effects of diagnostic x-ray exposures from conventional radiographic examinations during childhood (119,120). Generally, the very low radiation doses involved in these examinations (median cumulative effective doses around 5 μSv) were not associated with a risk of leukaemia or solid tumours (119,120). However, the studies presented some potential for recall bias, residual confounding due to the socioeconomic status of the patients and inadequate dosimetry.

As previously mentioned, CT scans confer substantially higher doses to organs and tissues in the scanning field than do conventional radiographies. Five epidemiological studies on CT scan exposure during childhood and long-term cancer risk have been published recently (34,82,121–123), with quite consistent results mostly pointing towards an increase in radiation-induced cancer risks in children. Three of them (Pearce (82), Mathews (121) and Krille (34)) found increased risks for leukaemia and brain tumours associated with CT scan exposure. A fourth study by Huang and co-authors (122) did not evaluate leukaemia risks but also found an increased risk of benign brain tumours associated with paediatric head CT examinations. Journy (123) also found increased risk for leukaemia, lymphoma and central nervous system tumours associated to CT exposures though these were not statistically significant (124). Krille *et al.* found that the standardised incidence ratio (SIR) for lymphomas and solid cancers decreased substantially when those subjects with medical conditions

possibly associated with an increased risk of cancer were excluded from the analysis (34). In contrast, the SIR for leukaemia changed only marginally in the same study.

Table 7 summarizes the main characteristics of the studies assessing the association of radiation exposure from CT examinations and cancer, and the main criticisms received.

Table 7. Features of the studies assessing the cancer risk after CT scan in young people (size of the study, risk assessment and criticisms that could invalidate the results)

Country, publication year	Population size and age range	Risk measures of main outcomes (95% CI)	Main criticisms
United Kingdom, 2012	178,604 patients 0-22 years old	ERR/mGy leukaemia = 0.036 (0.005–0.120) ERR/mGy brain tumour = 0.023 (0.010–0.049)	- Potential bias by indication - Organ-dose errors
Australia, 2013	10.9 million people 0-19 years old	IRR brain cancer after CT= 2.44 (2.12–2.81)	- Exposure misclassification
France, 2014	67,274 patients 0-10 years old	ERR/mGy leukaemia = 0.057 (-0.079–0.193) ERR/mGy brain tumour = 0.022 (-0.016–0.061)	- Small number of cases - Short follow-up
Taiwan, 2014	24,418 patients 0-18 years old	HR benign brain tumour= 2.97 (1.49–5.93)	- Short follow-up - No dose estimation - Short exclusion period
Germany, 2015	80,000 patients 0-15 years old	SIR leukaemia= 1.72 (0.89–3.01) SIR CNS=1.35 (0.54–2.78)	- Potential reverse causation and confounding by indication

ERR/mGy: Excess relative risk; proportional increase in risk over the background absolute risk (in the absence of exposure) per unit of radiation (mGy).
IRR: Incidence rate ratio; the incidence rate among the exposed portion of the population, divided by the incidence rate in the unexposed portion of the population.
HR: Hazard ratio; ratio of the hazard rates of exposed versus non-exposed.
SIR: Standardised incidence ratio; observed / expected cases.

Despite the apparent consistency of these results, these studies received criticism for several reasons, as exposed in the table. In the

Pearce study (82) the possible inclusion of patients with cancer predisposing syndromes (Down syndrome or neurofibromatosis type-1 patients, among others) and, benign conditions with malignant transformation potential could invalidate the results (125). There was some potential for organ-dose errors in said study. Additionally, it is worth mentioning that, in Pearce, once the myelodysplastic syndromes (MDS) were excluded from the risk estimates, the ERR/mGy was still positive but not statistically significant (ERR: 0.019 (95% CI: -0.012, 0.079), demonstrating the influence of MDS in the study (126). Still, the risk estimates for leukaemia are compatible with what was observed in the LSS study, whereas the ERR/mGy for brain tumours were higher than what was observed in the LSS.

In the Mathews study (121) limited dosimetric methods were used, and an average effective dose from the published literature was imputed to each type of CT, potentially leading to substantial exposure misclassification. Furthermore, it has been hypothesised that reverse causation could be behind the early appearance of solid cancers after CT, and the absence of expected cancers in radiosensitive tissues (breast) or the significantly high IRR for melanoma and Hodgkin's lymphoma (which have not been observed in larger radiation studies) are of concern. The all-cancer IRR (24% higher for the exposed population) is somehow surprising and far from being comparable with the LSS estimates.

As for Journy and colleagues (123), the follow-up of the patients after exposure to the CT scan was short (4 years on average), which prevented the study to provide any conclusive results about radiation-induced risks given the fact that the latency period of cancer, and particularly of solid tumours, could require several decades before disease manifestation.

Diverse criticism were also raised for Huang (122), including a short follow-up of the participants, absence of any dosimetric reconstruction impeding the study of dose-response relationships and short exclusion periods of incident cases after the first exposure, potentially allowing for some confounding by indication (lag period of 2 years).

Krille *et al.* (34) published results on the German component of the EPI-CT study and, based on small numbers of cases, the authors concluded that still potential for reverse causation and confounding by indication could not be discarded when interpreting the excess of observed cases compared with the expected number of cancer cases.

1.2.3. Selected health outcomes

This section will delve on leukaemia and brain cancer, which are the main radiation-induced neoplasms that will be assessed in the EPI-CT international study, which motivated the setup of the Spanish EPI-CT cohort described in this thesis. The selection of these health endpoints was driven by the fact that, in the age-range of the exposed cohort members, brain cancer and leukaemia are the most common malignancies. In Spain (as in Europe), the rates of cancer incidence among young population are dominated by leukaemia and central nervous system (brain) cancer, with rates standardized to the world standard population of 38.9 and 25.6 per 100,000 population (0-19 years), respectively (127). Additionally, ionising radiation is the only established environmental risk factor for both diseases (128,129).

Cells of different tissues demonstrate different response rates for different endpoints for the same radiation dose (130). The induction of stochastic effects, and particularly of cancer, varies widely across different tissues depending on the absorbed dose, dose rate, quality of radiation, and of the specifics of the cells composing the irradiated tissue (71).

Nowadays, radio-responsiveness of cellular tissue is considered dependant on the inherent cellular radiosensitivity, the kinetics of the tissue (turnover cycle), and the way cells are organized in that tissue. Rubin and Casarett established a theory on cell radiosensitivity based on cellular proliferation, differentiation and life span (131) and generated the following classification of cell sensitivity to radiation. Table 8 displays the classification of cells according to relative radiosensitivity based on the criterion of cell death, from the more radiosensitive category (vegetative intermitotic cells) to the less radiosensitive category (fixed postmitotic cells).

Table 8. Classification of cells according to relative radiosensitivity; from Rubin and Casarett (131).

Cell type	Properties	Examples
Vegetative Intermitotic	Cells that divide regularly and have no differentiation	- Stem cells of hematopoietic tissue - Spermatogonia - Ovarian cells - Intestinal crypt cells (small intestine)
Differentiating Intermitotic	Cells that divide regularly (limited number of divisions), some of which are differentiated	- Dividing differentiated cells of hematopoietic tissue - Differentiated spermatogonia - Spermatocytes - Ovocytes
Multipotential connective tissue cells:	Cells that may divide irregularly or sporadically in time and differentiate following stimuli.	- Endothelial cells - Fibroblast - Mesenchymal cells
Reverting Postmitotic	Cells that do not divide regularly, except if major damage implies depletion of similar cells. Different degrees of differentiation.	- Duct cells in salivary glands, liver, kidney, and pancreas - Basal cells of the thyroid and adrenal glands
Fixed Postmitotic	Cells that do not divide and are highly differentiated	- Long-lived neurons - Muscle cells

According to the Rubin and Casarett theory, cells with a high turnover rate will lead to earlier radiation responses in the tissue, due to the relatively short lifespan of mature functional cells whereas slow cell division or infrequent cell division will lead to a delayed radiation response and a slower appearance of the damage.

On the other hand, undifferentiated cells, which typically have no specialised function, are actively dividing and have a long dividing future compared with highly differentiated cells, which usually have less reproductive activity than undifferentiated cells. Therefore, radiation damage in differentiated cells will be less critical than in undifferentiated cells (stem cells and precursor cells), which will divide many times (131).

This may explain why some organs may be immediately affected by radiation whereas for others it may take longer to express any deleterious effect.

Neoplasms of the hematopoietic system: leukaemia

Description of the hematopoietic tissue:
The hematopoietic system is responsible for the production of balanced levels of blood cells over the lifetime of a human being mainly through the bone marrow, its central hematopoietic tissue. The regional distribution of the active bone marrow in infants and children changes with age. In newborns, the skull and many of the longer bones of the lower extremities contain red marrow with hematopoietic elements (132). In adults, however, it is mostly located in flat bones such as the hip bone, thoracic vertebrae and ribs (132).

The continued production of the different blood cells depends directly on the presence of hematopoietic stem cells; the pleuripotential cells that are the ultimate source of all the hematopoietic elements, such as white and red blood cells, macrophages, and platelets (133). The main characteristics of the hematopoietic stem cells are their long-term self-renewal ability through mitotic cell division and their capacity for differentiation of their daughter cells.

Description of the hematopoietic neoplasm: Leukaemia
Leukaemias are neoplastic proliferative diseases of the hematopoietic system characterized by an abnormal growth of a single type of immature blood cells. Leukaemic cells rapidly accumulate in the bone marrow, ultimately replacing most of the normal cells that circulate in the peripheral blood (134). Among the general population leukaemia is the second most common incident blood neoplasia, after lymphomas (135), with an age adjusted rate of 7 cases per 100,000 population in Europe, and a slightly smaller age adjusted rate in Spain (6.5 cases per 100,000 population)(136). Among the younger population it is the most common childhood malignancy, accounting for 30% of all the cancers diagnosed in children under 15 years of age in industrialized countries (137). In Spain, among the 0–14 years old age group population, leukaemia presented an aged adjusted rate of 47.0 cases per million children whereas in Europe the rate was 44.0 cases. Leukaemias tend to peak in the 1-4 year old age group, accounting for 45% of all the malignancies in this age group (138).

Leukaemia is typically more frequent in males than females. A recent paper indicated that in Spain, in the 0-14 years old age group, precursor cell leukaemias of the lymphoid lineage (mostly B-cell leukaemias) were the most frequent haematological malignancies, accounting for 60% of all malignancies with an age-adjusted incidence rate of 42.7 per million children-years) (139).

If we look at the time trends of the age-specific rates of leukaemia, as reported by the 7 Spanish population-based cancer registries participating in the Cancer Incidence in Five Continents initiative, little stability over time is observed due to the low incidence of the disease (135) (see Figure 3). A recent work assessing the time trends in incident childhood leukaemia in Spain from 1983 to 2007 pointed out that an increase in childhood leukaemia (0 to 14 years) was observed up to 1991, with no evidence of an increase in more recent years, probably reflecting improvements in diagnostic techniques and data registration up to 2007. Over the same time period, leukaemia incidence for adolescents (15 to 19 years) did not show significant changes (118).

Figure 3. Combined leukaemia incidence time trends by age groups reported by 7 population-based cancer registries in Spain, obtained from the Cancer Incidence in Five Continents website (140).
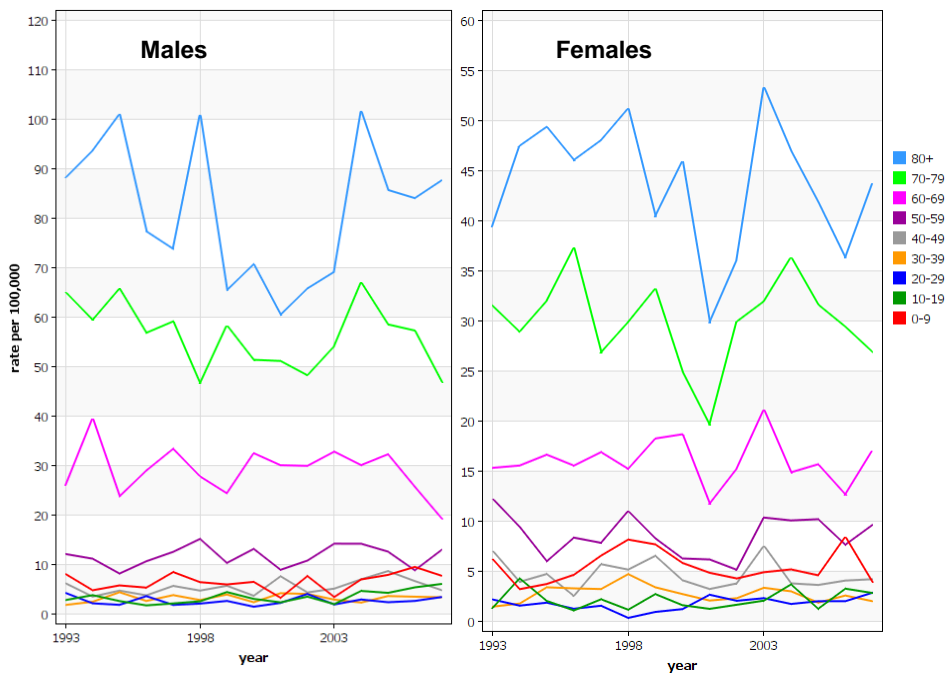
The all-ages European mortality due to leukaemia is estimated to be 4.8 per 100,000 males and 2.9 per 100,000 females and the time trends have shown declines in both sexes over the last decades, particularly in children and the young. The observed declines may be attributable to therapeutic advancements, the availability of radiotherapy treatments and better diagnostic techniques (141). The 2005-2007 age-standardised mortality rates from leukaemia in the European Union (EU) are estimated to be 0.88 and 0.69 per 100,000 boys and girls, respectively (142).

Leukaemias are classified by the WHO in myeloid and lymphoid leukaemias according to their cell lineage derivation, although lineage plasticity is expected in immature neoplasms and/or in the clinical course of the disease (143). As mentioned, the two main categories of leukaemia are:

- Myeloid leukaemias, which are clonal hematopoietic stem cell disorders characterised by hypercellularity of one or more cells of the myeloid lineage in the bone marrow (143), typically neutrophils and monocytes.
- Lymphoid leukemias, are a group of diseases characterised by the proliferation of precursor cells of the lymphoid lineage leading to excessive white blood cells in the bone marrow and other organs (143).

Leukaemias are also subdivided according to the maturity/differentiation of their originating cells, where neoplasms developed from precursor cells (i.e.: acute myeloid leukaemias and lymphoblastic leukaemias) are considered separately from neoplasms developed from more mature cells (B-cell lymphocytic leukaemia, for example). Figure 4 pretends to illustrate the classification of the main types of leukaemias according to their lineage and cell differentiation.

Figure 4. Illustration of the hematopoietic stem cell, its further division in precursor cells or blasts (lymphoid blast, myeloid blast, erythroblast and megakaryoblast) and their differentiated progeny, adapted from the figure in Cancer Research UK (144).
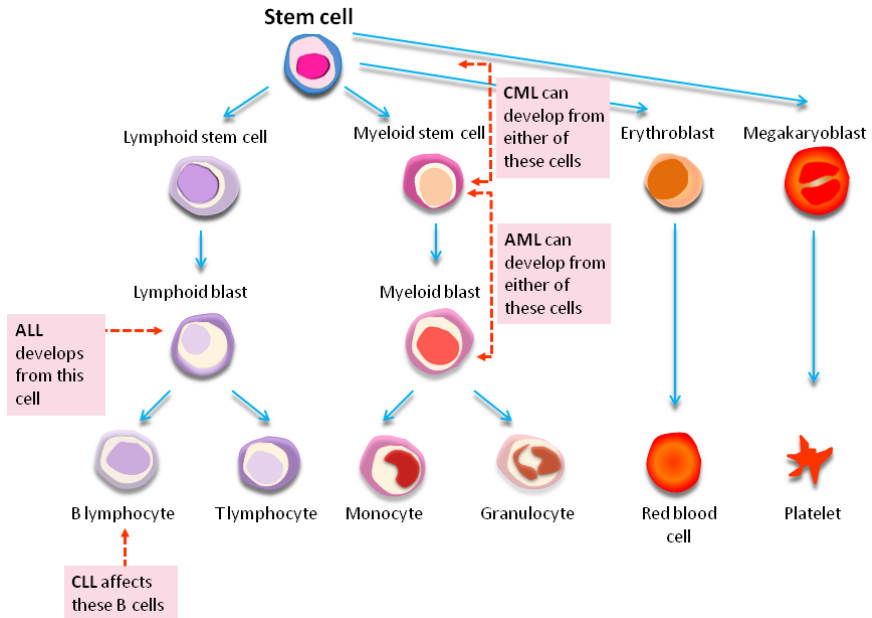
The main four types of leukaemia are described below in Table 9.

Table 9. Epidemiology, annual incidence and risk factors of the main leukaemia types.

Major leukaemia types	Epidemiology	Annual incidence	Risk factors
Acute lymphocytic leukemia (ALL)	The most common leukaemia in children, accounting for 75% of all acute leukaemia cases in children aged 0-14 years. Its peak prevalence is between ages of 2 and 5 years, but it can occur in adults, especially over age 65. Risk factors known for only 5% of cases.	4.2 cases per 100.000 persons in children aged less than 15 years in Spain. 30 cases per million in western countries among children, 40 among white adult population.	- Previous cancer treatment - Exposure to ionising radiation. - Genetic predisposing disorders. Down syndrome, etc. - Exposure to benzene
Acute myeloid leukemia (AML)	The second most frequent type of leukaemia in childhood although it occurs in adults too.	3.3 - 4 cases per 100.000 persons in Europe	- Previous cancer treatment - Exposure to ionising radiation. - Genetic predisposing disorders. Down syndrome, etc. - Exposure to benzene
Chronic myeloid leukemia (CML)	Occurs mostly in adults, its peak prevalence is beyond age 50 but it can occur at any age. It represents between 1 and 3% of the childhood leukaemias.	1 - 1.5 cases per 100,000 persons in Europe	- Exposure to ionising radiation.
Chronic lymphocytic leukemia (CLL)	The most common leukaemia in adults and it is almost never seen in children. It represents 35% of all leukemias	3-7 per 100.000 persons in Europe	- Familiar history - Historically not linked to ionising radiation exposure

The incidence rate of lymphoid leukaemia in both Spanish males and females has increased from 28.2 cases per million children-years (up to 14 years old) in 1983 to 34.5 in 2007 (145). Acute myeloid leukaemias (AML) account for 17.6% of all the Spanish leukaemia cases in this age range, with an ASRw of 8.1 cases per million children-years and with the highest incidence rates observed among the infant group (<1 year old) (145). Chronic myeloproliferative leukaemias accounted for 2% of all leukaemias in children with an ASRw of 0.9 cases per million children-years

and the highest incidence observed among those younger than 1 year (145). Besides ionising radiation exposure, the possible causes for most leukaemias are not known (128) and the risk factors that have been identified explain only a small fraction of the total number of cases (145).

Radiation induced leukaemia:
There are many unanswered questions regarding our understanding of the mechanisms underlying the unequivocal association between ionising radiation and the development of leukaemia. However, it is well known that the hematopoietic stem and progenitor cells are exquisitely vulnerable to the radiation-induced reactive oxygen species (ROS) (146,147) and that the regulation of the intracellular ROS levels is critical to preserve the self-renewal – proliferation – differentiation equilibrium of the multipotent haematopoietic cells (148). It has been demonstrated that the deregulated presence of ROS above normal concentrations in the hematopoietic stem cells leads to an abnormal hematopoiesis (and to an impaired hematopoietic function, as a consequence) and altered lineage commitment (147,149). It also results in cumulative DNA damage affecting the hematopoietic stem cell cycling, which could be the underlying mechanism explaining the onset of the hematopoietic malignancies (148).

Radiogenic leukaemia presents no distinctive clinical features from the spontaneously occurring leukaemia and there are not any known specific DNA abnormalities related to this malignancy that uniquely correlate with radiation exposure (1).

The onset of radiogenic leukaemia seems to be highly influenced by the genetic make-up of the exposed individual, where inherited variations are of clear clinical importance for their contribution to leukemogenesis (150). With the exception of chronic lymphocytic leukemia which exhibits a weak link (although questioned (151)) with radiation exposure, exposure to ionising radiation increases the risk of onset of all forms of leukemia, and extensive epidemiological research provide a sound scientific base beyond anecdotal correlation (92).

Several studies have shed light on the interval needed to allow sufficient time after radiation exposure for leukaemia to manifest

itself, with a minimum latency of 2 to 5 years between exposure and leukaemia onset in young people (1).

Regarding radiogenic leukaemia mortality, epidemiological evidence from protracted low-dose and low-dose-rate exposures to γ-rays indicated that the baseline leukaemia risk (i.e. risk for a group of unexposed persons) increases by 19% after exposure to a dose of 100 mGy, closely agreeing with what was observed in the LSS cohort, suggesting similar risks in protracted and in acute exposures (152).

Neoplasia of the brain

Description of the brain
The brain is the main organ of the human central nervous system. It is composed of approximately 100 billion neurons and trillions of support cells called glia (mainly oligodendrocytes and astrocytes), which are devoted to optimise the brain functions. The main differences between neurons and glial cells are found in their cellular differentiation status and proliferative capabilities. Whereas neurons are highly differentiated cells with low proliferation after birth, glial cells can divide infinitely at a slow turnover cycle and have the capacity to differentiate into specific cell progeny (astrocytic, oligodendroglial cells, among others).

Description of brain cancer:
Brain neoplasms consist of a highly heterogeneous group of pathologies, featuring different cell origin, cell behaviour and genetic diversity.

The world age-standardized incidence (for all ages) of primary malignant brain tumor cases per year is estimated to be approximately 3.9 per 100,000 males and 3.0 per 100,000 females (136). These numbers are below the age-standardized incidence rates (adjusted to world population) for Spain in 2014, which were 6.5 and 4.0 cases per 100,000 males and females, respectively (153). These primary tumours are rare among adults, representing a 2% of all the adult cancer cases. However, in newborns and young children brain tumours, though very rare, are the second most common incident neoplasm, following leukaemia, and the first

among solid tumours, accounting for 15-20% of all cancer cases in the population below 15 years of age (154–156). In general, malignant brain tumours are more common in boys than in girls, whereas benign brain tumours are more common among girls (157).

An annual increase of 1.7% in the incidence of central nervous system (CNS) tumors (and miscellaneous intracranial and intraspinal malignancies) among the 0-14 years old population was observed from 1978 to 1997 in Spain and in Europe. The highest average annual percent of change was observed among European newborns, with an increase of 2.4% of cases per year (158). In recent years, the age-standardized incidence seems to be approaching stabilization both in children and in adults, as can be observed in the following figure (Figure 5) for age groups in Spain (135).

Figure 5. Brain (and CNS) cancer incidence time trends (age-standardised incidence rate – world per 100,000) by age groups reported by 7 population-based cancer registries in Spain, obtained from the Cancer Incidence in Five Continents website (140).

(ICD-10: C70-C72)
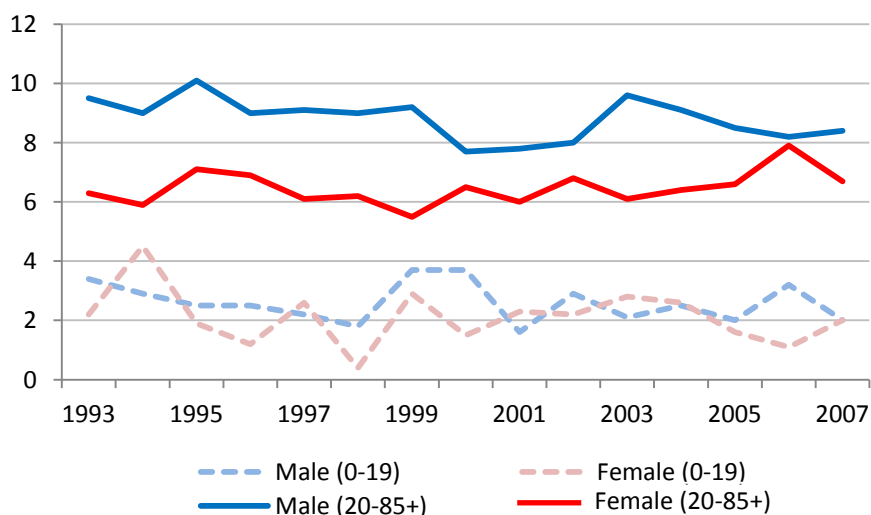
With respect to brain cancer mortality, it is important to bear in mind that the primary tumours of the central nervous system (CNS) are the most lethal malignancies among all childhood tumours (0–14 year old) in Europe (159). However, contrary to other

malignancies, childhood cancer of the central nervous system harbors a better prognosis with increasing age (136). The age-standardised mortality rate in the so-called "more developed countries" is 4.0 per 100,000 population (136) and trends suggested a sharp decrease in childhood CNS cancer mortality over the 1999 to 2007 period in Europe and a stable mortality rate in adults over a similar period (1994-2002)(160). In Spain, mortality for CNS tumours in children could have been stabilised as a result of advances in both diagnostic imaging techniques and therapeutic resources. Figure 6 shows an unclear pattern in the mortality rates for Spain over time for the young population, reflecting the small number of cases of this disease diagnosed each year.

Figure 6. Brain cancer mortality time trends (crude mortality rates per 100,000) by sex and age groups in Spain, from data obtained at the WHO mortality data website.

(ICD-10: C71)
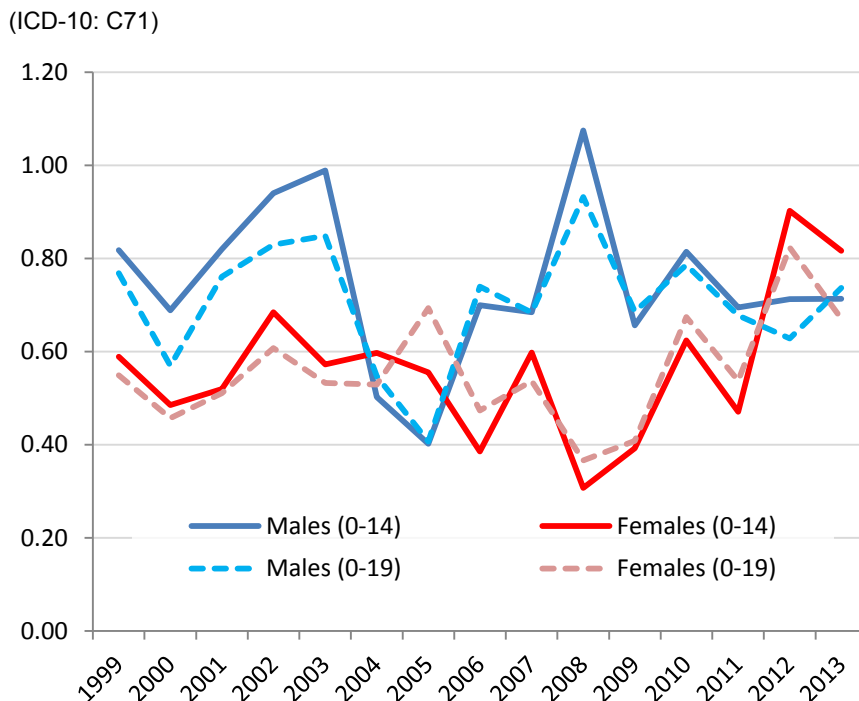
Although there is little concluding information, the topographical location and histology of brain tumors seems to present some variation throughout childhood, adolescence and adulthood, suggesting an increased susceptibility to specific tumour occurrence

in specific age groups (155). In a comprehensive publication on CNS tumors by age in England, it was observed that the proportion of tumors located in the cerebellum, pons and brainstem decreased with the aging of the subject, whereas the opposite was observed for tumors located in the cerebrum and the meninges (156). With respect to their histological distribution, the proportion of neuroepithelial tissue tumors (astrocytic, oligodendroglial, oligoastrocytic, ependymal, choroid plexus, neuronal and mixed neuronal-glial, pineal and embryonal tumours) was higher among the youngest (specially astrocytomas and ependymomas) and decreased with increasing age (156). The proportion of germ cell tumors was similar between the 0-14 years and 15-24 years age groups. On the other hand, tumors of the pineal gland and of the sellar region (craniopharyngeal duct and pituitary gland) were more frequent among adolescents and young adults (15-24-years) (156). Figure 7 portrays the distribution of tumours by histology groups.

Figure 7. Proportion of CNS tumours by histology group, adapted from the *Arora et al.* 2009 publication (156).
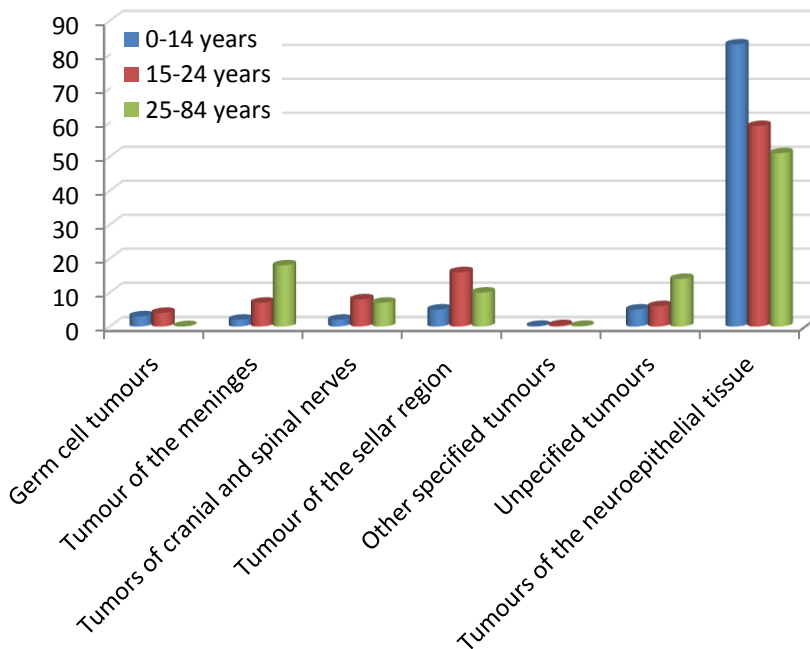
These differences in tumor type by age group may be partially related to the only risk factors consistently related to brain cancer: hereditary syndromes and exposure to moderate-to-high doses of ionising radiation (156) .

Radiation induced brain tumours:
The Central Nervous System had been historically considered radioresistant due to the low cell division rate of terminally differentiated neurons (161). The discovery that glia and neuron cells keep a lifelong dividing and proliferating activity led to a thoroughly revision of the epidemiological evidence and animal model studies by the Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation (the BEIR VII Committee) and to the reconsideration of the brain radiosensitivity (1). Neural stem cells, which appear in the early phases of the embryo development and remain active in the CNS during adulthood maintaining their self-renewal and pluripotentiality capabilities are a potential target of ionising radiation exposure (162,163). Additionally, scientific evidence supports the origin of carcinogenesis in stem cells rather than somatic mature cells (164–166). Although the exact mechanism of radiation-induced brain cancer is unclear, malignant brain cancer development is thought to be based on the stepwise accumulation of genetic and phenotypic changes over time, resulting in the transformation of undifferentiated precursor cells into brain cancer cells (161).

Again, radiogenic brain cancers do not present differentiating clinical characteristics to be considered distinct entities from naturally occurring tumours.

With varying association strength across studies, ionising radiation exposure has been mainly linked to the induction of meningioma (167), in studies such as the LSS cohort (children) (168) and studies on dental radiography (adults) (169). Alto, an increased risk of meningioma has been related to doses of 1.4-1.5 Gy to the brain from *tinea capitis* treatment. Finally meningioma has been associated to high-doses from 22 to 87 Gy following radiation treatment for cancer (167).

Radiation induced glioma, astrocytoma and intracranial tumours have been observed in children following a wide dose range (from

0.00015 Sv in skull radiographs to above 0.2-45 Gy in cancer therapy) (170). In adults, radiogenic gliomas (and other neuroepithelial tumours, such as glioblastoma and anaplastic astrocytoma) were observed in the LSS (171). They have also been observed in cohorts of patients following therapeutic radiation (170). An increased risk of gliomas after 3 or more CTs was described in patients with family cancer history (172).

The LSS cohort suggested an increased risk for radiogenic schwannomas that has not been confirmed in any other epidemiologic study (173). Overall, ionising radiation seems to have a higher impact on the risk of meningiomas in comparison with gliomas, with higher risk estimates across all the studies of ionising radiation and brain tumours (173).

The BEIR VII committee evaluated the mortality data on all solid cancers fitting risk models with different minimal latent periods and based on the lack of statistically significant differences associated with using longer periods decided to use a minimal latent period of 5 years in the calculations of risks (1).

1.2.4. Conclusions

In summary, the statistical limitations at doses below 100 mSv (less than 42 times the average annual background radiation levels of 2.4 mSv) challenge the assessment of cancer risk in humans (1). Evidence from the cohort of atomic-bomb survivors, the Japanese Life Span Study (LSS) suggests a significant increased risk of cancer in the dose-range of 5 - 150 mSv (110), which is the range of doses associated with CT scans. Risks in other exposed groups of population are generally consistent with those observed in the LSS (87). Also, lifetime solid cancer risk estimates for those exposed during childhood might be 2-3 times higher than those exposed as adults due to children's unique physiology (29). Most studies point to a consistent risk of cancer in children exposed to CT scan doses (82,121,122). At the dose levels typical of CT scan, the predominant radiation effect is thought to be indirect DNA damage induced by the presence of ROS.

The trade-off of the invaluable information provided by the CT is likely to be a small but non negligible risk of a radiation-induced malignancy. As of today, it is assumed that this risk is cumulative over a lifetime (1). Given the fact that CT imaging accounts for the majority of the total radiation exposure from medical applications and has a significant contribution in the average radiation exposure per capita in Western countries, it is important to adequately quantify the risk of radiation-induced deleterious effects. Herein lies the underlying rationale of the EPI-CT study.

1.3. Factors potentially affecting the leukaemia and brain cancer risks

The present section reviews the potential impact of different factors which may impact the assessment of the risk of brain / CNS cancers and leukaemia attributable to CT imaging.

1.3.1. <u>Age at exposure and time since exposure / attained age</u>

As discussed in the previous section "Epidemiological evidence for ionising radiation exposure and cancer", in some of the more informative radiation studies the modifying effects of age at exposure and attained age on the risk of solid cancers and leukaemia were evaluated. In summary, all the studied subtypes of leukaemia (acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia and adult T-cell leukemia) showed dependencies on age at exposure and time elapsed since the exposure. Specifically, relative risks were higher and decreased more rapidly over time among those exposed at a younger age. Leukaemia manifests a strong correlation between age and histologic type, and this fact determines that there is a higher incidence of acute lymphoblastic leukaemia among those exposed early in life compared to those exposed later, for which myelogenous leukaemias, both acute and chronic, present a higher incidence.

Evidence from published epidemiological studies pointed out that the excess relative risks per dose unit for solid tumours was also greater for those exposed at young ages, and decreased with both increasing age at exposure and with attained age. The absolute number of solid cancer deaths increased with attained age and decreased with increasing age at exposure.

A notable aspect of the pattern of the leukaemia excess risk is that it peaks within approximately 6-10 years after exposure and then it decreases to baseline rates over an extended period of time (decades). On the other hand, for solid cancer it usually peaks later

in life and an elevated risk appears to remain until death at all ages of exposure.

The modifying character of age at exposure and time since exposure / attained age is typically included in the quantitative assessment of radiation risks.

1.3.2. Sex

The sex of an individual confers one of the greatest known unalterable risk patterns for cancer and haematological malignancies. Excess relative risks for leukaemia after radiation exposure was higher for females than males and risks decreased in a slower fashion for women than for men. Regarding solid cancer mortality, the excess relative risk for females was about twice that for males.

1.3.3. Cancer predisposing syndromes

Cancer predisposition syndromes are a group of genetically heterogeneous disorders characterised by bestowing the individual with an increased risk of developing a solid tumour or leukaemia (174). Several molecular mechanisms are deemed responsible for oncogenesis associated to each disorder. DNA damage repair defects play a role in Fanconi anemia (FA), ataxia-telangiectasia (A-T), Nijmegen breakage syndrome (NBS), Lynch syndrome and Bloom syndrome (BS) among others (175). On the other hand cycle checkpoint defects are present in the Li-Fraumeni syndrome. Other disorders such as neurofibromatosis type 1 (NF-1), Noonan and Noonan-like syndromes (NS) present increased risk of malignancies due to mutations in tumor suppressor genes and dysregulated control over cell cycle and cell differentiation (175). Aneuploidy-associated disorders such as Down syndrome are considered cancer-prone due to chromosome instability, defective DNA repair processes, and downregulation of tumour suppressor genes (69,176–178).

The following Table 10 displays the leukaemia types and specific brain tumors that have been related to some selected predisposing syndromes.

Table 10. Selected cancer predisposing syndromes and related leukaemia and brain tumours, based on several publications (69,177,179–183)

Cancer syndrome	Main related histologic leukaemia type	Main related histologic brain tumour types
Cardio-facio-cutaneous syndrome	ALL	
Cystic Fibrosis	LL	
Down syndrome	ALL, AML	
Fanconi anemia	AML	
GATA2 haploinsufficiency syndrome	AML	
Leopard syndrome	AML	
Severe congenital neutropenia	AML	
Noonan syndrome	JMML/ALL	Neuroblastoma
Ataxia telangiectasia		Lymphomas, leukemia multiple types
CBL syndrome		JMML
Gorlin syndrome		Medulloblastoma
Fetal alcohol syndrome		Medulloblastoma
Li-Fraumeni		Brain tumours
Neurofibromatosis type 1 (NF1)		Optic pathway glioma, glioblastoma, medulloblastoma
Sotos syndrome		Neuroblastoma
Tuberous sclerosis		Astrocytoma
Turner syndrome		Meningioma, brain tumours

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; JMML, juvenile myelomonocytic leukemia;

In addition to the increased genetic susceptibility to primary malignancies, a few of these disorders such as retinoblastoma (Rb), neurofibromatosis type 1 (NF1), Li-Fraumeni syndrome (LFS) and nevoid basal cell carcinoma syndrome (NBCCS) have shown an even greater risk of malignancies by sensitivity to ionising radiation in patients treated with radiotherapy (176).

Below, Table 11 displays (i) a few selected predisposition syndromes, (ii) their frequency per 100,000 newborns, (iii) the penetrance (proportion of individuals with the disease-causing mutation who exhibit clinical symptoms), (iv) the primary malignancy that these syndromes are associated with, (v) the existence of radiation interaction and (vi) the second primary cancers these disorders are related to.

Table 11. Selected predisposition syndromes and their radiation interaction

Syndrome (Gene symbol)	Freq. in 10^5 births*	Penetrance of the mutation	Primary tumour* (related neoplasms)	Gene-radiation interaction and radiation-related neoplasm
Molecular mechanism: Tumor suppressor gene				
Hereditary retinoblastoma (RB1) (176,184)	5	80-90% in highly penetrant families; and very low in low-penetrant mutations	Retinoblastoma (Bone sarcoma, Pinealoma, Leukaemia, Lymphoma)	Definite: Bone Marrow and soft tissue sarcomas in the head
Neurofibroma-tosis type 1 (NF1) (176,185)	36	Complete	Neurofibroma, optic pathway and CNS glioma (MPNST, leukaemia)	Probable for MPNST and glioma
Neurofibroma-tosis type 2 (NF2) (182,186)	4	Nearly 100%	Vestibular schwannomas (other schwannoma, meningioma, ependymoma astrocytoma)	Possible for MPNST
Li- Fraumeni (p53) (176,182)	2	100% lifetime risk in females, 75% in males	Breast cancer, glioma	Possible for sarcoma
Gorlin syndrome (PTCH) (176,182)	Rare	Complete	Basal cell cancer (Medulloblastoma)	Definite for basal cell carcinomas
Molecular mechanism: DNA damage repair defects				
Ataxia telangiectasia (ATM)(68,181,187,188)	0.4 -1	100%	Lymphoid tumors, lymphoma, leukaemia	Definite for breast
Nijmegen Breakage Syndrome (NBN / NBS1) (69,189)	1	100%	Leukaemia, non-Hodgkin lymphoma, breast cancer, prostate cancer, medulloblastoma	Possible for epithelial tumors (thyroid and lung) and lymphomas

MPNST: malignant peripheral nerve sheath tumours

It is important to clarify if at the dose range relevant to CT scans any of these disorders may pose a threat in terms of invalidating the risk measures between ionising radiation exposure to CT scans and cancer risk. Two epidemiological studies have so far assessed the impact of these underlying conditions in the leukaemia and brain tumours risks associated to CT scans (123,180). Journy reported that these associations could be affected by potential confounding by indication, presenting lower excess relative risks once the risk estimates are controlled by a dichotomic variable indicating that the child had a cancer predisposing syndromes (CPS) or not (123). The publication generated several responses indicating that the risk estimates for the children without CPS were similar to the unadjusted risk estimates for brain cancer (and lymphoma) (124,190). However, among subjects with CPS, the ERRs/mGy for brain tumour, leukaemia and lymphoma were very close to 0, suggesting that any effect of low doses of radiation would be too small to detect given the already very high cancer risk among these subjects in the absence of radiation (124,190). A recent publication by the same author suggested that CPS were effect modifiers and not confounders of the association between CT radiation dose and cancer risk (191).

The second study estimated the confounding bias of relative risks (RR) for categories of radiation exposure based on the patterns of CT scan use among CPS patients (180). It concluded that the previous associations of leukemia and brain tumors with CT scans described in the literature were unlikely to be biased due to unmeasured CPS (180,192).

1.3.4. <u>Socioeconomic status</u>

Populations with certain socioeconomic status may have higher access to diagnostic techniques that have an elevated cost (193), especially in countries without a universal health-care system. Additionally, socioeconomic characteristics are known to be associated with a number of health outcomes, including cancer incidence and mortality (194), resulting in a potential confounding effect.

A long-held view links relatively affluent communities or populations with higher socioeconomic status (SES) to higher rates of childhood leukaemia (195). Possible explanations include under-diagnosis of leukaemia in children from poorer communities, and/or association of higher SES with hypothesised risk factors, such as population mixing and delayed exposure to infection (195).

Recent studies though, have challenged this paradigm exhibiting associations in the opposite direction. A review published in 2006 (196) showed that individual-level measures of family income, mother's education, and father's education were consistently associated with childhood leukaemia in the negative direction, with higher rates associated with lower SES levels. Parental occupational category, however, whether measured at the ecological or individual level, was associated with childhood leukaemia just as consistently in the opposite direction, with higher rates associated with higher SES (196). These associations did not appear to vary with leukaemia subtype, possibly due to participation bias.

A 2008 review (197) (with a literature search from 2002 to 2008) suggested that (1) no clear evidence supported a relationship between SES and childhood leukaemia; (2) there were some support for an association between SES at birth (rather than later in childhood) and childhood leukaemia; and (3) if there were any associations, these would be weak, limited to the most extreme SES groups (the 10-20% most or least deprived) (197).

With respect to brain tumours, little is known about what increases its risk in young people and adults besides the already known risk factors (ionising radiation and certain rare medical conditions). At present, little information is available about a possible relationship between SES and brain tumours in young people. One study found that the association with SES variables varied considerably among the subtypes of adult brain tumour, including between low-grade and high-grade glioma (198). Positive associations were observed with household income for low-grade (pilocytic and fibrillary) glioma, meningioma, and acoustic neuroma, but not for high-grade (anaplastic) glioma (198). Positive associations were observed with level of education for low-grade glioma and acoustic neuroma, but not for high-grade glioma or meningioma. The general pattern was

for associations with indicators of affluence and education to be stronger for tumours that tend to grow more slowly and have less catastrophic effects, although the evidence was mixed for meningioma (198).

Another study observed that demographically adjusted rates of adult glioma by race, age and sex were statistically significantly elevated in US counties of higher socioeconomic position (199). One study in the US found no association (200).

1.3.5.   Reverse causation

The inclusion of CT scans related to the diagnosis of an eligible cancer in the studies assessing the cancer risks related to the ionising radiation exposure during a CT scan was mentioned as one of the potential underlying explanations for the risk estimates obtained in some of the studies (201).

1.3.6.   Conclusions

The magnitude of the effect of the exposure to ionising radiation on the onset of CNS tumours and leukaemia may differ depending on third factors, such as the age at which the primary exposure occurs, the time elapsed since the primary exposure, and individual patient characteristics such as the sex of the exposed patient. At the same time, the quantitative assessment of the risks attributable to CT scans could be misestimated by factors correlating with a higher risk of CT scan exposure or disease occurrence.

All these potentially distorting factors need to be considered in an early phase, when approaching the study design. The difficulties of reliably interpreting the results of a study evaluating the health impact of ionising radiation exposure are illustrated by the severe criticism that the studies on CT imaging in young population have received recently (41,125).

2. RATIONALE

About 22% of the ionising radiation exposure to the general public comes from artificial sources and almost all of it is due to medical radiation, whose primary source is CT scan procedures (30). Time series indicate that, worldwide, the young population's exposure to CT scans is increasing, although the paucity of data on the use of CT scans precludes us from confirm a similar trend in Spain.

As of today, the conventional radiobiology model in use estimates, via linear extrapolation from higher doses, that the individual risk of cancer resulting from exposure to ionising radiation during a scan is small but not negligible, in particular at the population level. Several studies aimed at directly assessing the risk from paediatric CT exposures have suggested an increased risk consistent (or even higher for brain tumours) with predictions from higher dose studies. Substantial controversy has followed, particularly in the radiation protection and radiological world, about whether the relatively small doses used in paediatric CT scanning can indeed lead to increased cancer risks.

Direct evidence of cancer risks resulting from low doses of radiation conducted in large and carefully designed studies is critical to address this issue, which is of growing importance for radioprotection and public health. Furthermore, epidemiologic data on medically irradiated children and young population are particularly relevant given the enhanced sensitivity of this group.

The understanding of how ionising radiation interacts with our organism at low doses is important from a public health point of view, given the preventable character of this risk factor. Additionally, an assessment of the burden of cancer related to the current intensity of use of CT scans in Spain may be of utility in order to warrant preventive strategies in health care delivery to avoid unnecessary exposure. In addition, it may be useful for the risk-benefit dialogue between the health-care provider requesting a CT examination and the patient (and their families). It may provide information to assess, from a balanced perspective, the magnitude of the risks associated with CT scanning in the decision-making

process related to the use of these radiological medical procedures for the patient's management.

This thesis is aimed to contribute to the understanding of the use of this diagnostic procedure, to the assessment of potential confounders that may invalidate the observed results of previous studies, and to assess the potential health impact related to the exposure to low levels of ionising radiation during a CT examinations.

3. OBJECTIVES

3.1. Overall objective

The main objective of this thesis is to estimate the health effects associated with the exposure to low-doses of ionising radiation during a CT scan in population exposed at young ages.

3.2. Specific objectives

• Establish a Spanish cohort of paediatric and young adult patients who underwent CT scans in order to build up a large international collaborative cohort for long-term follow-up.

• Describe the patterns of use of CTs over time.

• Assess the potential confounding of the patient's socioeconomic status in the Spanish cohort that could invalidate the estimates of cancer risk resulting from exposure to ionising radiation during a CT scan.

• Assess the potential cancer burden in Spain related to the current use of CT scan in young population.

• Evaluate the radiation related risk of leukaemia, haematological malignancies and brain cancer mortality. The selection of these outcomes is based in two main reasons: the elevated incidence of both malignancies in children and the fact that both organs/tissues have demonstrated to be radiation-sensitive. The selection of the cancer mortality endpoint over cancer incidence is based on scientific interest and current availability of data.

4. METHODS

The present thesis is based on the results obtained from the Spanish EPI-CT cohort, which was set-up as part of the thesis-related work of the present PhD candidate following the common international protocol of the EPI-CT study. At the end of the Methods section (4.4 Paper I), a paper reviewing the epidemiological challenges posed by a study on the health impact of paediatric CT scan is included. The paper also describes how the protocol of the European collaborative EPI-CT study planned to address all the potentially invalidating challenges.

4.1. Study population in Spain

In agreement with the inclusion criteria of the study protocol, the Spanish branch of the EPI-CT international cohort consists of 177,034 patients that underwent at least one recorded CT scan before they turned 21 years old. The study population was defined on the basis of the the radiology departments of 24 hospitals with some of the largest paediatric radiology services in Spain. As illustrated in Figure 8, the hospitals were distributed in 6 Autonomous Communities (Catalonia, Valencian Community, Murcia Region, Navarre, Basque country and Madrid Community). The participating Autonomous Communities were selected because of their high density of children and young adults. Additionally, the presence of a population-based cancer registry (albeit not available in all of them) or of a realistic and feasible mechanism for cancer incidence follow-up was a criterion.

All in all, 291,664 CT scans were extracted from the Radiology Information System (RIS), a widespread-adopted electronic system for the management and recording of basic patient data in the imaging departments. The information collected includes demographic characteristics of the patient and limited information of the CT scan, such as type and modality of examination and scan date. Prior to the implementation of the RIS, which occurred between 1991 and 2010 in the 24 participating hospitals, CT scan records were found in optic discs that were not possible to recover. Prior to this, only hard copies of CT scans were kept, with no

availability of electronic records and no mechanism to confirm that the hard copies were consistently stored at the hospitals.

Figure 8. Autonomous Communities where the Spanish branch of the EPI-CT study has been implemented

4.2. Ethics

Prior to the commencement of the data extraction in each of the participating hospitals, clearance from the appropriate Ethics Authorities was sought. Obtaining the Ethics approval was an heterogeneous process among hospitals and Autonomous Communities in terms of required supporting documentation, interlocutor and time elapsed between submission of the Research Ethics Application and corresponding approval. In 17 out of the 24 participating hospitals, Research Ethics approval was granted by the Hospital Ethics Board, in 5 hospitals the Health Department at the Autonomous Community level was the Ethics authority responsible for the approval, and, in 2 hospitals the approval from the Ethics Board of the Parc de Salut Mar (the ethics board that oversees proposals from IS Global / CREAL) was sufficient to allow the commencement of data collection. Among the 24 participating

hospitals, the duration of the Ethics approval process varied from 4 months up to 2 years.

Additionally, within the time frame of the study, the European Parliament carried out a major overhaul of the data protection regulations of the EU, which sought to secure the control of the population over their personal data in this increasingly globalised exchange of personal information. In 3 of the participating Autonomous Communities, data collection was severely impacted by this regulation review. Hence, the Spanish EPI-CT procedures for data collection had to be reassessed and alternative mechanisms for data collection involving the respective Autonomous Community Health Departments had to be sought. Moreover, in October 2014, the Catalan Parliament asked for a review of the Visc + project (202), which is the provider of anonymized data for more than 50% of the patients of the Spanish EPI-CT cohort. The request for the Visc + review was a result of the strong opposition of some members of the Catalan Parliament to the cession of anonymized clinical data without informed consent of the patient, regardless of the public health or epidemiologic aim of the study. This issue has caused major delays in the data collection in Catalonia, where the health outcome data collection is still underway.

4.3. Dosimetry

The official dosimetry for the study is being developed by the IARC and the dose estimates will be based on a multi-level approach aimed to integrate information on the CT imaging protocols from hospital questionnaires, surveys, scientific publications, expert opinion and parameter values obtained directly from the Picture archiving and communication system (PACS) at the hospitals (203), for the time period after this became available.

Missing parameters of importance for the estimation of doses, such as tube current (mAs), peak tube potential (kVp), pitch (table distance traveled in one 360° rotation divided by the total collimated width of the X-ray beam), manufacturer and model of the CT machine, will be individually represented by a probability density function to allow for the range of possible true parameter

values. The potential values of each of these parameters will be obtained from the aforementioned different sources of information and the parameter values will be representative of the conditions during each appropriate time period. Several sets of doses will be calculated for each cohort member using 2 Dimension Monte-Carlo simulations, where in each iteration different values of the parameters will be selected from the appropriate PDFs while maintaining proper correlations between parameters.

The IARC official dosimetry has been delayed and it has not been possible to obtain an estimation of the doses received by the Spanish patients within the time frame of this thesis.

Therefore, for the present thesis, an alternative dosimetry was produced to estimate organ doses using only real imaging parameters (e.g. Kvp, mAs, pitch) from pediatric and young adult CT examinations performed in the participating hospitals. This approach was selected with the aim of reducing the uncertainty in dose estimates. Within the framework of the EPI-CT study, the Luxembourg Institute of Science and Technology (previously known as Public Research Centre Henri Tudor) developed the software PerMoS (204) which queries and collects individual scans from the PACS at the hospitals. PerMoS extracts all the critical values for the dose estimation (mAs, kVp, pitch, manufacturer and model of the CT machine) from the DICOM header of each queried CT scan, in order to process them and produce a set of organ doses for each CT scan using the NCI-CT 2.4 (205) built-in applicability.

A total of 113,589 headers from the digital images of individual CT examinations performed between 2001 and 2015 were extracted in 9 participating hospitals in Catalonia and the Valencian Community. These 'DICOM' headers include detailed data about the technical parameters of the scans performed. Subsequent quality controls were performed and a significant amount of the examinations was discarded due to inadequacy / missing critical parameters. Additionally to the extracted technical parameters of each CT scan, the start and end of the exposed body region in each type of CT examination were defined by a radiologist using a computational age-specific anthropometric model and validated by an independent pediatric radiologist.

An ad-hoc set of organ doses was produced for the two drafts included in the present thesis (Paper IV: risks projection and Paper V: cancer mortality) using NCI-CT 2.4. A detailed description of the dosimetry is included in the methods section of each of them.

4.4. Paper I

EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT.

5. RESULTS

5.1. Paper II

Trends and patterns in the use of computed tomography in children and young adults in Catalonia — results from the EPI-CT study.

Bosch de Basea M, Salotti JA, Pearce MS, Muchart J, Riera L, Barber I, et al. Trends and patterns in the use of computed tomography in children and young adults in Catalonia — results from the EPI-CT study. Pediatr Radiol. 2016 Jan 15;46(1):119–29. DOI: 10.1007/s00247-015-3434-5

5.2. Paper III

CT scan exposure in Spanish children and young adults by socioeconomic status.

Authors: <u>Bosch de Basea M</u>, Espinosa A, Gil M, Figuerola J, Pardina M, Vilar J, Cardis E.

CT scan exposure in Spanish children and young adults by socioeconomic status

Authors:

Magda Bosch de Basea [1,2,3*], Ana Espinosa [1,2,3], Mariona Gil [1,2,3], Jordi Figuerola [1,2,3], Marina Pardina [4], José Vilar [5], E Cardis [1,2,3]

[1]Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain
[2]Universitat Pompeu Fabra (UPF), Barcelona, Spain
[3]CIBER Epidemiología y Salud Pública (CIBERESP)
[4]Hospital Universitari Arnau de Vilanova, Lleida, Spain
[5]Hospital Universitario Doctor Peset, Valencia, Spain

* corresponding author: M. Bosch de Basea,
Barcelona Institute for Global Health (ISGlobal)
Parc de Recerca Biomèdica de Barcelona
Dr. Aiguader, 88
08003 Barcelona
Spain
Telephone: +34 93 214 7322. Fax: +34 93 214 7302
e-mail: magda.boschdebasea@gmail.com

Abstract

Background: Recent publications reported that children in disadvantaged areas undergo more CT scanning than others. The present study is aimed to assess the potential differences in CT imaging by socioeconomic status (SES) in Spanish young scanned individuals and if such differences vary with different indicators or different time point SES measurements.

Methods: The associations between CT scanning and SES, and between the CT scan rate per patient and SES were investigated in the Spanish EPI-CT cohort. Various SES indicators were studied to determine whether particular SES dimensions were more closely related to the probability of undergoing one or multiple CTs. Comparisons were made with indices based on 2001 and 2011 censuses.

Results: We found evidence of socio-economic variation among young people, mainly related to autonomous communities of residence. A slightly higher rate of scans per patient of multiple body parts in the less affluent categories was observed, possibly reflecting a higher rate of accidents and violence in these groups. The number of CT scans per patient was higher both in the most affluent and the most deprived categories and somewhat lower in the intermediate groups. This relation varied with the SES indicator used, with lower CT scans per patients in categories of high unemployment and temporary work, but not depending on categories of unskilled work or illiteracy. The relationship between these indicators and number of CTs in 2011 was different than that seen with the 2001 census, with the number of CTs increasing with higher unemployment.

Conclusions: Overall we observed some differences in the SES distribution of scanned patients by Autonomous Community in Spain. There was, however, no major differences in the frequency of CT scan per patient by SES overall, based on the 2001 census. The use of different indicators and of SES data collected at different time points led to different relations between SES and frequency of CT scans, outlining the difficulty of adequately capturing the social and economic dimensions which may affect health and health service utilisation.

Key words

Background

Almost 4 million computed tomography (CT) scans are performed annually in Spain [1], allowing for non-invasive detailed imagery of human anatomical inner structures. Despite its clinical advantages, the low to moderate doses of ionising radiation imparted in CT scanning have been associated with an increased risk of brain tumours and leukaemia in children and young adults [2–4].

Two recent papers have reported higher radiation doses and CT scan use in children living in disadvantaged areas. In both, this finding was attributable to a higher disease and injury rate compared to more affluent areas [5, 6]. The influence of the socioeconomic status (SES) in the variation of disease burden among adults is widely accepted by the scientific community [7], but less clear for children. While little is known about brain tumours, higher incidence of childhood leukaemia (the most common type of childhood cancer) has been historically related with affluent communities in occidental societies [8]. Recent studies have challenged this long-held view associating higher childhood leukaemia rates with less affluent individuals [9]. A systematic review concluded that the results of these studies varied by the SES measures utilised [10]. Higher disease rates where associated with lower SES levels when individual–level measures of family income, mother's education and father's education were used. Occupational class, however, whether measured at the ecological or individual level, was positively associated with childhood leukaemia [10]. Different SES indicators could be capturing diverse risk factors, potentially explaining some of the observed differences in between studies.

Further, in most studies SES is studied as a static measure of the relative position of an individual within a hierarchical social structure, including a single-time-point SES measurement due to data availability and logistics. This may fail to reflect realistically the socioeconomic situation of a specific

population in longitudinal studies, particularly after marked changes in the economy.

Universal health care coverage is intended to reduce social inequalities in health and burden of disease [11] but SES is still a strong predictor of differential use of health care services [12]. In Spain, though an overall increase in use of universal health care services has been observed in the last two decades, the use of specialised services is less frequent among those in the lower SES categories [12]. Nevertheless, lower SES individuals are more likely to use emergency services when compared to more affluent social classes [12]. Official Spanish indicators of CT scan distribution by educational level and socioeconomic status are available [1] though not for the 0-20 years of age. The comprehension of a possible differential use of CT imaging by socioeconomic strata in countries with universal health care may help to identify potential disparities in the delivery and use of health care services and in health risk perception, and contribute to assess the possibility that SES may confound the association between CT scan exposure and childhood diseases.

The objective of the present study was to determine whether there are differences in rates of CT imaging by SES in Spanish paediatric and young adult patients. The secondary aim was to study whether and how these differences may vary with the use of different indicators of social deprivation, as well as the implications of using SES indicators measured at different times.

Methods

Study population

EPI-CT, a multinational study to evaluate the relation between radiation dose from CT scans in young population and cancer risk, is currently underway [13]. The present analysis is based on the Spanish EPI-CT cohort and includes patients who received at least 1 CT scan when they were younger than 21 years old between 1991 and 2013, in twenty public hospitals and Autonomically-subsidised hospitals (private hospitals with governmentally contracted services) of five Spanish Autonomous Communities (Catalonia, Valencia Community, Murcia region, Navarre and Madrid Community). Four additional participating hospitals from the Basque country were excluded because patient residence was not available. All participating hospitals belong to the Spanish National Public Healthcare System, which is the sole health care provider for 86.2% of the general population, ranging from 73.7% in the Community of Madrid to 95.6% in Navarre [14]. Among young people, the Public Health system is the exclusive healthcare provider for 83.9, 86.8 and 89.6% of patients in the 0-4, 5-14 and 15- 24 years-old age groups, respectively [14]. Ethical approvals were obtained from all appropriate authorities.

Radiological data source

Information on CT scans was obtained from the Radiological Information System (RIS) since its implementation in the hospitals (between 1991 and 2010) until December 2013. An adaptation [5] of the categories defined by Mettler [15] was used to group the examination descriptions into six categories: head/neck, thorax, abdomen/pelvis, spine, extremities and "several parts" (a composite of several scan locations scanned in a single examination, e.g. head and thorax).

Socioeconomic status

The residential address of each patient, as reported at his/her last CT scan or hospital visit (and the latest available address for 0.5% patients with reported address) was abstracted from the RIS, and geocoded using ARCGis (Esri, United States), Cartociudad (Instituto Geográfico Nacional, Ministerio de Fomento, Spain), ICC (Institut Cartogràfic i Geològic de Catalunya, Generalitat de Catalunya, Spain) and Google maps (Map data, Google, United States). For 24,604 addresses, the softwares did not provide any reliable location and addresses were manually geocoded. The geocoded addresses of the participants were linked to the Population and Housing Census to obtain the census tract to which they belonged. Each census tract is characterised by a set of values for several social indicators and indexes compiled in the Atlas of Vulnerability, that was developed by the Spanish Ministry of Development The main socioeconomic index used in our analyses, the Urban Vulnerability Synthetic Index (UVSI) is calculated as the census-tract percentage of 5 socioeconomic indicators (proportion of unemployed population, young unemployed population, uneducated population (including illiterate and unschooled population), temporary employment and unskilled employment), each one of which is standardised to the average national level. The UVSI is based on 2001 census data and tract limits (unavailable for 2011) and ranges between 0 (less vulnerable) and 1 (more vulnerable). The 5 individual indicators included in the UVSI were also used to examine whether one SES dimension was more closely related to CT scan exposure. To assess the impact of using an up-to-date SES versus the traditionally used one-point SES-estimation, both 2001 and 2011 census data on the 5 SES indicators previously mentioned were obtained and assigned to those patients who had their last CT scan/hospital visit past 2006 (70.01 % of all geocoded patients). The year 2006 was selected as the cut-off point because it marked the mid-point

between the 2001 and 2011 censuses. Therefore for those whose last CT scan/hospital visit happened past 2006 we had complete certainty that their SES level is assigned using the latest socioeconomic indicators.

Statistical methods

In order to identify differences that could bias any relation between CT scans and SES, the homogeneity of the demographic characteristics between geocoded and non-geocoded individuals was tested using a square test for independence.

The association between SES and demographic characteristics of the study participants were studied using the Kruskal-Wallis and Fisher's exact tests for continuous and categorical variables, respectively.

Generalised Additive Models (linear and splines) were used to examine the relation between rate of CTs per patient and the different SES measures. The ratios of number of scans per patient in the different quintiles of SES to the number in the most affluent quintile, modelled as incident rate ratio (IRR), were estimated using mixed effect negative binomial models including Autonomous Community (AC) of residence as a random effect, and sex and age at the time of the last CT scan because its inclusion substantially modified the results. A robust estimator of variance was used to account for the overdispersion within cluster-correlated data.

The correlation between the summary index (UVSI) and each of the 5 indicators which constitute it (standardised to the average national value) was evaluated.

For those patients who had their last CT scan past 2006, the relationship between CT scan rate per patient and SES was analysed using both 2011

and 2001 census-tract data, to assess the impact of updating the SES indicator after a major economic event, fitting mixed effect negative binomial regression models using a robust estimator of variance and a random effect component. Statistical association was set at a 0.05 significance level and a two-sided alternative hypothesis. Data analysis was performed using STATA 14.0 (StataCorp LP, Tx USA).

Results

Over 79.7% (123,729 individuals) of the 155,309 children who received at least one CT scan between 1991 and 2013 in the participating hospitals and resided within the 5 AC had sufficient data to geocode their address to the census-tract level. Success of the geocoding process was independent of the number of scans per patient (p=0.09) (web table 1).

Socio-economic differences in CT scanning

A total of 205,541 CT scans were performed in 123,729 individuals. The distribution of age at the time of the first CT scan follows a bimodal distribution, with 8.1% of scanned patients below 1 year old and over 32.1% of patients being15 years or more (median=12.2 and interquartile range (IQ)=5.2-17.0 years old) (figure 1).

Characteristics of the patients are given in table 1 by UVSI quintiles. Patients in the 1st and 2nd quintiles (more advantaged groups) were slightly younger than in the lower quintiles. 56.3% of scanned patients were males, with a similar distribution across UVSI quintiles. The different population sizes and study periods in the participating ACs led to an unequal contribution of subjects to the study, with Catalonia providing, overall, almost half of the scanned patients (49.0%), followed by the Madrid (25.0%) and Valencia Communities (14.9%). The population distribution by SES quintiles varied substantially between ACs of residence; in Catalonia and Navarre privileged patients where overrepresented whereas in Murcia region, and Madrid and Valencia Communities a higher percentage of disadvantaged population was observed.

65.0% of all first CT examinations were performed in the head and neck, followed by thorax (10.4%) and abdomen and pelvis (5.6%), and a similar distribution was observed across UVSI quintiles. Results were similar

when considering all CT scans rather than the first CT (not shown). The scans involving several body locations were significantly more frequent in the two lower SES quintiles (21.4% and 27.8% respectively) whereas the highest percentage of examinations with unknown body part was observed in the most affluent quintiles (table 1). During the study period (1991-2013) 72.5% of the patients received 1 CT scan, 24.2% received 2 and a very small fraction (3.3%) received 3 or more (table 1). The proportion of subjects with 11 CTs or more was highest in the most affluent categories and decreased with decreasing level of SES. In general, the most affluent group tended to have more examinations than the other categories.

Variation in number of CT scans per patient by SES

The relationship between the total number of CT scans per patient and UVSI was not linear (figure 2), with the rate being highest in the 2 most privileged followed by the 2 least privileged quintiles and lowest in between. Cubic splines did not adequately describe this relationship, as shown with categorical results.

In general, the number of CT scans per patient for those individuals from the 2nd to the 5th quintile decreased by a factor of 0.985 to 0.973 (1 to 3%) when compared to the reference category (1st SES quintile or highest SES), (table 2). It was statistically significant for the 4th quintile only. The overall effect was driven by the biggest ACs (Catalonia and Madrid community).

The effect differed by AC of residence. In Catalonia, subjects with lower SES showed a decrease in CT scans per patient (statistically significant for the 4th and 5th quintiles) compared with the most affluent quintile. In Valencia community, compared to the reference category, subjects from the 2nd, 3rd and 4th socioeconomic quintile had a lower rate of CT scans per patient (statistically significant for the 2nd and 3rd quintile), and those belonging to the most deprived socioeconomic level (5th quintile) showed

an increased rate (IRR= 1.068; 95% CI=1.007-1.133) (table 2). In Madrid community, the rate in the 2nd and 3rd quintiles increased by a factor of 1.03; it decreased in the most deprived socioeconomic quintiles compared to the reference category. In Navarra and Murcia region, though there was variability in the IRR, numbers were small and there was no statistical evidence for a difference across SES levels.

No major differences were observed in rates of CT scans per patient by UVSI for most body parts scanned. For "thorax" examinations, the rate per patient decreased with decreasing SES when compared with the more privileged group. For "several parts" examinations, the rate decreased by a factor of 0.786 to 0.641 for those patients belonging to lower socioeconomic groups (quintile 2nd to 5th) compared to the reference category.

Comparison of individual SES indicators with the UVSI

Web figure 1 shows a strong correlation (correlation coefficient 0.82-0.86) between UVSI and "temporary employment", "unskilled work" and "illiteracy".

Table 3 shows the relationship between number of CT scans per patient and each of the socioeconomic indicators composing the UVSI. For those who received a CT scan from 2006 onwards, results are shown using both 2001 and 2011 census data. With the 2011 census data, an increased IRR was seen for subjects in the 2nd, 3rd, 4th and 5th quintiles of "unemployment" (statistically significant for the 2nd quintile). When using "young people unemployment" as the SES indicator, an increased IRR was observed for the 3rd and 4th quintiles, and a decrease for the 2nd and 5th, compared to the 1st. No major differences were observed using indicators of "temporary work" and "illiteracy". When using cut-off points based on quintiles of the 2001 indicators, one notes that overall

"unemployment" and among the young has grown considerably over the 2001-2011 time period, while "illiteracy" has declined.

Using indicators based on the 2001 census in this population, unlike the 2011 indicators, reduced IRRs were observed in the 2nd, 3rd, 4th and 5th quintiles of global "unemployment", "unemployment in young people" and "temporary work". When using "illiteracy" as the SES indicator the rate of CT scans per person decreased by a factor of 0.989 to 0.998 depending on the quintile, and increased by a factor of 1.028 for those from the 2nd SES quintile. Finally, when the 2001 census data was used to assign a SES to those whose last registered CT scan happened prior to 2006, a decrease in IRR for subjects in the 2nd to 5th quintiles of the indicators of "unemployment", "unemployment in young people" and "temporary work" was observed in the population similar to decreases seen in those with later scans using the 2001 Census. No association was seen with the indicators for "unskilled work" and "illiteracy".

Compared to the other indicators, the "percentage of unemployment among young people (16 to 29 years old)" was the socioeconomic dimension that showed the greatest changes between the 2001 and 2011 census, since the SES quintile remained unchanged for only 21.7% of all geocoded participants over the 10 years between both censuses. The second most unstable socioeconomic indicator was the "percentage of unemployment among active population (16 to 65 years old)" with 30.4% of the subjects SES unchanged. This was followed by "percentage of temporary employment", "percentage of unskilled employment" and the "percentage of illiterate population" with 35.1%, 36.5% and 39.6% of the subjects SES unchanged, respectively (data not shown).

Discussion

Using data from the Spanish EPI-CT cohort and the 2001 census, we found evidence of socio-economic variation in a cohort of CT scanned young individuals, mainly related to AC of residence – with more patients scanned in the most affluent groups in Catalonia and Navarra, and the reverse in the Madrid, Murcia and Valencia communities. Although social security coverage in Spain is universal, it is administered at the autonomic level since 2001. While there was little difference by SES for most types of scans, we noted a higher rate of scans of multiple body parts in the less affluent categories, possibly reflecting a higher rate of accidents and injuries.

A more in-depth analysis, controlling by age and sex of the patient, showed that although the rate of CT scans per person was slightly lower in the most disadvantaged groups than in the higher SES group, the difference did not reach statistical significance. This suggests that overall, when all ACs are combined, there are no SES differences in the chance to receive a CT scan for the diagnosis and follow-up of medical conditions. The relationship between the CT scan rate per person and SES was U-shaped, with the most disadvantaged SES group having a higher CT scan rate per person than the 2nd, 3rd and 4rth SES quintiles. When the relationship between SES and CT scan rate per patient was studied by AC, however, differences were observed: in Catalonia a decreasing rate of CT scans per patient was observed with decreasing SES, while in Madrid community the decrease was only in the lowest socioeconomic groups. These observed disparities by Autonomous Community are likely to be related to the territorial differences in health care management and the related effects on access and use of health care facilities. They may also be related to clinical practice, and to the technological supply available in

each community. The widest differences in the rate of CT scans per person by SES were observed in the Valencia and Madrid Communities.

It is worth noticing that the SES distribution of scanned individuals in our cohort differed from that in the general Spanish population: there was an overrepresentation of the more advantaged population in Catalonia, Valencia Community and Navarre, and an overrepresentation of disadvantaged population in Murcia and Madrid community [1].

Interestingly, when the relative socioeconomic position of the patients was measured using the 2001 five- UVSI constituent indicators, a significant decrease in the number of CT scans per patient was seen with decreasing SES, both for the indicators related to "unemployment" and "temporary employment". Including a more up-to-date (2011 census data) SES information led to results in different directions when "unemployment" and "temporary employment" were used as SES indicators.

The study pointed out that unemployment and young population unemployment were the social dimensions most impacted by the global financial crisis that started in 2007-08. Job insecurity and unemployment are considered stressors related to poor health [16, 17], although the causal direction of these relationship is not completely evident. When using data prior to 2006, the results suggested that the rate of CT scans per person decreased with increasing unemployment and job insecurity in the children's area of residence. With more recent data, the results specifically for "unemployment" suggested the opposite, reflecting a potential higher injury and disease rate in the most deprived areas.

The results of the analyses also outlined a socioeconomic mobility among quintiles for more than 2 thirds of the studied population between 2001 and 2011 and therefore the potential relevance of time-dependant measures of SES in epidemiological studies. Major societal changes, such

as the 2007/2008 financial crisis, may have a profound effect on class relations, reshaping socioeconomic class ties over time [11].

When analysing the impact of each SES dimension on the number of CT scans per person we need to bear in mind that composite measures and individual indicators may capture different aspects of societal relationships. Therefore it is not unusual to find that some individual measures are weakly correlated with the composite index (UVSI) and that the observed relation with CT scanning varies with the indicator chosen. In our study, employment and working conditions-based SES measures may be strongly related to social status and privilege and therefore, they may be capturing easier access and better quality health care [18]. The education-based indicator may reflect the health-related knowledge asset of the progenitors [18], and measure the parents' choices and constraints over the health of the progeny. Thus, the individual indicators of SES may not be equally significant in their impact on health care access and use, and as a consequence, may not contribute equally to the cumulative rate of CT scans per patient. This is important to consider when comparing results of studies which may have used different available indicators.

The findings of this study differed from those two papers reporting use of CT scan by SES, where the highest CT scan use was observed in less affluent areas than in more comfortable areas [5, 6]. Interestingly enough, this results were seen in countries with different health care systems (public vs. private). The initial results of the Dutch EPI-CT cohort showed that children with lower SES (measured as household income) were overrepresented in the CT scanned cohort [19] though overall, little association between SES and total number of scans was observed. In the present analysis, a higher rate of CTs per patient was seen in the most disadvantaged groups only in some ACs, as well as for CT scans related to multiple body parts scanned, but not overall. Differences with previous

studies may, as indicated above, reflect the use of different SES indicators and, within Spain, different access to the technology.

The strengths of this analysis include its large young population with geographically-rich socioeconomic information, the use of a wide-range of univariate SES indicators, and the inclusion of an updated SES measure. There are also, however, several limitations that should be acknowledged. The 5 socioeconomic indicators used in these analyses were based on the 2001 and 2011 SES census household surveys which presented some differences. Specifically, the former was a non exhaustive sampling of approximately 12% of all Spanish households. Additionally, the 2011 census had no information on the 5 indicators of interest for 1 to 9% of the census tracts. There is a small but non-negligible possibility that the non exhaustive sampling of 2011 census data could have affected the precision and accuracy of our categorisation. Additionally, when using the 2001 census data in subjects for whom the hospitals had no updated address after 2005, we were assuming that they had not changed addresses, so there is some potential for socioeconomic status misclassification.

Conclusions

Overall we observed some differences in the SES distribution of scanned patients by autonomous community. There were, however, no major differences in the frequency of CT scans per patient by SES in public and Autonomically-subsidised hospitals by our main measure of SES. The use of different indicators and of data on SES collected in different time points led to different relations between SES and frequency of CT scans, outlining the difficulty of adequately capturing the social and economic dimensions which may affect health and health service use.

List of abbreviations used

AC Autonomous Community
CI Confidence intervals
CT Computed Tomography
IQ Interquartile range
IRR Incident rate ratios
PACS Picture Archiving and Communication System
RIS Radiology Information System
SES Socio-Economic status
UVSI Urban Vulnerability Synthetic Index

Human Participant Protection

The Ethics Committee of the International Agency for Research on Cancer approved the study protocol (IARC IEC 12-35). The protocol has also been approved by all appropriate hospital ethics committees in Spain, prior to commencing the epidemiological study.

References

1. Spanish Ministry of Health, Social Services and Equality: Database of Key Indicators of the National Health Care System [Base de Datos de Indicadores Clave Del Sistema Del Sistema Nacional de Salud]. 2013.

2. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de González A: **Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study.** Lancet 2012, **380**:499–505.

3. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, Giles GG, Wallace AB, Anderson PR, Guiver TA, McGale P, Cain TM, Dowty JG, Bickerstaffe AC, Darby SC: **Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians**. BMJ 2013, **346**:f2360.

4. Huang W-Y, Muo C-H, Lin C-Y, Jen Y-M, Yang M-H, Lin J-C, Sung F-C, Kao C-H: **Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study**. Br J Cancer 2014, **110**:2354–2360.

5. Pearce MS, Salotti JA, McHugh K, Kim KP, Craft AW, Lubin J, Ron E, Parker L: **Socio-economic variation in CT scanning in Northern England, 1990-2002**. BMC Health Serv Res 2012, **12**:24.

6. Freeman K, Strauchler D, Miller TS: **Impact of socioeconomic status on ionizing radiation exposure from medical imaging in children**. J Am Coll Radiol 2012, **9**:799–807.

7. Mackenbach JP, Stirbu I, Roskam A-JR, Schaap MM, Menvielle G, Leinsalu M, Kunst AE: **Socioeconomic inequalities in health in 22 European countries**. N Engl J Med 2008, **358**:2468–2481.

8. Kroll ME, Stiller CA, Murphy MFG, Carpenter LM: **Childhood leukaemia and socioeconomic status in England and Wales 1976-2005: evidence of higher incidence in relatively affluent communities persists over time**. Br J Cancer 2011, **105**:1783–1787.

9.   Adam M, Rebholz CE, Egger M, Zwahlen M, Kuehni CE: **Childhood leukaemia and socioeconomic status: what is the evidence?** Radiat Prot Dosimetry 2008, **132**:246–254.

10. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G: **Socioeconomic status and childhood leukaemia: a review**. Int J Epidemiol 2006, **35**:370–384.

11. Leiulfsrud H, Bison I, Solheim E: Social Class in Europe II. The European Social Survey 2002-2008. NTNU, Department of Sociology and Political Science; 2010.

12. Palència L, Espelt A, Rodríguez-Sanz M, Rocha KB, Pasarín MI, Borrell C: **Trends in social class inequalities in the use of health care services within the Spanish National Health System, 1993-2006**. Eur J Health Econ 2013, **14**:211–219.

13.   Bosch de Basea M, Pearce MS, Kesminiene A, Bernier M-O, Dabin J, Engels H, Hauptmann M, Krille L, Meulepas JM, Struelens L, Baatout S, Kaijser M, Maccia C, Jahnen A, Thierry-Chef I, Blettner M, Johansen C, Kjaerheim K, Nordenskjöld A, Olerud H, Salotti JA, Andersen TV, Vrijheid M, Cardis E: **EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT**. J Radiol Prot 2015, **35**:611–628.

14. Spanish Ministry of Health, Social Services and Equality: National Survey of Health in Spain 2011/12 [Encuesta Nacional de Salud de España 2011/12]. 2013.

15. Mettler FA, Thomadsen BR, Bhargavan M, Gilley DB, Gray JE, Lipoti JA, McCrohan J, Yoshizumi TT, Mahesh M: **Medical radiation exposure in the U.S. in 2006: preliminary results**. Health Phys 2008, **95**:502–507.

16. McKee-Ryan F, Song Z, Wanberg CR, Kinicki AJ: **Psychological and physical well-being during unemployment: a meta-analytic study**. J Appl Psychol 2005, **90**:53–76.

17.   Kim TJ, von dem Knesebeck O: **Is an insecure job better for health than having no job at all? A systematic review of studies investigating the health-related risks of both job insecurity and unemployment**. BMC Public Health 2015, **15**.

18. Galobardes B, Lynch J, Smith GD: **Measuring socioeconomic position in health research**. Br Med Bull 2007, **81-82**:21–37.

19. Meulepas JM, Ronckers CM, Smets AMJB, Nievelstein RAJ, Jahnen A, Lee C, Kieft M, Laméris JS, van Herk M, Greuter MJW, Jeukens CRLPN, van Straten M, Visser O, van Leeuwen FE, Hauptmann M: **Leukemia and brain tumors among children after radiation exposure from CT scans: design and methodological opportunities of the Dutch Pediatric CT Study**. Eur J Epidemiol 2014, **29**:293–301.

Table 1 Characteristics of the patients by quintiles of the Urban Vulnerability Synthetic Index - UVSI (2001 census data).

	Total	UVSI 1	2	3	4	5
	N = 123,729	N= 26,252	N=25,363	N=22,645	N=25,520	N=23,949
Age at the first CT – Med. [IQ]	12.2 [5.2 - 17.0]	12.0 [5.4 - 16.9]	12.0 [5.1 - 16.9]	12.2 [5.2 - 17.0]	12.4 [5.2 - 17.1]	12.4 [5.0 - 17.2]
Sex - N (%) patients						
Males	69,681 (56.3)	14,923 (21.4)	14,209 (20.4)	12,626 (18.1)	14,307 (20.5)	13,616 (19.5)
Females	54,048 (43.7)	11,329 (21.0)	11,154 (20.6)	10,019 (18.5)	11,213 (20.7)	10,333 (19.1)
Autonomous Community residence - N (%) patients						
Catalonia	60,635 (49.0)	15,568 (25.7)	14,605 (24.1)	10,993 (18.1)	10,965 (18.1)	8,504 (14.0)
Madrid Community	30,884 (25.0)	5,743 (18.6)	4,574 (14.8)	5,160 (16.7)	7,487 (24.2)	7,920 (25.6)
Murcia region	4,618 (3.7)	195 (4.2)	349 (7.6)	626 (13.6)	789 (17.1)	2,659 (57.6)
Navarre	9,197 (7.4)	3,137 (34.1)	2,811 (30.6)	2,051 (22.3)	928 (10.1)	270 (2.9)
Valencia Community	18,395 (14.9)	1,609 (8.7)	3,024 (16.4)	3,815 (20.7)	5,351 (29.1)	4,596 (25.0)
Body part scanned in first CT scanned - N (%) patients						
Head and neck	80,390 (65.0)	16,338 (20.3)	16,281 (20.3)	14,752 (18.4)	16,921 (21.0)	16,098 (20.0)
Thorax	12,975 (10.5)	2,879 (22.2)	2,677 (20.6)	2,293 (17.7)	2,673 (20.6)	2,453 (18.9)
Abdomen and pelvis	7,011 (5.7)	1,568 (22.4)	1,524 (21.7)	1,216 (17.3)	1,416 (20.2)	1,287 (18.4)
Spine	4,233 (3.4)	1,006 (23.8)	886 (20.9)	769 (18.2)	844 (19.9)	728 (17.2)
Extremities	6,745 (5.5)	1,362 (20.2)	1,299 (19.3)	1,152 (17.1)	1,539 (22.8)	1,393 (20.7)
Several parts	3,243 (2.6)	613 (18.9)	483 (14.9)	551 (17.0)	695 (21.4)	901 (27.8)
Unknown	9,122 (7.4)	2,485 (27.2)	2,213 (24.3)	1,912 (21.0)	1,431 (15.7)	1,081 (11.9)
CT scans/patient - Med. [SD]	1[1.8]	1 [1.9]	1 [1.9]	1 [1.8]	1 [1.7]	1 [1.7]
Number of CT scans - N (%) patients						
1	89,709 (72.5)	19,088 (21.3)	18,410 (20.5)	16,552 (18.5)	18,493 (20.6)	17,166 (19.1)
2	29,940 (24.2)	6,209 (20.7)	6,098 (20.4)	5,343 (17.8)	6,234 (20.8)	6,056 (20.2)
3 - 10	3,053 (2.5)	699 (22.9)	641 (21.0)	555 (18.2)	603 (19.8)	555 (18.2)
11 -20	905 (0.7)	227 (25.1)	181 (20.0)	172 (19.0)	170 (18.8)	155 (17.1)
> 20	122 (0.1)	29 (23.8)	33 (27.0)	23 (18.9)	20 (16.4)	17 (13.9)

Table 2 Estimates and 95% confidence intervals (95% CI) for the association between number of CT scans per patient and socioeconomic status measured by the Urban Vulnerability Synthetic Index (UVSI), controlling for sex and age at the time of the last CT scan, as well as for Autonomous Community

Model*	IRR	95% CI	p-value
Number of CT scans, UVSI (continuous)	0.944	(0.829 - 1.075)	0.387
Number of CT scans, UVSI*			
1 SES quintile (less vulnerable) **	1.000		
2 SES quintile	0.985	(0.958 - 1.013)	0.287
3 SES quintile	0.983	(0.950 - 1.016)	0.308
4 SES quintile	0.973	(0.948 - 0.999)	0.043
5 SES quintile (more vulnerable)	0.987	(0.935 - 1.042)	0.637
Number of CT scans, UVSI in Catalonia			
1 SES quintile (less vulnerable) **	1.000		
2 SES quintile	0.976	(0.951 - 1.001)	0.062
3 SES quintile	0.980	(0.953 - 1.007)	0.146
4 SES quintile	0.955	(0.929 - 0.981)	0.001
5 SES quintile (more vulnerable)	0.957	(0.929 - 0.985)	0.003
Number of CT scans, UVSI in Valencian Community			
1 SES quintile (less vulnerable) **	1.000		
2 SES quintile	0.936	(0.881 - 0.994)	0.031
3 SES quintile	0.924	(0.870 - 0.981)	0.009
4 SES quintile	0.990	(0.935 - 1.049)	0.745
5 SES quintile (more vulnerable)	1.068	(1.007 - 1.133)	0.030
Number of CT scans, UVSI in Murcia Region			
1 SES quintile (less vulnerable) **	1.000		
2 SES quintile	0.960	(0.830 - 1.111)	0.585
3 SES quintile	0.907	(0.777 - 1.060)	0.221
4 SES quintile	0.958	(0.843 - 1.088)	0.505
5 SES quintile (more vulnerable)	0.964	(0.856 - 1.086)	0.548
Number of CT scans, UVSI in Navarre			
1 SES quintile (less vulnerable) **	1.000		
2 SES quintile	1.029	(0.984 - 1.077)	0.209
3 SES quintile	1.021	(0.970 - 1.075)	0.421
4 SES quintile	1.016	(0.957 - 1.079)	0.600
5 SES quintile (more vulnerable)	0.963	(0.877 - 1.057)	0.425

(continued)

Model*	IRR	95% CI	p-value
Number of CT scans, UVSI in Madrid Community			
1 SES quintile (less vulnerable) **	1.000		
2 SES quintile	1.034	(0.990 - 1.081)	0.135
3 SES quintile	1.030	(0.989 - 1.073)	0.159
4 SES quintile	0.974	(0.940 - 1.010)	0.150
5 SES quintile (more vulnerable)			

* including Autonomous community of residence as a random effect
**Reference category

Table 3 Rate of CT scans per patient by socioeconomic status quintile using the individual socioeconomic indicators that constitute the UVSI as the SES measures. Comparison of patients with CT scans performed between 1991 and 2005 with those with CT scans performed between 2006 and 2013. In the later group, results based on both the 2001 and 2011 censuses are shown for comparison. All estimations used the distributional quintile cut-off points, that is, groups comprising 20% of the population aged 0 to 20, and are adjusted by sex and age at the time of the last CT scan and include Autonomous Community of residence as a random factor.

| Rate in number of CT scans per patient | CT scans performed from 1991 to 2005 (N = 37,096 subjects) | | | | CT scans performed from 2006 to 2013 (N = 86,633 subjects) | | | | | | | |
| | CENSUS 2001 | | | | CENSUS 2001 | | | | CENSUS 2011 | | | |
	% categories in the quintiles of the indicator	IRR	95% CI	p-value	% categories in the quintiles of the indicator	IRR	95% CI	p-value	% categories in the quintiles of the indicator	IRR	95% CI	p-value
By SES quintiles based on % of unemployment in the census tract												
SES 1	(0.0 - 8.2)	1	-	-	(0.0 - 8.2)	1	-	-	(1.9 - 17.6)	1	-	-
SES 2	(8.2 - 10.1)	0.968	(0.949 - 0.988)	0.002	(8.2 - 10.1)	0.970	(0.944 - 0.996)	0.026	(17.6 - 22.8)	1.006	(1.001 - 1.011)	0.016
SES 3	(10.1 - 11.8)	0.971	(0.954 - 0.988)	0.001	(10.1 - 11.8)	0.952	(0.905 - 1.002)	0.058	(22.8 - 28.1)	1.005	(0.993 - 1.017)	0.438
SES 4	(11.8 - 14.1)	0.965	(0.913 - 1.020)	0.209	(11.8 - 14.1)	0.949	(0.902 - 0.998)	0.043	(28.1 - 35.2)	1.002	(0.986 - 1.018)	0.800
SES 5	(14.1 - 39.1)	0.960	(0.903 - 1.022)	0.200	(14.1 - 39.1)	0.937	(0.892 - 0.984)	0.009	(35.2 - 93.9)	1.005	(0.959 - 1.052)	0.844
By SES quintiles based on % of unemployment in young people in the census tract												
SES 1	(0.0 - 10.9)	1	-	-	(0.0 - 10.9)	1	-	-	(1.8 - 25.2)	1	-	-
SES 2	(10.9 - 13.5)	0.985	(0.960 - 1.012)	0.280	(10.9 - 13.5)	0.968	(0.937 - 0.999)	0.045	(25.2 - 35.8)	0.998	(0.963 - 1.036)	0.931
SES 3	(13.5 - 15.8)	0.962	(0.942 - 0.981)	0.000	(13.5 - 15.8)	0.960	(0.931 - 0.990)	0.009	(35.8 - 46.5)	1.033	(0.992 - 1.075)	0.115
SES 4	(15.8 - 18.9)	0.955	(0.899 - 1.015)	0.138	(15.8 - 18.9)	0.952	(0.897 - 1.010)	0.101	(46.5 - 60.4)	1.026	(1.010 - 1.041)	0.001
SES 5	(18.9 - 54.0)	0.919	(0.888 - 0.952)	0.000	(18.9 - 54.0)	0.946	(0.883 - 1.014)	0.116	(60.4 - 100.0)	0.993	(0.972 - 1.014)	0.503
By SES quintiles based on % of temporary work in the census tract												
SES 1	(3.9 - 16.8)	1	-	-	(3.9 - 16.8)	1	-	-	(0.8 - 10.3)	1	-	-
SES 2	(16.8 - 20.3)	0.980	(0.967 - 0.992)	0.001	(16.8 - 20.3)	0.957	(0.938 - 0.976)	0.000	(10.3 - 14.1)	0.994	(0.971 - 1.017)	0.586
SES 3	(20.3 - 23.9)	0.982	(0.968 - 0.996)	0.010	(20.3 - 23.9)	0.956	(0.934 - 0.978)	0.000	(14.1 - 18.0)	1.001	(0.970 - 1.032)	0.955
SES 4	(23.9 - 28.6)	0.986	(0.964 - 1.009)	0.240	(23.9 - 28.6)	0.963	(0.936 - 0.991)	0.010	(18.0 - 23.7)	0.988	(0.944 - 1.035)	0.611
SES 5	(28.6 - 81.8)	1.000	(0.900 - 1.112)	0.999	(28.6 - 81.8)	0.979	(0.912 - 1.050)	0.543	(23.7 - 100.0)	1.005	(0.947 - 1.067)	0.858

Rate in number of CT scans per patient	CT scans performed from 1991 to 2005 (N = 37,096 subjects)				CT scans performed from 2006 to 2013 (N = 86,633 subjects)							
	CENSUS 2001				CENSUS 2001				CENSUS 2011			
	% categories in the quintiles of the indicator	IRR	95% CI	p-value	% categories in the quintiles of the indicator	IRR	95% CI	p-value	% categories in the quintiles of the indicator	IRR	95% CI	p-value
By SES quintiles based on % of unskilled work in the census tract												
SES 1	(0.0 - 6.6)	1	-	-	(0.0 - 6.6)	1	-	-	(0.3 - 4.8)	1	-	-
SES 2	(6.6 - 9.0)	0.978	(0.928 - 1.031)	0.407	(6.6 - 9.0)	1.013	(0.993 - 1.034)	0.203	(4.8 - 8.2)	1.003	(0.982 - 1.024)	0.807
SES 3	(9.0 - 11.7)	0.972	(0.922 - 1.024)	0.283	(9.0 - 11.7)	1.008	(0.974 - 1.044)	0.649	(8.2 - 12.0)	1.024	(1.009 - 1.040)	0.002
SES 4	(11.7 - 15.0)	1.003	(0.976 - 1.030)	0.845	(11.7 - 15.0)	0.982	(0.967 - 0.996)	0.015	(12.0 - 17.5)	1.013	(0.976 - 1.052)	0.483
SES 5	(15.0 - 77.1)	0.963	(0.906 - 1.023)	0.221	(15.0 - 77.1)	0.973	(0.935 - 1.013)	0.181	(17.5 - 87.5)	0.984	(0.940 - 1.030)	0.487
By SES quintiles based on % of illiterate population in the census tract												
SES 1	(0.0 - 6.3)	1	-	-	(0.0 - 6.3)	1	-	-	(0.2 - 4.2)	1	-	-
SES 2	(6.3 - 9.9)	1.029	(0.948 - 1.118)	0.493	(6.3 - 9.9)	1.028	(1.002 - 1.055)	0.032	(4.2 - 7.2)	1.003	(0.993 - 1.013)	0.568
SES 3	(9.9 - 14.0)	1.045	(0.948 - 1.151)	0.381	(9.9 - 14.0)	0.998	(0.975 - 1.022)	0.888	(7.2 - 10.5)	1.001	(0.984 - 1.018)	0.911
SES 4	(14.0 - 20.0)	1.059	(0.945 - 1.186)	0.328	(14.0 - 20.0)	0.992	(0.960 - 1.025)	0.617	(10.5 - 15.4)	0.996	(0.961 - 1.032)	0.805
SES 5	(20.0 - 77.7)	1.045	(0.927 - 1.178)	0.469	(20.0 - 77.7)	0.989	(0.944 - 1.037)	0.654	(15.4 - 66.8)	0.978	(0.932 - 1.026)	0.357

Figure 1 Frequency of age of the individuals at the time of their first CT scan

Frequency of age of the individuals at the time of their first CT scan
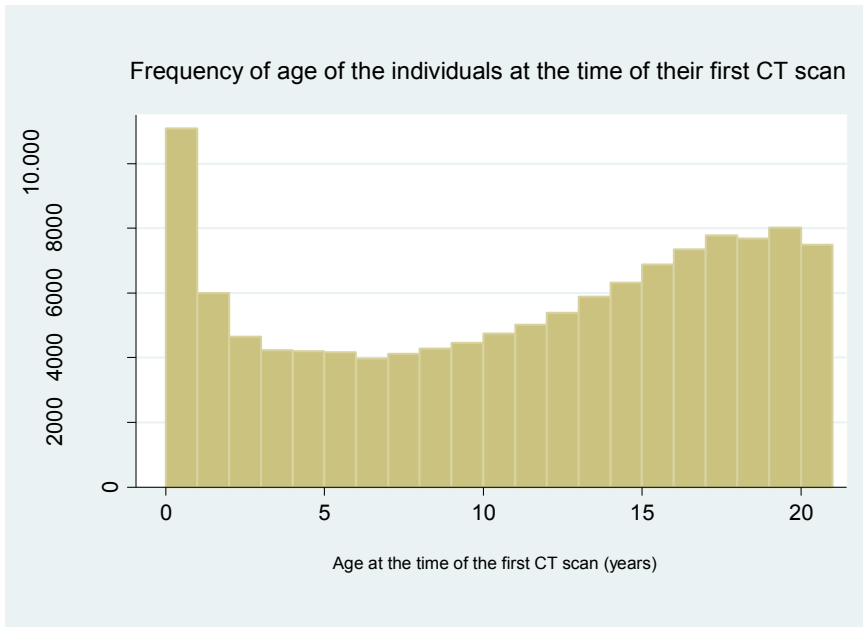
Figure 2 Estimated number of CT scans per patient as a function of various measures of SES. Results for continuous measure (solid line), categorical variable in quintiles (step function) and cubic spline model (dashed curve), adjusted for sex and age at the time of the last CT scan and including the autonomous community of residence as a random effect. Scatter points at the bottom are the observed values for Measure.
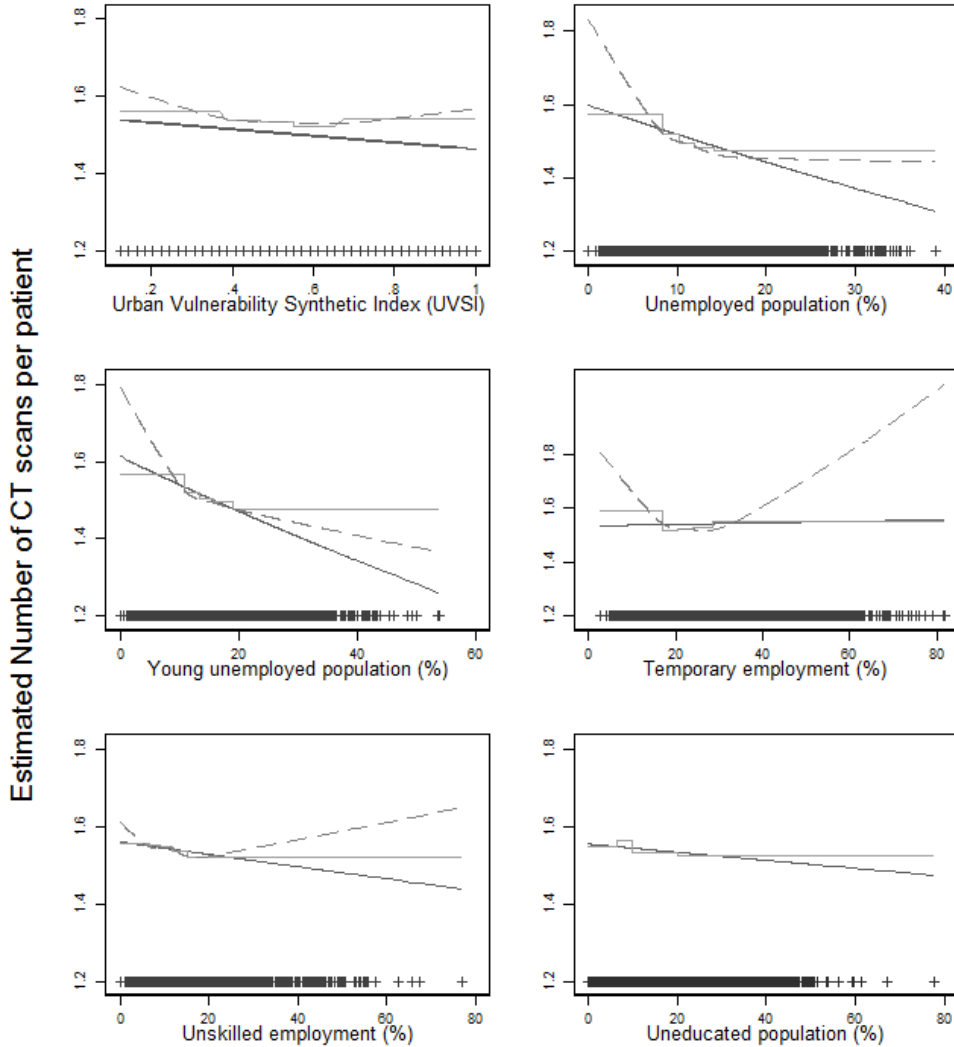
Figure 3 CT scan multiplying factor (CT scan incidence rate ratio) by SES quintile for different body parts scanned in children 0-20 years old
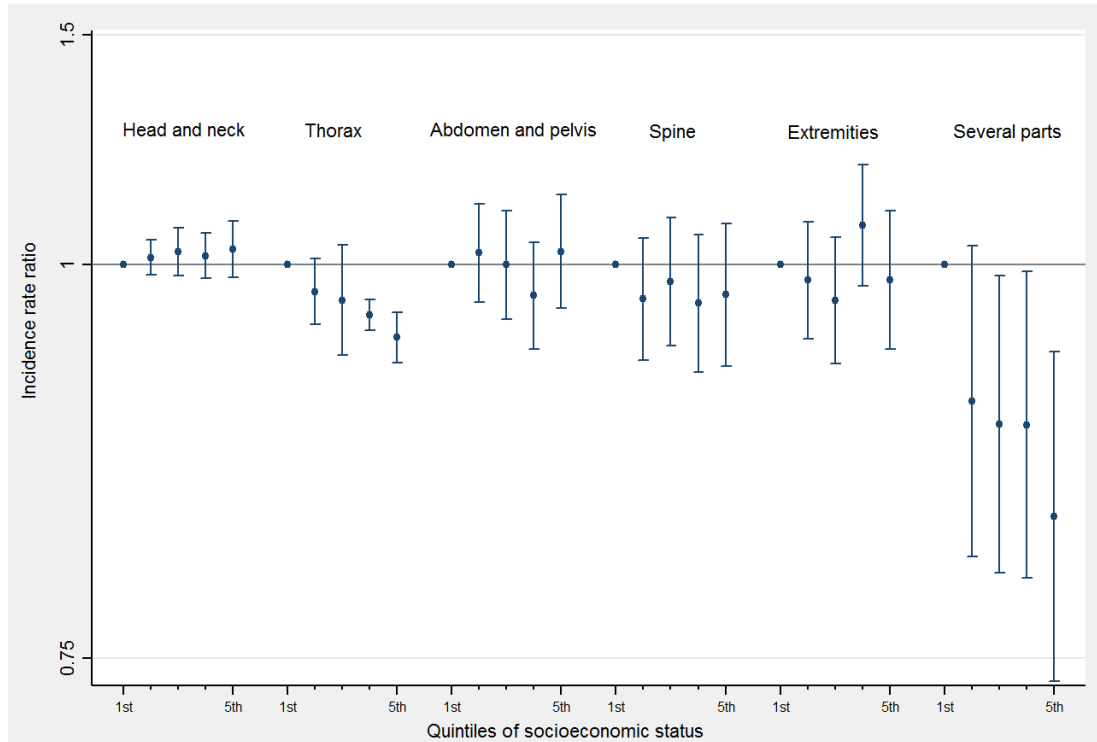
Supplementary material of paper III

CT scan exposure in Spanish children and young adults by socioeconomic status.

Web Table 1 Distribution of demographic characteristics in children 0-20 years by geocoding success

		No geocoded subjects	Geocoded subjects
		N = 123,729	N = 31,441
Sex	Male	18,065 (20.6%)	69,680
	Female	13,515 (20.0%)	54,049
Autonomous Community where they had their first CT scan	Catalunya	13,397 (18.0%)	60,853
	Valencian Community	8,105 (30.7%)	18,289
	Murcia region	892 (16.6%)	4,482 (83.4%)
	Navarre	697 (7.1%)	9,184 (93.0%)
	Madrid Community	8,489 (21.5%)	30,921
Year of birth	1970 - 1975	206 (25.0%)	617 (75.0%)
	1976 - 1980	592 (17.0%)	2,894 (83.0%)
	1981 - 1985	1,638 (14.5%)	9,644 (85.5%)
	1986 - 1990	5,262 (20.1%)	20,952
	1991 - 1995	7,854 (21.5%)	28,766
	1996 - 2000	6,102 (20.8%)	23,247
	2001 - 2005	4,788 (19.5%)	19,800
	2006 - 2010	4,050 (21.8%)	14,530
	2011 - 2013	1,088 (24.9%)	3,279 (75.1%)
Number of CT scans per person	1	22,831 (20.3%)	89,709
	2	7,616 (20.3%)	29,940
	3 - 10	829 (21.4%)	3,053 (78.7%)
	11 -20	269 (22.9%)	905 (77.1%)
	> 20	35 (22.3%)	122 (77.7%)

WEB table 2 Distribution of the referring department in the first CT scan in children 0-20 years by sex and Urban Vulnerability Synthetic Index (UVSI) quintiles (census 2001). – (1= least deprived and 5= most deprived socioeconomic status).

Referring department	Total	Boys	Girls	1	2	3	4	5
	Sex			**UVSI quintiles**				
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Radiology & nuclear medicine	33077 (31.2)	18469 (31.0)	14608 (31.4)	7435 (34.3)	8105 (37.4)	6596 (33.9)	6505 (29.5)	4436 (20.8)
Pediatrics	14508 (13.7)	8127 (13.6)	6381 (13.7)	3175 (14.7)	3022 (13.9)	2617 (13.5)	2844 (12.9)	2850 (13.4)
Emergency	11189 (10.5)	6896 (11.6)	4293 (9.2)	2439 (11.3)	2008 (9.3)	1872 (9.6)	2337 (10.6)	2533 (11.9)
Surgery & post-surgery	9382 (8.8)	5452 (9.1)	3930 (8.5)	1922 (8.9)	1949 (9.0)	1779 (9.2)	1912 (8.7)	1820 (8.5)
Neurologic diseases	8681 (8.2)	4561 (7.6)	4120 (8.9)	1546 (7.1)	1496 (6.9)	1532 (7.9)	1942 (8.8)	2165 (10.1)
Otorhinolaryngology	6162 (5.8)	3403 (5.7)	2759 (5.9)	1153 (5.3)	1224 (5.6)	1112 (5.7)	1320 (6.0)	1353 (6.3)
Orthopedics & traumatology	5272 (5.0)	3033 (5.1)	2239 (4.8)	727 (3.4)	741 (3.4)	826 (4.3)	1306 (5.9)	1672 (7.8)
Not classifiable & unknown	4343 (4.1)	2398 (4.0)	1945 (4.2)	696 (3.3)	813 (3.7)	850 (4.4)	1070 (4.8)	914 (4.2)
Internal medicine	2308 (2.2)	1195 (2.0)	1113 (2.4)	308 (1.4)	295 (1.4)	380 (2.0)	551 (2.5)	774 (3.6)
Oncologic & hematopoietic diseases	1657 (1.6)	946 (1.6)	711 (1.5)	339 (1.6)	293 (1.4)	253 (1.3)	331 (1.5)	441 (2.1)
Respiratory diseases	1139 (1.1)	631 (1.1)	508 (1.1)	195 (0.9)	183 (0.8)	172 (0.9)	250 (1.1)	339 (1.6)
Nursing and neonatology	1063 (1.0)	636 (1.1)	427 (0.9)	188 (0.9)	164 (0.8)	188 (1.0)	254 (1.2)	269 (1.3)
Intensive medicine	975 (0.9)	613 (1.0)	362 (0.8)	157 (0.7)	169 (0.8)	147 (0.8)	214 (1.0)	288 (1.4)
General, familiar med.	936 (0.9)	486 (0.8)	450 (1.0)	221 (1.0)	184 (0.8)	154 (0.8)	167 (0.8)	210 (1.0)
Ophthalmology	912 (0.9)	516 (0.9)	396 (0.9)	183 (0.8)	189 (0.9)	155 (0.8)	181 (0.8)	204 (1.0)
Oral cavity	764 (0.7)	350 (0.6)	414 (0.9)	210 (1.0)	204 (0.9)	135 (0.7)	126 (0.6)	89 (0.4)
Digestive diseases	736 (0.7)	373 (0.6)	363 (0.8)	117 (0.5)	130 (0.6)	125 (0.6)	161 (0.7)	203 (1.0)
Vascular & cardiac diseases	621 (0.6)	375 (0.6)	246 (0.5)	170 (0.8)	123 (0.6)	101 (0.5)	96 (0.4)	131 (0.6)
Infectious diseases	482 (0.5)	277 (0.5)	205 (0.4)	72 (0.3)	65 (0.3)	86 (0.4)	110 (0.5)	149 (0.7)
Genitourinary system diseases	414 (0.4)	209 (0.4)	205 (0.4)	61 (0.3)	59 (0.3)	67 (0.3)	85 (0.4)	142 (0.7)
Psychiatry and psychology	382 (0.4)	249 (0.4)	133 (0.3)	83 (0.4)	58 (0.3)	86 (0.4)	65 (0.3)	90 (0.4)
Anesthesiology and pain management	319 (0.3)	188 (0.3)	131 (0.3)	77 (0.4)	59 (0.3)	40 (0.2)	79 (0.4)	64 (0.3)

(continued)

Referring department	Sex			UVSI quintiles				
	Total	Boys	Girls	1	2	3	4	5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Endocrinology and Nutrition	215 (0.2)	59 (0.1)	156 (0.3)	38 (0.2)	36 (0.2)	34 (0.2)	46 (0.2)	61 (0.3)
Physical medicine & physical therapy	204 (0.2)	110 (0.2)	94 (0.2)	39 (0.2)	46 (0.2)	43 (0.2)	40 (0.2)	36 (0.2)
Obstetrics and gynecology	174 (0.2)	11 (0.0)	163 (0.4)	40 (0.2)	22 (0.1)	42 (0.2)	28 (0.1)	42 (0.2)
Dermatology	127 (0.1)	59 (0.1)	68 (0.1)	38 (0.2)	24 (0.1)	18 (0.1)	23 (0.1)	24 (0.1)
Rheumatology	122 (0.1)	42 (0.1)	80 (0.2)	19 (0.1)	18 (0.1)	19 (0.1)	32 (0.1)	34 (0.2)

WEB Figure 1 Graphical correlation and Spearman coefficients between the Urban Vulnerability Synthetic Index and the univariate indicators that compound the Index, standardized to the national level of each indicator. The x-axis scales vary accordingly to the number of times the percentage (%) of, for example, unemployed population aged 16-29 years out of the total active population aged 16 to 29 in a census-tract is above or below the national value of unemployed population in this age range.

5.3. Paper IV

Expected cancer burden in Spain from CT scanning in young people.

Authors: <u>Bosch de Basea M</u>, Moriña D, Figuerola J, Jahnen A, Lee Ch, Cardis E.

Status: Advanced manuscript

Expected cancer burden in Spain from CT scanning in young people

Authors:

Magda Bosch de Basea[1,2,3], David Moriña[4,5], Jordi Figuerola[1,2,3], (…) , Andreas Jahnen[6], Chonsik Lee[7], E Cardis[1,2,3]

[1] Institut de Salut Global (ISGlobal), Centre de Recerca en Epidemiologia Ambiental, Parc de Recerca Biomèdica de Barcelona (PRBB),
  Carrer del Dr. Aiguader 88, E-08003 Barcelona, Spain.
  Telephone: +34 93 214 7322
  Corresponding author: magda.boschdebasea@gmail.com

[2] Universitat Pompeu Fabra (UPF), Barcelona, Spain

[3] CIBER Epidemiología y Salud Pública (CIBERESP)

[4] Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Program
  (CERP), Catalan Institute of Oncology
  (ICO)-IDIBELL,
  Av Gran Via, 199-203, 08908 L'Hospitalet de Llobregat, Barcelona, Spain.

[5] Departament d'Economia i Història Econòmica, Grups de Recerca d'Àfrica i
  Amèrica Llatines (GRAAL), Unitat de Fonaments de l'Anàlisi Econòmica,
  Universitat Autònoma de Barcelona,
  Carrer d'Emprius 2, 08202 Sabadell, Barcelona, Spain.

[6] Luxembourg Institute of Science and Technology (LIST),
  Esch-sur-Alzette, Luxembourg, Luxembourg

[7] National Cancer Institute (NCI), Division of Cancer Epidemiology and Genetics
  Rockville, Maryland, United States

NUMBER OF:

Words, main text: 5067

Words, abstract: 287

Tables: 4 (+ 2 supplementary tables)

Figures: 0

References: 35

Key words

CT scan · Risk · Cancer · Young population · Cancer

Abbreviations

CT Computerised Tomography
LSS Life Span Study
AQuAS Agència de Qualitat i Avaluació Sanitàries de Catalunya (Agency of Quality and Healthcare Evaluation of Catalonia)
DICOM Digital Imaging and Communications in Medicine
PerMoS Performance Monitoring Server for Clinical Data
LAR Lifetime attributable risk
LBR Lifetime baseline risk

Abstract

Background: CT scan is a life-saving medical tool entailing higher levels of ionising radiation exposure than conventional radiography, which may result in a slight increase in cancer risk, particularly in children. Despite the extensive tradition of CT scan imaging in Spain, there is little information regarding its intensity of use and its potential health effects among young population.

Objective: This paper is aimed to estimate the number of future cancers to be expected due to the use of CT scan in Spanish children and young adults in 2013. Prior to that, we estimated the number and type of CT scans used.

Methods: The Catalan CT scan distribution was extrapolated to the Spanish level. Organ doses were estimated based on the 17,406 CT examinations extracted from radiology wards. Age and sex specific data on cancer incidence and life tables were obtained for the Spanish population and age and sex specific risk models were used, together with the dose estimates to derive the lifetime attributable risks of cancer in Spain due to one year of CT scanning.

Results: Over 100,000 CT scans were estimated to have been performed in the population younger than 21 years old in 2013. The highest radiation-related cancer risks were found for breast and lung cancer but the CT scan distribution and exposed organs favoured the projection of primarily oral cavity and pharynx and brain cancers. Overall, 81 future cancers were predicted to arise from the over 94.000 CT examinations performed in 2013 in young Spanish population.

Conclusions: Despite the undeniable medical effectiveness of CT scan, this risk assessment suggests a non-negligible increase in the burden of cancer; a groups of diseases that is the second leading cause of disease-related death in the Spanish population.

Background

Computerised tomography (CT) scanning is routinely used in patient management from diagnostic and treatment planning, to the follow-up of their conditions. Since its introduction in 1976 in Madrid, Spanish hospitals have progressively embraced this diagnostic technique for its recognised clinical value. Currently there are approximately 750 CT scanners in use in Spain (1), which annually perform more than 4.3 million CT scans (90.6% in the public healthcare system (2)). CT imaging in children and adolescents is estimated to account for 3% to 11% of the total CT activity (3), although no definite figures are available on Spanish young population. In this age group, typical CT organ doses range between the tens of mGy for an organ in the scanning field to hundreds of μGy for a distal organ (4,5).

Epidemiological studies have shown that radiation exposure in childhood is linked to a dose-related increase in the background rates of benign brain tumours, leukaemia, breast and thyroid cancer (6–9), with higher lifetime risk of cancer per unit dose of radiation than adults (7). Because little direct evidence is available on risks at doses below 100 mGy, a linear no-threshold model is generally used to extrapolate risk of cancer for doses lower than this (9). This has been the case for estimating the effect of doses received during CT scan examinations: several studies have projected the risk of incident primary cancers associated with diagnostic CT scan doses in young people (10–13), adults (14,15) or in both (16–18) in different countries applying risk models derived by the BEIR VII

(9). These studies estimated that a small, but non-negligible, increase in cancer risk can be expected in relation to the widespread use of CT scanning (10,11,14,16)

A number of studies have, in recent years, attempted to estimate directly the magnitude to the radiation induced cancer risk from paediatric CT scanning in the UK (19) and Australia (20), providing estimates of risk of the same order or larger than those based on extrapolations from higher dose studies, but methodological limitations prevent, at present, the derivation of precise risk estimates from these studies. A large scale European study is currently underway, including over one million patients, and methodological sub studies to remedy the limitations of studies published to date (21). In the meantime, however, the most solid basis for predicting risk from CT scanning in young people remains extrapolation from higher dose studies.

We assessed the potential impact on the cancer burden of Spain of the current practices of paediatric and young adult CT scanning.. This is a useful approach to patient protection safety by identifying potential higher-risk CT examinations and age-sex groups in the population that may be at higher risk of developing a radiation induced cancer in the future.

Methods

Study population and related data

The Spanish National health care system reported that the annual number of CT scans in Spain increased from 3,830,238 CT scans (17% in private hospitals) in 2010 to 4,307,391 in 2013 (22), the most recent year for which such statistics are available.

In order to assess the impact of current practices, we have therefore chosen to use statistics from that year.

The distribution of CT scans by age, sex and body part scanned was not available at the country level. However, the Agency of Quality and Healthcare Evaluation of Catalonia (Agència de Qualitat i Avaluació Sanitàries de Catalunya; AQuAS) of the Catalan Department of Health, made it accessible for the year 2015 for Catalonia, the 2nd most populated Autonomous Community of Spain were 15.9% of its population reside. The Catalan relative distribution was therefore applied to the 2013 national figures in order to estimate the age, sex and site-specific distribution of CT scans performed in Spain, assuming stable (over the years) and similar CT distributions between Catalonia and Spain.

In order to estimate number of cancer cases induced by CT scan radiation, we used the most up-to-date age and sex-specific Spanish cancer incidence rates available in the *Cancer Incidence in Five Continents- CIV* (23) series to infer the background rates of cancer among patients undergoing a CT scan. Due to the lack of a national population based registry, the incidence data are based on the 2007 CIV rates provided by the 7 population-based Spanish cancer registries. In the absence of more recent data we had to assume the

rates were similar in 2013 and will continue to be stable in the future (23). 2013 age and sex-specific survival data was obtained for Spain at the National Statistics Institute (Instituto Nacional de Estadística) (24). As in Berrington's risk projections (16), using the Spanish branch of the EPI-CT cohort study we estimated that an overall 6.64% of CTs were performed in young people that would not survive long enough (at least 5 years) to develop a potentially radiation-induced cancer and were discarded by age bands, sex and body area scanned.

An important indication for CT scanning is suspicion of, and follow-up for cancer. These CT examinations have to be excluded from our risk prediction analyses because their related CT scan radiation would not be responsible for the onset of the cancer they were used to monitor. Therefore, we used the data from the only Spanish EPI-CT participating hospital that provided complete reason for the scan to estimate that, in 2013, out of the 2,624 CT scans performed in patients aged 0 to 20 years, 8.8% were related to a cancer code (either suspicion, diagnosis or follow-up of the condition). Therefore a similar proportion of CT scans with similar age-sex- body part distribution was excluded.

Dosimetry at the organ level

For the dose estimation, protocol parameters (kvp, mAs and pitch), machine specifications (model and manufacturer), anonymous patient characteristics (age and sex), and the descriptions of the anatomical areas scanned were collected using PerMoS (Luxembourg Institute of Science and Technology, Luxembourg) in

9 EPI-CT participating hospitals. Data from the DICOM headers of 33,947 CTs scans conducted on patients below 21 years old between 2010 and 2013 were extracted and after discarding 16,541 examinations due to missing parameters, absorbed organ doses (mGy) were estimated for 17,406 CTs using the NCICT 2.4 software (25). The start and end of the exposed body region in each type of CT examination were defined by a radiologist in computational age-specific anthropometric models and validated by an independent pediatric radiologist. When no CT scans of a specific age, sex and anatomical area were available to extract all the protocol parameters, the organ doses from a patient of the same age and alternative sex or same sex and one year older/younger who received a CT in the same anatomic area were used to estimate the organ-doses. 222 CT examinations were used to impute doses in these circumstances.

The minimum - maximum number of CT scans used to estimate doses for a specific combination of age, sex, and body part were 1 and 699 examinations.

Eventually, a look up table (Web table 1) of "standard" organ doses was compiled by patient age and sex and examination type. The organ-doses were assigned to each of the 2013 examinations.

Lifetime attributable risk models for several cancer sites

Given the site-specific irradiation and resulting heterogeneous organ-doses related to CT imaging, the lifetime risk of cancer incidence (per 100,000 exposed children and young adults) was estimated for 17 different organs based on the organ-doses

delivered by the different CT scan types. Cancer-sites included in the analyses were Oral cavity and pharynx, brain, colon, lung, urinary bladder, breast, stomach, thyroid, liver, pancreas, kidney, prostate, oesophagus, ovaries, rectum, uterus and leukaemia. Lifetime attributable risks (LAR), which are defined as the cumulative age-specific lifetime risks of cancer due to CT radiation exposure, were estimated. The models used took into account the age and sex distribution of the scanned population, life tables (providing the probability of surviving to any given age), and the age and sex cancer incidence, excluding the latency period. The LAR by dose (D) and age of exposure (e) are calculated using the probability of surviving until attained age (a) conditional on surviving to age of exposure (S(a)/S(e)), the general hazard models (excess relative (ERR) and excess absolute (EAR) risk models), plus the sex-age-specific incidence of each cancer site (λ_I^c).

$$LAR(D,e) = \frac{1}{DDREF} \int_{e+L}^{110} I(D,e,a) \frac{S(a)}{S(e)} da,$$

where I(D,e,a) = ERR(D,e,a) λ_I^c(a) or I(D,e,a)=EAR(D,e,a) and L is the latency period (years) to allow enough time from exposure to manifestation of the malignancy, chosen as L=5 for solid cancers and L=2 for leukemia. To correct for the extrapolation from cancer risks assessed at a high dose and a high-dose rates to estimate risks at a low-dose and a low-dose rates, a dose and dose-rate effectiveness factor (DDREF) defined by a lognormal distribution with a geometric mean of 1.5 and geometric standard deviation

equal to 1.35 was applied as a divisor of the estimated risks of solid cancers for doses below 100 mGy, following the same approach used in Berrington de González *et al*. (26).

The ERR and EAR models used, which are common measures of the relationship between the incidence rate of disease of those exposed and unexposed, were developed by the BEIR VII using LSS cancer incidence data for solid tumours and cancer mortality data for leukaemia (9). The thyroid and breast cancer models were calculated using pooled data from A-bomb survivors and medical cohort data (9). Berrington de González from the National Cancer Institute (NCI) developed risk models for the remaining sites (Web table 2) using also data from the Japanese Atomic bomb survivors. For most solid tumours the BEIR VII and NCI sex (s) specific EAR and ERR models are of the form:

$$\text{EAR or ERR} = \beta_s \, D \, \exp(\gamma e^*) \, (a/60)^{\eta}$$

where D is the dose (Sv) to the organ, β_s is the sex-specific ERR per Sv or the sex-specific EAR (excess deaths per 10^4 PY/Sv) for exposure at age above 30 and attained age 60, and e* is (age at exposure (years) - 30)/10 for those exposed below age 30 and 0 for those exposed at age 30 or above. For the ERR model, the parameter γ quantifies the decrease of the radiogenic risk of cancer for every decade increase in age-at-exposure up to age 30 and η quantifies the decrease in ERR with increasing attained age. In the EAR model (which is understood as the excess cases per 10,000 person years per Sv) the radiogenic risk decreases with age-at-exposure and increases with increasing attained age.

For leukaemia the EAR and ERR models are linear-quadratic functions of dose and both risk models decrease with time since exposure (t) of the form:

EAR or ERR= β_s D (1+θD) exp [(γe*+ δ log(t/25) + ϕ e* log(t/25)] where D is the dose to the bone marrow (Sv), t is the time since exposure (years) and β_s is the sex-specific ERR per Sv or the EAR (excess deaths per 10^4 PY/Sv), and e* is (age at exposure (years) - 30)/10 for those exposed below age 30 and 0 for those exposed at age 30 or above. For the ERR model, the dose-response parameter θ quantifies the degree of curvature of the linear-quadratic function of dose, which is independent of sex, age at exposure or time since exposure, γ quantifies the decrease / increase of the ERR/EAR respectively for every decade increase in age-at-exposure up to age 30, δ indicates the dependence on time since exposure, and ϕ describes how the dependence on time since exposure varies with age of exposure.

The parameter to use in the ERR and EAR models were estimated by the BEIR VII committee (9) and the Berrington de Gonzalez *et al.* (26), which are reproduced in web table 2. The weighting factors used to combine the ERR and EAR models (when appropriate) for the transfer of excess risk between populations are displayed in this table and are justified by mechanistic considerations based on the promoter/progression-inducer character of radiation, favouring the relative over the absolute risk transport projection for most-cancer sites (9). The rationale used in Berrington de González *et al* (26) for solely using the multiplicative risk model for brain-central nervous

system (CNS) and thyroid cancer-sites and the additive risk model for breast cancer was applied here, due to the two latter cancer sites have unusual relationships with age at exposure and attained age.

The lifetime baseline risk (LBR) represented the spontaneous risk of developing cancer from birth to the end of life, considered as 110 years of age, and it was calculated as the cumulative sex-age-specific incidence for each cancer site (λ_I^c), taking into account the probability of surviving to that age (i.e., survival function) per 100,000 Spanish population.

The risk analyses were performed with R and STATA 14.0 (StataCorp LP, Tx USA) and the mean LAR estimates and the LARs obtained using the1st and 3rd quartile of the organ-dose distribution were reported.

Results

The AQuAS provided us with the age and sex distribution of 374,270 CT scans by anatomic area performed in Catalonia in 2015 on the general population aged 0 to 100 years, out of which only approximately 3% were performed in population below 21 years of age. Based on this, we extrapolated the Catalan frequencies to the Spanish level, resulting in an estimated 105,802 CT scans performed in Spain in 2013 among those aged 20 years or less. Of this, 11,195 CT scans of the spine, lumbar spine, sacrum, whole body, arms and 'unknown anatomical area' were not included in this risk projection exercise due to the paucity of PACS-recorded CT scans in these locations to be used for dose estimation.

The estimated distribution of the remaining 94,607 CTs by age group, sex and type of scan is displayed in table 1. 52,283 scans (55.3%) and 42,324 (44.7%) were undergone by male and female patients, respectively, with a male : female ratio of CT scans of 1.45 : 1 among those below 10 years old which decreased to 1.1 : 1 among those in the 15-20 age group. Approximately 57.0% of all the 2013 CTs in young people were performed in the age group of 15 -20 years of age. The proportion of CT scans across age groups was generally similar for males and females, though it was somewhat higher in females aged 15 - 20 years old (59.97% of all CTs in females) than in males (54.68% CTs of all male CT imaging). In both sexes the three more prevalent anatomical areas scanned were, in order of frequency, the head, the abdomen and the thorax, accounting for 62.6% (59,239 CTs), 13.3% (12,578 CTs) and 10.32% (9,768 CTs) of all CTs.

As it can be observed in Table 2, the sex-averaged median organ doses for the brain, oral cavity and pharynx, esophagus, stomach, colon, rectum, pancreas, liver, kidney and urinary bladder were consistently higher among the oldest patients for almost all CT scan types. Brain-doses progressively increased with age, with head examinations providing a range of doses from 22.3 mGy in newborns to 34.4 mGy among those older than 15 years of age. The active bone marrow doses received during chest, thoracic spine, abdomen, pelvis and trunk CT also increased with age whereas the bone marrow doses received during head, face and cervical spine CT examinations showed a different pattern: they initially increased for those between 1 and 4 years of age and then decreased for the older groups of age. CT examinations of the neck and leg delivered doses to the bone marrow that consistently decreased with age, ranging from 2.4 mGy and 7.1 mGy among those below 1 year old to 1.2 and 3.1 mGy, respectively, among those between 15 and 20 years.

Some differences were observed when comparing male and female organ-doses across age groups and CT scan types. In males, all CTs exposing the thyroid gland provided thyroid doses that increased with increasing age whereas in females the opposite was observed related to thoracic spine CT. In females, the breast tissue received increasing doses with age, but for thoracic spine and trunk CT the doses decreased among those older than 14 years of age at the time of the exposure.

Wide variability of organ-doses was identified among those combinations of age, sex and scan type for which fewer

examinations were available for dose estimation, such as trunk and thoracic spine CT (data not shown). A large variability was observed when looking at maximum vs. minimum organ-dose calculated for a specific combination of CT scan types and age group (table 2), with the highest differences seen for oral cavity doses among all age groups. In particular, a 3 orders of magnitude difference was found between the maximum (80.7 mGy) and minimum (0.032 mGy) oral cavity doses in the age group 15-20 years due to a head CT (table 2).

With respect to the organ doses received from different CT types, brain doses due to a head CT ranged from 22.3 mGy to 34.4 mGy, in the youngest and oldest age group, respectively, whereas a scan in the face delivered mean brain doses in the range of 2.8 to 16.7 mGy in the same age groups. Similarly, the thyroid gland of those younger than 1 year old received 12.7 mGy (average of median doses of males and females) during a cervical spine CT, slightly above 11 mGy from a neck and thoracic spine CT, and 7.4 mGy from a chest CT. In the oldest age group, a cervical spine CT delivered an averaged median dose to the thyroid of 39.4 mGy, while thyroid doses from a neck, thoracic spine and chest CT delivered 19.0, 14.3 mGy and 21.1 mGy to the thyroid, respectively. In table 3, the lifetime accumulated baseline (LBR) and the additional radiation-related probability of cancer incidence (LAR) are displayed for a number of cancer sites selected for being in or proximal to the scanning field. For each cancer type, a single LBR value is provided due to the cumulative nature of the risk from birth to the end of life.

As observed, the prostate, breast, colon and lung cancer were the dominant baseline risks with sex-averaged LBRs in the order of 13,500, 9,400, 5500 and 5,200 per 100,000 unexposed Spanish population, respectively. The lowest LBRs were observed for uterus, esophagus, thyroid and brain cancer, with sex-averaged LBRs on the order of 240, 470, 530 and 790 per 100,000 unexposed Spanish persons, respectively. The LBR for brain and pancreatic cancer, as well as for leukaemia, were remarkably similar between sexes (data not shown), whereas lung, urinary bladder, oral cavity and pharynx, rectum and colon cancer LBRs were generally higher for males than females. Thyroid cancer was the only cancer site where women had higher LBR than men, with LBR=772.96 per 100,000 unexposed females compared to LBR=292.51 per 100,000 unexposed males (data not shown).

Lifetime attributable risks per 100,000 exposed patients were led by breast cancer for women who received a trunk, thoracic spine or a thorax CT, closely followed by lung cancer from thoracic spine CTs and urinary bladder cancer from pelvis CT scans. Considering all cancer sites together, the examinations that conferred higher LARs were, in order of relevance: trunk CT, thoracic spine CT and thorax CT scan. The examination type that conferred the lowest LAR was neck CT.

The lifetime attributable risks showed a strong dependence on age at exposure, with consistently higher risks among those exposed at older ages (15-20 year olds) compared with lower ages (<1 year) for lung, stomach and breast cancer, whereas for other cancer types such as thyroid, pancreas, liver, kidney and colon cancer the pattern

was not as clear. LARs showed a wide variability according to the scan type. The risks for leukaemia related to all kinds of CT scans consistently decreased with increasing age at the time of the exposure, except for cervical spine and chest CT, where the patterns were not clear. Among the oldest age group (15-20 year olds) the highest predicted risks (LAR x 10^{-5}; LAR of Q1 organ-doses – LAR of Q3 organ-dose) were observed for breast cancer among women following a trunk CT (LAR= 153.6; 79.0-161.5), chest CT (LAR= 87.0; 34.3-21.7) and thoracic spine CT (LAR=80.8; 30.3-95.6). Among the two youngest groups (<1 year olds and 1-4 year olds) the highest risks were observed for breast cancer following a CT scan of the trunk, thoracic spine and chest CT, and lung cancer as a result of the radiation doses from a thoracic spine CT.

The highest lifetime risks for leukaemia were estimated to result from the dose received during a head CT with LARs x 10^{-5} (LAR of Q1 (25th percentile) organ-doses – LAR of Q3 (75th percentile) organ-dose) ranging from 22.9 (13.1-35.9) among those below 1 year old at the time of the exposure to 4.0 (2.3-4.6) among the older ones (15 to 20 years of age). Although organ-doses were available for the testes, no risk model was available for this location, and therefore LAR was not calculated.

Applying the LARs to the estimated age-sex and body part scanned distribution of the CT examinations in 2013 among those aged 0 to 20 in Spain, we concluded that approximately 81 (46-107) additional cancer cases may occur over the life course of this population due to the doses received during CT scanning. This is in comparison to the approximately 39,028 cancers expected over life

due to other causes, hence an attributable risk percent (AR%) of about 0.2% (0.1%-0.3%).

The CT scans that contributed most to the projected cancer cases are shown in table 4. The predicted incident cancer cases were, in order of frequency, cancers of the oral cavity and pharynx cancer (n=14; 17.0%), brain cancer (n=10; 12.3%) and colon (n=9; 10.8%), closely followed by lung cancer (n=8; 10.2%) and leukaemia (n=8; 9.6%). The majority of the projected cancer cases were found among those in the highest age group at the time of the exposure, accounting for 57% of all the incident cases (n=46). Overall, 37.3% (n=30) and 31.1% (n=25) of all the predicted cancer cases are estimated to result from head and abdomen CT imaging, respectively. Although the LARs of a single head CT taking into account all the potential cancer sites were inferior to that of an abdomen examination (299.19 vs. 881.70 per x 10^{-5}), the elevated head scan frequency (62.6% of all procedures) translated into a substantial number of predicted cancer cases (n=30), in particular, 97% of all the brain cancer cases and 89% of the oral cavity and pharynx cancers. On the other hand, abdomen CT accounted only for 13.3% of the entire scan practise but presented relatively high projected risks (LARs) for stomach and colon cancer. Thorax, leg, trunk cervical spine and pelvis CT accounted for most of the remaining expected cancers (17.0, 4.4, 3.9, 1.4 and 1.5%, respectively) while the rest of the CT scans contributed minimally to the predicted future cancer cases.

Head CT would be the main contributor to the leukaemia cases, too, as observed in table 4, again due to the extremely high frequency of this type of examination.

Discussion

To our knowledge this is the first estimation of the excess site-specific cancer cases resulting from the CT imaging practices in Spain, in young people. For that reason, CT scan frequency of use in Spain in young population was estimated, suggesting that in 2013 up to 105,000 CT scans were performed in young population, dominated by far by head CTs, followed by abdomen CTs.

For the purpose of calculating the lifetime risk, doses were based on a sizeable amount of contemporary clinical examination-level data providing a reliable source for dose-estimation. This is an alternative approach to other dosimetric strategies observed in similar studies based on surveys (16) and scanner protocols (11,12) or derived from smaller samples of clinical data (10). The similarity of the estimated doses with what was previously published for CT imaging confirmed the validity of several dosimetric approaches (10,11,27). For example, our estimation of brain doses for the youngest patients (under 1 year of age) was 22.3 mGy, 21.0 mGy in Journy *et al.*(11) and 28.0 in Pearce *et al.* (27)*.* and 1.4 - 3.5 fold larger than those described by Lee *et al.* (4) on his reference-doses paper (6.2 to 15.8 mGy, depending on the tube current of the CT scanner). We also estimated red bone marrow doses of 2.2 mGy for those undergoing a chest CT when they were between 5 and 9 years of age, whereas Journy *et al.*(11)*,* Miglioretti *et al.* (10) and Pearce *et al.* (27) reported red bone marrow doses of 1 mGy, 3.9 mGy and 3.0 mGy for the same procedure and age group, respectively. Thyroid doses were aligned with those estimated in Journy *et al.* for a chest CT (11) and slightly larger than what reported Su *et al.* (13).

Although greater attenuation (and therefore lower organ-doses) of the incident radiation would be expected in the older patients compared to those exposed early in life, some differences in solid organ-doses could be explained by (1) the variable size-adaptation of protocols according to patient height and weight, (2) the clinical indications that warranted performing the CT scan (3) the application of more conservative doses in younger patients and the use of adult protocols in the oldest ones.

The predicted gender-averaged LBR of brain cancer and leukaemia were slightly higher for the Spanish compared to the French population (11), whereas the opposite was observed for thyroid and breast cancer, although in general terms the LBR for the cancer sites assessed in both studies were similar in orders of magnitude, reflecting similar cancer incidence and survival.

In our study, the highest excess risks (LARs) following CT scan radiation exposure were found for breast, lung and urinary bladder. Breast and lung cancer are two malignancy types for which radiation exposure is a well-documented risk factor (9,28–32). The radiation risks related to bladder cancer are not as clear and further research is needed to elucidate its relationship with ionising radiation exposure (33). Higher risks of breast cancer were reported also in the French study (11) whereas for those exposed when they were older than 5 years old, the lifetime risks of brain cancer per 100,000 exposed to a head CT were similar in order of magnitude (11).

Trunk CTs were the CTs that conferred higher lifetime risks when taking into account all the cancer sites. This is due to the substantial

organ-doses to organs known for their elevated radiosensitivity such as breast, active bone marrow and colon, especially after exposures at young ages. The current analysis estimated that the 2013 CT imaging in young population would produce 81 additional cancers over life due to the radiation doses received in different organs (e.g. oral cavity and pharynx, and brain cancer due to head CT frequency) and due to higher radiosensitivity of their constituent cells (e.g. intestinal epithelium lining, and (30)). This number might be conservative given the fact that over 11,000 CT scans (10%) were discarded due to unavailable parameters for dose estimation. Berrington de González *et al.*(16) projected primarily lung and colon cancers resulting from one year of CT imaging in a wider age range population (0 to >85 years)(16). As in the LSS study, our risk assessment projected a number of leukaemias, lung, bladder, and breast cancer cases (9). The selection of risk models for lifetime risk projections implicitly carried some uncertainties given the fact that most of the LSS population exposed at younger ages is still at risk of expressing radiation-induced malignancies and we do not know how this risk may vary in the future.

Because data on CT scanning in young people for the whole country was not available, we had to extrapolate it from the Catalan distribution. To our knowledge there is no *a priori* reason to believe CT scanning would differ between regions of Spain given that the entire county is covered by universal public health coverage. This does, however, introduce further uncertainty in our estimates of the burden of cancer from CT scanning in young people in Spain.

Another source of uncertainty is that cancer incidence was assumed stable from 2007 to 2013, although some variability was observed in the previous years. Due to the annual fluctuation of such a rare group of diseases, we were not able to extrapolate the site-specific cancer incidence of 2007 onwards to 2013. Therefore, if cancer incidence in 2013 was somewhat higher or lower than in 2007 a slightly increased or decreased risk would be expected given that the ERR model contributes substantially in the predictions for most cancer sites. However, no major changes would be expected for breast cancer due to the fact that it relies entirely on the EAR model. Finally, the assumption of stability over time of the life table data is another source of uncertainty.

This risk assessment estimated the independent risks attributable to one CT scan, which is aligned with the fact that most population in this age-range will receive a single CT, as observed in a previous study (34). Although the methods used here are valid, the lack of patient-specific radiation doses for the analysis, the limitations of the risk models and the assumptions made regarding the Spanish CT distribution and cancer incidence enlarge the margins of uncertainty of this assessment exercise. Overall, the statistical, dosimetric and modelling methodology we applied for this risk assessment is consistent with the published literature.

Despite the undeniable medical effectiveness of CT scan, this paper provides some clues about the related increase in the public health burden of cancer; a group of diseases that is the second leading cause of disease-related death in the Spanish population (35). Our best estimate of the effect of 1 year of CT scanning in young

people, 81 cases, corresponds to 0.2% of the total number of cases expected over life in that population. It should be noted that this estimate is based on current / recent practices in CT scanning in young people in Spain. Data from various studies indicate that increased consciousness of the potential health consequences of CT scanning in the radiological and radiation protection communities have impacted both the frequency of scanning in young people as well as dose levels (36,37). Hence a similar exercise conducted on CT scanning in earlier years would most likely have resulted in a higher lifetime burden of cancer.

In the absence of precise and accurate direct estimates of risk from epidemiological studies, the risk projection studies provide important information to enforce the use of CT indication guidelines at the hospital level in order to minimise the number of CT scans without a clear medical benefit.

This paper adds some decision-support evidence for complex medical decisions regarding the use of ionising radiation for medical purposes in young population.

Funding

Acknowledgements

Disclosure of interests: The authors declare that they have no

competing financial interests.

Human Participant Protection

The Ethics Committee of the International Agency for Research on Cancer approved the EPI-CT study protocol (IARC IEC 12-35). In Spain the protocol was approved by the Ethics committee of the Parc Salut Mar in Barcelona (the ethics committee of CREAL -1SGlobal) as well as by all appropriate hospital ethics committees, prior to commencing the epidemiological study.

References

1. Ministerio de sanidad, servicios sociales e igualdad [Spanish Ministry of Health, social services and equality]. Equipos de Alta Tecnología disponibles por Comunidad Autónoma. Catálogo Nacional de Hospitales [Internet]. 2015. Available from: http://www.msssi.gob.es/ciudadanos/hospitales.do?tipo=equipos

2. Servicios generales de información sanitaria e innovación. Ministerio de sanidad, servicios sociales e igualdad [Ministry of health, social services and equality]. Indicadores Clave Sistema Nacional de Salud Versión 1.0 [Internet]. [cited 2016 Jul 28]. Available from: http://inclasns.msssi.es/?show=true

3. UNSCEAR. Sources, effects and risks of ionising radiation. Vol. II, Annex B - Effects of radiation exposure in children [Internet]. United Nations, New York; 2013. (UNSCEAR 2013 Report). Available from: http://www.unscear.org/docs/reports/2013/UNSCEAR2013Report_AnnexB_Children_13-87320_Ebook_web.pdf

4. Lee C, Kim KP, Long DJ, Bolch WE. Organ doses for reference pediatric and adolescent patients undergoing computed tomography estimated by Monte Carlo simulation. Med Phys. 2012 Apr;39(4):2129–46.

5. Santa-Olalla I, Corredoira E, Plaza R, Martín G, Huerga C, Serrada A, et al. Dosis en TC pediátricos [Doses in pediatric CT scans]. Revista de Física Médica. 2005;6(3):231–5.

6. Wakeford R, Little MP, Kendall GM. Risk of childhood leukemia after low-level exposure to ionizing radiation. Expert Rev Hematol. 2010 Jun;3(3):251–4.

7. Land CE. Early-onset breast cancer in A-bomb survivors. The Lancet. 1993;342(8865):237.

8. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res. 1995 Mar;141(3):259–77.

9. National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation. Health

risks from exposure to low levels of ionizing radiation : BEIR VII Phase 2. Washington, D.C.: National Academies Press; 2006.

10. Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013 Aug 1;167(8):700–7.

11. Journy N, Ancelet S, Rehel J-L, Mezzarobba M, Aubert B, Laurier D, et al. Predicted cancer risks induced by computed tomography examinations during childhood, by a quantitative risk assessment approach. Radiat Environ Biophys. 2013 Oct 9;

12. Egan KR, Muchow RD, Peppler WW, Anderson PA. Theoretical breast cancer induction risk from thoracic spine CT in female pediatric trauma patients. Pediatrics. 2012 Dec;130(6):e1614-1620.

13. Su Y-P, Niu H-W, Chen J-B, Fu Y-H, Xiao G-B, Sun Q-F. Radiation dose in the thyroid and the thyroid cancer risk attributable to CT scans for pediatric patients in one general hospital of China. Int J Environ Res Public Health. 2014 Mar;11(3):2793–803.

14. Smith-Bindman R, Miglioretti DL, Johnson E, Lee C, Feigelson HS, Flynn M, et al. Use of Diagnostic Imaging Studies and Associated Radiation Exposure For Patients Enrolled in Large Integrated Healthcare Systems, 1996–2010. JAMA [Internet]. 2012 Jun 13 [cited 2016 Apr 11];307(22). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3859870/

15. Richards PJ, Summerfield R, George J, Hamid A, Oakley P. Major trauma & cervical clearance radiation doses & cancer induction. Injury. 2008 Mar;39(3):347–56.

16. Berrington de González A, Mahesh M, Kim K-P, Bhargavan M, Lewis R, Mettler F, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med. 2009 Dec 14;169(22):2071–7.

17. Sodickson A, Baeyens PF, Andriole KP, Prevedello LM, Nawfel RD, Hanson R, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. Radiology. 2009 Apr;251(1):175–84.

18. Gibson DA, Moorin RE, Semmens J, Holman DJ. The disproportionate risk burden of CT scanning on females and younger

adults in Australia: a retrospective cohort study. Aust N Z J Public Health. 2014 Oct;38(5):441–8.

19. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. The Lancet. 2012;380(9840):499–505.

20. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;346:f2360.

21. Bosch de Basea M, Pearce MS, Kesminiene A, Bernier M-O, Dabin J, Engels H, et al. EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT. J Radiol Prot. 2015 Jul 30;35(3):611–28.

22. Consulta Interactiva del Sistema Nacional de Salud (SNS). Sistema de información de atención especializada. Actividad asistencial. Actividad diagnóstica. [Internet]. [cited 2016 Mar 21]. Available from: http://pestadistico.inteligenciadegestion.msssi.es/publicoSNS/comun/DefaultPublico.aspx

23. Forman D, Bray F, Brewster D, Gombe Mbalawa C, Kohler B, Piñeros M, et al. Cancer Incidence in Spain (2007) [Internet]. Cancer Incidence in Five Continents, Vol. X (electronic version). Lyon: International Agency for Research on Cancer. [cited 2016 Jun 15]. Available from: http://ci5.iarc.fr

24. Instituto Nacional de Estadística. INE base. Tablas de mortalidad de la población de España 1991-2013. Tablas de mortalidad de la población de España por año, sexo, edad y funciones. [Internet]. [cited 2016 Jun 15]. Available from: http://www.ine.es/jaxi/Tabla.htm?path=/t20/p319a/serie/p01/l0/&file=01001.px&L=0

25. Lee C, Williams JL, Lee C, Bolch WE. The UF series of tomographic computational phantoms of pediatric patients. Med Phys. 2005 Dec;32(12):3537–48.

26. Berrington de Gonzalez A, Iulian Apostoaei a, Veiga LHS, Rajaraman P, Thomas B a, Owen Hoffman F, et al. RadRAT: a radiation risk assessment tool for lifetime cancer risk projection.

Journal of radiological protection : official journal of the Society for Radiological Protection. 2012 Sep;32(3):205–22.

27. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012 Aug 4;380(9840):499–505.

28. Howe GR, McLaughlin J. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. Radiat Res. 1996 Jun;145(6):694–707.

29. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res. 2005;7(1):21–32.

30. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. Lippincott Williams & Wilkins; 2006. 566 p.

31. Hall P. Radiation-associated urinary bladder cancer. Scand J Urol Nephrol Suppl. 2008 Sep;(218):85–8.

32. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. Radiat Res. 2012 Mar;177(3):229–43.

33. UNSCEAR. UNSCEAR 2006 Report, Scientific Report: Effects of Ionising Radiation, Vol. 1: Scientific Annex A - Epidemiological studies of radiation and cancer. United Nations, Vienna; 2008.

34. Bosch de Basea M, Salotti JA, Pearce MS, Muchart J, Riera L, Barber I, et al. Trends and patterns in the use of computed tomography in children and young adults in Catalonia - results from the EPI-CT study. Pediatr Radiol. 2016 Jan;46(1):119–29.

35. Instituto Nacional de Estadística. (National Statistics Institute). Death Statistic according to Cause of Death. Year 2014. [Internet]. [cited 2016 Aug 18]. Available from: http://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176780&menu=resultados&idp=1254735573175

36. Singh S, Kalra MK, Moore MA, Shailam R, Liu B, Toth TL, et al. Dose Reduction and Compliance with Pediatric CT Protocols

Adapted to Patient Size, Clinical Indication, and Number of Prior Studies. Radiology. 2009 Jul 1;252(1):200–8.

37. Brady SL, Moore BM, Yee BS, Kaufman RA. Pediatric CT: implementation of ASIR for substantial radiation dose reduction while maintaining pre-ASIR image noise. Radiology. 2014 Jan;270(1):223–31.

T1. Estimated distribution of CT scans by sex and age groups in Spain, in 2013

CT scan type	< 1 N (%)	1 - 4 N (%)	5 - 9 N (%)	10 - 14 N (%)	15 - 20 N (%)	Total N (%)
Male						
Head	2,191 (66.3 %)	3,820 (75.3 %)	4,256 (66.9 %)	6,012 (67.1 %)	16,938 (59.3 %)	33,217 (63.5 %)
Abdomen	377 (11.4 %)	101 (2.0 %)	373 (5.9 %)	746 (8.3 %)	4,954 (17.3 %)	6,551 (12.5 %)
Thorax	566 (17.1 %)	755 (14.9 %)	1,051 (16.5 %)	1,051 (11.7 %)	2,060 (7.2 %)	5,483 (10.5 %)
Leg	12 (0.4 %)	15 (0.3 %)	128 (2.0 %)	412 (4.6 %)	1,520 (5.3 %)	2,087 (4.0 %)
Face	12 (0.4 %)	37 (0.7 %)	175 (2.8 %)	223 (2.5 %)	927 (3.2 %)	1,374 (2.6 %)
Cervical sp.	35 (1.1 %)	110 (2.2 %)	110 (1.7 %)	204 (2.3 %)	726 (2.5 %)	1,185 (2.3 %)
Neck	21 (0.6 %)	195 (3.8 %)	176 (2.8 %)	100 (1.1 %)	652 (2.3 %)	1,144 (2.2 %)
Trunk*	23 (0.7 %)	13 (0.3 %)	21 (0.3 %)	83 (0.9 %)	404 (1.4 %)	544 (1.0 %)
Pelvis	58 (1.8 %)	13 (0.3 %)	40 (0.6 %)	90 (1.0 %)	185 (0.6 %)	386 (0.7 %)
Thoracic sp.	12 (0.4 %)	15 (0.3 %)	27 (0.4 %)	38 (0.4 %)	220 (0.8 %)	312 (0.6 %)
Female						Total 52,283
Head	1,494 (66.2 %)	2,564 (71.0 %)	2,802 (65.2 %)	3,683 (54.4 %)	15,479 (61.0 %)	26,022 (61.5 %)
Abdomen	253 (11.2 %)	96 (2.7 %)	233 (5.4 %)	816 (12.0 %)	4,629 (18.2 %)	6,027 (14.2 %)
Thorax	346 (15.3 %)	746 (20.7 %)	709 (16.5 %)	848 (12.5 %)	1,636 (6.4 %)	4,285 (10.1 %)
Leg	12 (0.5 %)	4 (0.1 %)	117 (2.7 %)	692 (10.2 %)	1,233 (4.9 %)	2,058 (4.9 %)
Face	1 (0.0 %)	4 (0.1 %)	131 (3.0 %)	276 (4.1 %)	654 (2.6 %)	1,066 (2.5 %)
Neck	35 (1.6 %)	71 (2.0 %)	116 (2.7 %)	231 (3.4 %)	437 (1.7 %)	890 (2.1 %)
Cervical sp.	12 (0.5 %)	70 (1.9 %)	84 (2.0 %)	99 (1.5 %)	487 (1.9 %)	752 (1.8 %)
Trunk*	35 (1.6 %)	15 (0.4 %)	5 (0.1 %)	38 (0.6 %)	406 (1.6 %)	499 (1.2 %)
Pelvis	58 (2.6 %)	26 (0.7 %)	61 (1.4 %)	44 (0.6 %)	243 (1.0 %)	432 (1.0 %)
Thoracic sp.	12 (0.5 %)	15 (0.4 %)	38 (0.9 %)	49 (0.7 %)	179 (0.7 %)	293 (0.7 %)
*Combined CT scan of chest, abdomen and pelvis					Total	42,324

T2. Sex-averaged (mean of) median organ-doses (mGy) across age groups for the relevant organs included in the scanned area by type of CT scan

CT type	<1 year			1 - 4 years			5 - 9 years			10 - 14 years			15 - 20 years		
Organ dose	$\bar{x}$	Min	Max	$\bar{x}$	Min	Max	$\bar{x}$	Min	Max	$\bar{x}$	Min	Max	$\bar{x}$	Min	Max
Head CT															
Brain	22.3	0.4	103.6	25.1	0.5	94.9	27.3	0.6	91.8	28.8	0.4	99.8	34.4	0.3	96.9
Oral Cavity	6.4	0.1	72.8	15.1	0.1	75.8	23.9	0.1	76.4	21.6	0.0	79.9	26.6	0.0	80.7
A. marrow	6.8	0.1	35.7	9.1	0.1	33.8	7.5	0.1	29.3	4.8	0.0	18.8	3.1	0.0	13.4
Face CT															
Brain	2.8	0.2	20.6	17.6	0.7	29.3	16.8	2.4	38.3	19.8	2.1	38.2	16.7	0.4	28.4
Oral Cavity	12.3	1.3	38.1	26.2	1.1	46.0	25.0	3.6	56.0	29.8	3.4	47.9	29.5	0.8	43.6
A. marrow	3.3	0.5	10.7	7.1	0.3	11.4	4.7	0.6	11.9	3.7	0.4	6.5	2.3	0.0	4.5
Cervical spine CT															
Thyroid	12.7	5.5	34.8	21.2	1.6	78.6	29.3	1.3	72.3	29.7	0.6	132.7	39.4	0.8	61.7
A. marrow	2.8	0.9	7.9	3.6	0.2	8.9	2.2	0.1	5.6	2.4	0.1	7.9	2.4	0.1	3.6
Neck CT															
Thyroid	11.1	1.1	30.2	9.0	0.2	32.9	16.7	0.9	61.2	18.1	0.5	49.3	19.0	2.1	66.0
A. marrow	2.4	0.2	7.4	1.9	0.2	7.3	1.6	0.1	4.8	1.5	0.6	3.2	1.2	0.3	4.0
Esophagus	3.2	0.2	7.2	3.7	0.2	11.1	4.1	0.3	13.4	4.0	0.2	9.9	2.8	0.4	9.2
Thoracic spine CT															
Thyroid	11.6	9.6	14.9	11.4	4.1	24.5	18.0	7.0	78.7	16.8	1.0	47.1	14.3	0.7	54.4
A. marrow	3.5	2.7	4.7	3.7	1.7	8.7	3.9	2.4	14.2	5.5	0.2	10.0	4.8	0.2	13.3
Breast*	7.4	7.4	11.7	11.9	5.2	27.7	13.4	8.3	51.9	16.6	0.6	31.0	7.9	0.8	44.7
Lungs	11.7	9.4	15.1	13.3	6.5	33.0	16.8	10.1	63.5	20.0	0.7	37.0	16.7	0.9	49.0
Esophagus	9.1	7.2	11.9	10.5	4.7	24.6	13.6	7.8	54.5	16.1	0.6	32.1	13.2	0.7	39.4
Chest CT															
Thyroid	7.4	0.1	47.6	7.3	0.5	125.0	10.7	1.4	98.9	13.2	0.9	94.9	21.1	0.8	86.6
A. marrow	3.0	0.5	16.7	2.6	0.2	37.6	2.2	0.3	21.8	3.2	0.2	21.9	5.6	0.3	24.8
Breast*	7.7	1.2	42.7	7.0	0.7	94.7	7.0	0.9	66.6	8.7	0.6	61.7	14.7	0.8	58.2
Lungs	7.9	0.9	44.8	8.6	0.9	116.6	8.9	1.1	81.7	11.1	0.6	73.7	17.3	0.9	66.0
Esophagus	6.0	0.6	38.7	6.8	0.6	102.0	7.6	0.9	70.5	9.4	0.5	66.1	14.6	0.7	56.4
Abdomen CT															
Stomach	5.8	0.1	34.5	7.0	1.2	63.8	12.4	1.1	62.0	17.8	0.9	63.0	22.0	0.8	56.0
Colon	6.1	0.7	36.9	8.1	1.3	60.4	14.0	1.3	73.4	20.4	1.3	75.1	26.0	0.9	67.5
Rectum	4.7	0.9	22.8	5.2	0.3	28.3	8.0	0.7	57.3	11.5	0.6	48.7	15.1	0.3	44.4
Pancreas	5.9	0.2	35.9	7.4	1.3	63.8	12.1	1.1	61.9	16.8	0.9	59.2	20.8	0.7	55.7
Liver	5.9	0.1	35.5	7.1	1.2	66.0	12.1	1.0	57.3	17.2	0.8	61.7	21.4	0.7	58.0
Kidney	6.4	0.3	39.5	8.4	1.5	71.9	14.2	1.3	72.8	20.1	1.1	70.3	25.9	0.8	74.2
Trunk CT															
Thyroid	5.6	0.4	22.4	5.4	0.4	20.9	8.8	0.6	64.6	20.4	0.3	53.3	23.4	0.4	67.5
A. marrow	2.9	2.2	12.8	3.8	0.6	15.7	5.9	0.5	25.8	16.2	0.6	32.2	15.0	0.5	33.4
Breast*	5.2	2.6	21.1	6.6	1.2	28.9	10.1	1.0	54.5	33.0	0.9	50.2	18.6	0.8	47.5
Stomach	5.9	5.4	24.3	8.4	1.4	34.8	13.2	1.2	64.5	30.4	1.2	61.8	24.4	0.8	54.6
Colon	6.1	5.4	24.4	8.7	1.5	36.5	14.0	1.4	67.7	32.1	1.3	65.1	25.8	0.9	59.3
Rectum	5.2	4.8	21.2	6.4	0.9	31.4	10.8	0.9	48.2	23.8	0.9	47.5	18.7	0.6	42.1
Pancreas	5.9	5.3	23.9	8.2	1.3	34.1	12.4	1.1	62.3	27.3	1.0	56.5	21.4	0.7	48.8
Liver	6.1	5.6	25.1	8.7	1.4	35.5	13.4	1.3	65.5	30.9	1.2	62.5	24.9	0.9	54.9
Kidney	6.5	5.5	26.2	9.4	1.5	38.7	14.4	1.3	71.1	32.3	1.2	66.1	26.0	0.9	58.9

CT type	<1 year			1 - 4 years			5 - 9 years			10 - 14 years			15 - 20 years		
Organ dose	x̄	Min	Max	x̄	Min	Max	x̄	Min	Max	x̄	Min	Max	x̄	Min	Max
Pelvis CT															
Urinary	16.6	0.5	39.5	16.5	0.9	61.1	20.0	1.1	80.0	24.0	0.6	69.9	29.2	0.7	59.9
Prostate**	16.0	0.0	27.5	12.8	0.0	33.2	10.9	0.0	55.8	16.9	0.0	71.3	25.8	0.0	42.2
Ovaries*	13.0	0.0	37.3	16.8	0.0	52.7	22.5	0.0	71.2	21.9	0.0	49.9	24.7	0.0	52.9
Uterus*	12.3	0.0	33.8	14.2	0.0	46.1	19.9	0.0	64.3	19.1	0.0	45.7	21.2	0.0	45.8
Leg CT															
A. marrow	7.1	0.2	9.3	7.1	0.2	9.3	6.4	0.2	9.3	7.1	0.2	10.1	3.2	0.0	8.8
Prostate**	30.3	0.0	46.4	30.3	0.0	46.4	19.2	0.0	46.4	44.7	0.0	45.6	28.5	0.0	58.4
Ovaries*	10.9	0.0	10.9	10.9	0.0	10.9	15.9	0.0	33.0	10.1	0.0	21.6	4.0	0.0	7.5
Uterus*	12.0	0.0	12.0	12.0	0.0	12.0	15.2	0.0	30.8	10.8	0.0	23.1	5.4	0.0	9.4

*	Only in females
**	Only in males
x̄	Mean

T3. Estimated sex-averaged (mean) median lifetime background risks (LBR) and lifetime attributable risks (LAR) of the tissues and organs exposed by CT scan type by age of exposure

CT type /	LBR x 10⁻⁵*	LAR x 10^{-5} from age at the time of the CT scan to age 110				
		<1 year	1 - 4	5 - 9	10 - 14	15-20
Head CT						
Brain	790.7	25.94	21.23	13.95	17.95	12.5
Oral Cavity	1435.7	9.66	17.58	21.69	23.83	20.3
Leukaemia	1281.4	22.90	23.35	14.18	6.70	3.62
Face CT						
Brain	790.7	2.60	10.23	9.71	9.53	5.26
Oral Cavity	1435.7	19.33	27.09	27.28	28.02	20.9
Leukaemia	1281.4	10.05	17.39	8.87	5.25	2.65
Cervical						
Thyroid	532.7	14.56	26.22	21.47	25.58	34.1
Leukaemia	1281.4	9.71	9.05	4.21	3.36	2.72
Neck CT						
Thyroid	532.7	16.98	10.40	15.32	18.97	14.2
Leukaemia	1281.4	8.01	5.06	3.04	2.05	1.36
Esophagus	477.7	1.27	1.74	1.69	1.27	0.72
Thoracic						
Thyroid	532.7	14.84	14.51	15.77	21.07	8.94
Leukaemia	1281.4	12.43	9.43	7.19	7.66	5.81
Breast***	9416.5	103.6	136.8	109.3	186.8	80.3
Lungs	5226.8	70.41	71.36	70.01	94.71	53.2
Esophagus	477.7	6.17	5.32	6.09	6.59	4.73
Chest CT						
Thyroid	532.7	10.41	8.19	12.52	11.74	14.0
Leukaemia	1281.4	9.91	6.64	4.09	4.31	6.31
Breast***	9416.5	113.5	77.27	76.99	73.95	87.0
Lungs	5226.8	44.30	38.89	44.25	41.34	52.9
Esophagus	477.7	2.83	2.78	3.66	3.37	4.48
Abdomen						
Stomach	1888.0	13.27	16.14	21.58	29.40	32.4
Colon	5571.0	21.84	28.02	38.42	54.34	61.2
Rectosigm. Gallbladde	2404.5	1.84	1.97	2.44	3.26	3.94
Pancreas	1379.5	3.57	4.49	5.73	7.77	8.79
Liver	1105.4	6.38	7.37	9.67	13.26	14.0
Kidney	1087.4	3.21	4.07	5.40	7.44	8.25

(continued)

CT type /	LBR x 10⁻⁵*	LAR x 10⁻⁵ from age at the time of the CT scan to age 110				
		<1	1 - 4	5 - 9	10 -	15-20
Trunk CT						
Thyroid	532.7	12.05	8.13	9.46	22.95	15.42
Leukaemia	1281.4	9.28	9.95	10.89	21.21	17.29
Breast***	9416.5	119.89	113.18	86.40	272.47	153.60
Stomach	1888.0	19.49	22.89	28.49	55.32	37.74
Colon	5571.0	25.75	33.55	51.88	81.46	61.49
Rectosigm.	2404.5	2.59	2.77	4.30	6.80	5.00
Pancreas	1379.5	4.83	5.77	7.52	13.28	9.31
Liver	1105.4	7.61	9.88	14.48	21.98	16.24
Kidney	1087.4	3.95	5.04	7.37	11.26	8.36
Pelvis CT						
Urinary	4561.3	73.94	48.34	51.12	50.15	71.68
Prostate**	13534.7	28.33	14.49	12.81	14.70	26.26
Ovaries***	1290.7	15.06	12.25	15.09	10.44	15.30
Uterus***	239.5	11.39	8.10	10.27	6.86	9.62
Leg CT						
Leukaemia	1281.4	22.67	17.61	11.54	10.02	3.81
Prostate**	13534.7	66.80	38.46	19.83	65.87	25.53
Ovaries***	1290.7	8.34	8.39	9.59	7.94	2.28
Uterus***	239.5	7.34	7.32	7.08	6.31	2.22

*   Calculated from birth to age 110
**   Only in male patients
***   Only in female patients

T4. Predicted cancer cases by cancer site and age group

Cancer site CT type	Total expected cancers	Expected number of cancers by age group in years (y) and selected CTs					Cancer cases by selected CT
		<1 year	1 - 4 y	5 - 9 y	10 - 14 y	15-20 y	
Oral cavity	**13.8**						
Head CT		0.40	1.19	1.50	2.43	6.77	
Face CT		0.00	0.01	0.08	0.13	0.33	**12.8**
Brain	**10.0**						
Head CT		1.10	1.53	1.03	1.95	4.13	**9.7**
Colon	**8.8**						
Abdomen CT		0.15	0.06	0.26	0.85	5.94	
Thorax CT		0.10	0.06	0.08	0.09	0.22	
Trunk CT		0.02	0.01	0.01	0.08	0.39	**8.3**
Lung	**8.3**						
Thorax CT		0.38	0.57	0.75	0.77	1.88	
Abdomen CT		0.07	0.02	0.09	0.24	1.18	
Head CT		0.14	0.25	0.21	0.18	0.41	**7.1**
Leukaemia	**7.8**						
Head CT		0.89	1.57	1.03	0.67	1.11	
Thorax CT		0.10	0.10	0.08	0.08	0.23	
Abdomen CT		0.03	0.01	0.04	0.14	0.95	**7.0**
Bladder	**7.1**						
Abdomen CT		0.11	0.05	0.12	0.34	3.42	
Trunk CT		0.01	0.01	0.01	0.06	0.32	**4.5**
Breast	**6.3**						
Thorax CT		0.39	0.59	0.54	0.64	1.42	
Abdomen CT		0.03	0.03	0.09	0.26	1.11	**5.1**
Stomach	**6.1**						
Thorax CT		0.16	0.21	0.29	0.29	0.77	
Abdomen CT		0.09	0.03	0.14	0.46	3.13	**5.6**
Remaining cancer sites							
Thyroid	**3.2**	0.19	0.35	0.49	0.57	1.62	
Liver	**2.8**	0.15	0.13	0.24	0.40	1.89	
Pancreas	**1.5**	0.07	0.05	0.10	0.20	1.06	
Kidney	**1.3**	0.06	0.05	0.09	0.18	0.97	
Prostate	**1.1**	0.04	0.02	0.05	0.29	0.74	
Esophagus	**0.9**	0.08	0.11	0.13	0.15	0.45	
Ovaries	**0.8**	0.02	0.01	0.03	0.12	0.63	
Rectum	**0.7**	0.03	0.01	0.03	0.12	0.52	
Uterus	**0.5**	0.02	0.01	0.02	0.08	0.39	
Total	**81.4**	**4.96**	**7.09**	**7.63**	**11.98**	**42.99**	

Supplementary material of paper IV

Expected cancer burden in Spain from CT scanning in young people.

Web Table 1 Estimated number of CT examinations performed in Spain in 2013, number of 2010-2013 CT scan headers used for dose estimation and age and sex-average median organ doses by type of CT scan (mGy).   * Only in males - ** Only in females

CT scan type	Examination number	Examinations with dosimetric parameters	Sex-age-averaged median organ dose by groups of age at the examination time																
			Active bone marrow	Brain	Oral Cavity	Thyroid	Oesophagus	Breast**	Lungs	Stomach	Colon	Rectosigmoid	Pancreas	Liver	Kidney	Urinary bladder	Prostate*	Ovaries**	Uterus**
<1 year																			
Skull/brain	3,685	1,133	6.85	22.29	6.35	2.43	1.15	0.30	0.66	0.19	0.08	0.05	0.14	0.23	0.15	0.03	0.01	0.01	0.01
Face	13	18	3.32	2.79	12.28	7.94	1.81	0.29	0.65	0.16	0.06	0.03	0.12	0.22	0.11	0.02	0.00	0.02	0.02
Cervical sp.	47	14	2.75	1.45	14.61	12.67	3.67	0.31	0.87	0.19	0.07	0.03	0.13	0.24	0.14	0.02	0.01	0.02	0.01
Neck	56	28	2.41	1.11	12.88	11.05	3.25	0.28	0.83	0.18	0.06	0.03	0.11	0.22	0.13	0.02	0.01	0.02	0.01
Thoracic	24	6	3.54	0.28	1.06	11.63	9.05	9.13	11.66	5.79	0.68	0.16	1.75	7.18	3.14	0.15	0.04	0.07	0.05
Chest	912	159	3.00	0.26	1.91	7.41	6.04	7.46	7.88	7.28	2.83	0.52	6.07	7.56	4.74	0.36	0.10	0.32	0.20
Abdomen	630	47	1.53	0.05	0.15	0.32	1.76	1.24	2.37	5.85	6.15	4.66	5.94	5.95	6.42	4.35	0.83	2.57	2.00
Trunk	58	8	2.85	0.21	1.29	5.63	4.72	5.04	5.80	5.92	6.12	5.25	5.93	6.09	6.52	5.79	2.55	2.77	2.43
Pelvis	116	14	2.75	0.02	0.05	0.12	0.29	0.17	0.40	1.80	11.87	14.90	2.95	1.52	3.74	16.64	8.02	6.51	6.16
Leg	24	9	7.11	0.02	0.03	0.05	0.09	0.08	0.13	0.34	2.53	17.18	0.61	0.33	0.91	28.60	15.14	5.45	6.01
1-4 years																			
Skull/brain	6,384	2,74	9.11	25.07	15.09	2.30	1.42	0.24	0.74	0.16	0.04	0.02	0.09	0.19	0.13	0.02	0.00	0.01	0.01
Face	41	65	7.06	17.60	26.24	5.32	3.86	0.39	1.20	0.24	0.06	0.03	0.13	0.27	0.17	0.02	0.00	0.01	0.01
Cervical sp.	180	67	3.59	2.24	22.52	21.25	8.38	0.41	2.16	0.31	0.06	0.02	0.15	0.35	0.21	0.02	0.01	0.01	0.01
Neck	266	67	1.92	1.62	11.45	8.96	3.70	0.19	0.91	0.14	0.03	0.01	0.07	0.15	0.10	0.01	0.00	0.01	0.00
Thoracic sp.	30	18	3.65	0.32	1.21	11.45	10.52	10.73	13.32	8.16	1.03	0.23	4.06	9.20	5.33	0.19	0.04	0.16	0.13
Chest	1,501	467	2.55	0.21	0.77	7.27	6.81	6.98	8.62	6.90	1.56	0.27	4.61	7.47	5.54	0.21	0.06	0.14	0.11
Abdomen	197	134	1.99	0.03	0.10	0.33	1.45	2.81	2.27	7.00	8.05	5.23	7.36	7.08	8.35	5.71	1.89	2.82	2.35
Trunk	28	96	3.76	0.20	0.70	5.41	6.63	7.03	8.71	8.44	8.72	6.43	8.20	8.68	9.37	7.15	2.54	3.41	2.88
Pelvis	39	38	2.78	0.02	0.03	0.09	0.21	0.15	0.31	1.72	11.46	14.38	3.49	1.49	3.70	16.51	6.41	8.38	7.10
Leg	19	36	7.11	0.02	0.03	0.05	0.09	0.08	0.13	0.34	2.53	17.18	0.61	0.33	0.91	28.60	15.14	5.45	6.01
5-10 years																			
Skull/brain	7,058	2,28	7.53	27.27	23.92	2.66	1.20	0.21	0.71	0.11	0.03	0.01	0.07	0.14	0.08	0.01	0.00	0.00	0.01
Face	306	142	4.74	16.77	25.02	4.48	2.01	0.25	0.87	0.13	0.03	0.01	0.07	0.16	0.09	0.01	0.00	0.00	0.01
Cervical sp.	194	82	2.24	2.00	21.63	29.31	6.90	0.26	1.46	0.16	0.03	0.01	0.09	0.21	0.11	0.01	0.00	0.00	0.00

183

CT scan type	Examination number	Examinations with dosimetric parameters	Active bone marrow	Brain	Oral Cavity	Thyroid	Oesophagus	Breast**	Lungs	Stomach	Colon	Rectosigmoid	Pancreas	Liver	Kidney	Urinary bladder	Prostate*	Ovaries**	Uterus**
Neck	292	59	1.59	1.89	14.63	16.72	4.15	0.17	0.91	0.11	0.02	0.01	0.06	0.13	0.07	0.00	0.00	0.00	0.00
Thoracic sp.	65	19	3.87	0.40	1.22	18.03	13.58	13.73	16.78	10.16	1.44	0.19	5.57	11.84	5.76	0.11	0.03	0.09	0.07
Chest	1,760	447	2.23	0.23	0.69	10.68	7.55	7.27	8.95	7.19	1.17	0.16	4.62	7.67	4.73	0.09	0.02	0.06	0.05
Abdomen	606	141	3.35	0.05	0.12	0.36	3.17	5.31	3.72	12.43	13.99	8.05	12.10	12.07	14.20	7.00	1.74	3.71	3.10
Trunk	26	57	5.92	0.29	0.82	8.85	10.15	10.82	13.20	13.15	13.95	10.79	12.36	13.37	14.36	11.75	5.16	5.26	4.59
Pelvis	101	42	4.26	0.01	0.02	0.04	0.19	0.14	0.20	1.22	13.27	18.45	2.47	1.01	3.86	19.97	5.47	11.25	9.94
Leg	245	58	6.42	0.02	0.03	0.04	0.06	0.06	0.10	0.22	1.76	12.20	0.39	0.22	0.63	20.14	9.58	7.97	7.59
10-15 years																			
Skull/brain	9,695	2,517	4.83	28.76	21.57	2.15	0.80	0.13	0.46	0.06	0.01	0.01	0.04	0.08	0.04	0.00	0.00	0.00	0.00
Face	499	234	3.73	19.81	29.82	4.02	1.35	0.17	0.62	0.07	0.02	0.01	0.04	0.10	0.05	0.01	0.00	0.00	0.00
Cervical sp.	303	104	2.43	2.33	30.10	29.66	6.50	0.19	1.38	0.12	0.02	0.01	0.07	0.16	0.07	0.00	0.00	0.00	0.00
Neck	331	38	1.48	1.77	18.24	18.09	4.00	0.12	0.89	0.07	0.01	0.00	0.04	0.10	0.05	0.00	0.00	0.00	0.00
Thoracic sp.	87	30	5.53	0.46	1.49	16.78	16.10	17.15	20.03	15.67	2.21	0.23	9.63	17.61	9.31	0.11	0.02	0.09	0.08
Chest	1,899	500	3.16	0.28	1.06	13.21	9.38	9.46	11.11	8.91	1.76	0.15	6.01	9.85	6.11	0.07	0.01	0.06	0.05
Abdomen	1,562	200	6.21	0.04	0.10	0.32	3.96	6.22	4.58	17.82	20.40	11.49	16.78	17.22	20.14	8.57	1.06	6.16	5.08
Trunk	121	59	16.16	0.63	1.94	20.40	22.88	25.04	29.53	30.37	32.13	23.80	27.29	30.91	32.26	25.51	5.78	17.07	15.01
Pelvis	134	84	6.78	0.01	0.01	0.02	0.12	0.08	0.14	1.00	12.10	22.07	1.78	0.71	2.72	23.99	8.47	10.93	9.56
Leg	1,104	88	7.07	0.02	0.02	0.02	0.04	0.04	0.07	0.17	1.50	15.76	0.30	0.15	0.52	28.35	22.34	5.05	5.41
15-20 years																			
Skull/brain	32,417	3,353	3.14	34.41	26.64	2.20	0.61	0.12	0.43	0.05	0.01	0.00	0.03	0.06	0.03	0.00	0.00	0.00	0.00
Face	1,581	231	2.29	16.68	29.46	3.34	0.83	0.12	0.48	0.05	0.01	0.00	0.02	0.07	0.03	0.00	0.00	0.00	0.00
Cervical sp.	1,213	139	2.41	1.69	28.41	39.41	5.86	0.18	1.68	0.11	0.02	0.01	0.06	0.16	0.06	0.00	0.00	0.00	0.00
Neck	1,089	76	1.18	0.84	14.44	19.00	2.80	0.09	0.82	0.05	0.01	0.00	0.03	0.08	0.03	0.00	0.00	0.00	0.00
Thoracic sp.	399	34	4.83	0.27	1.08	14.34	13.19	15.69	16.67	11.98	1.31	0.12	5.09	13.65	4.81	0.07	0.02	0.03	0.03
Chest	3,696	757	5.56	0.35	1.49	21.08	14.59	15.56	17.32	15.05	2.89	0.21	9.43	16.11	9.39	0.11	0.02	0.10	0.08
Abdomen	9,583	414	8.89	0.03	0.08	0.32	4.64	6.56	4.33	21.96	26.01	15.13	20.81	21.43	25.87	14.38	1.77	9.69	7.81
Trunk	810	85	15.00	0.43	1.72	23.37	19.31	21.52	23.84	24.39	25.78	18.66	21.42	24.93	25.98	20.57	8.90	9.24	7.85
Pelvis	428	98	8.80	0.01	0.01	0.02	0.13	0.08	0.14	1.02	13.50	24.99	2.17	0.77	3.46	29.23	12.89	12.36	10.61
Leg	2,753	86	3.19	0.01	0.01	0.01	0.02	0.03	0.04	0.08	0.63	8.74	0.15	0.06	0.26	13.82	14.23	2.01	2.70

Web Table 2. Parameter values for ERR and EAR models from BEIR VII and NCI (Berrington de González, et al.)

Cancer site	Origin	ERR model				EAR model				Final selected model
		β males	β females	γ*	η**	β males	β females	γ*	η**	
Brain /CNS	NCI	0.71 (0.26-1.34)	0.24 (0.09-0.47)	-0.3	-1.4	-	-	-	-	100% ERR
Oral Cavity and pharynx	NCI	0.23 (<0-0.66)	0.53 (0.13-1.24)	-0.3	-1.4	0.44 (0.08-1.1)	0.29 (0.06-0.66)	-0.41	2.8	70% ERR, 30% EAR
Thyroid	BEIR VII	0.53 (0.14-2)	1.05 (0.28-3.9)	-0.83	0	-	-	-	-	100% ERR
Esophagus	NCI	0.51 (<0-1.13)	0.82 (<0-3.1)	-0.3	-1.4	0.88 (0.11-2.1)	0.14 (<0-0.63)	-0.41	2.8	70% ERR, 30% EAR
Breast	BEIR VII	-	-	-	-	-	10 (7.0-14.2)	-0.5	1 or	100% EAR
Lung	BEIR VII	0.32 (0.15-0.70)	1.4 (0.94-2.1)	-0.3	-1.4	2.3 (1.1-5.0)	3.4 (2.3-4.9)	-0.41	5.2	30% ERR, 70% EAR
Stomach	BEIR VII	0.21 (0.11-0.4)	0.48 (0.31-0.73)	-0.3	-1.4	4.9 (2.7-8.9)	4.9 (3.2-7.3)	-0.41	2.8	70% ERR, 30% EAR
Colon	BEIR VII	0.63 (0.37-1.1)	0.43 (0.19-0.96)	-0.3	-1.4	3.2 (1.8-5.6)	1.6 (0.8-3.2)	-0.41	2.8	70% ERR, 30% EAR
Rectum	NCI	0.12 (<0-0.38)	0.12 (<0-0.38)	-0.3	-1.4	0.34 (0.09-1.1)	0.34 (0.09-1.1)	-0.41	2.8	70% ERR, 30% EAR
Pancreas	NCI	0.36 (<0-0.88)	0.36 (<0-0.88)	-0.3	-1.4	0.49 (0.09-1.1)	0.49 (0.09-1.1)	-0.41	2.8	70% ERR, 30% EAR
Liver	BEIR VII	0.32 (0.16-0.64)	0.32 (0.10-1.0)	-0.3	-1.4	2.2 (0.9-5.3)	1.0 (0.40-2.5)	-0.41	4.1	70% ERR, 30% EAR
Kidney	NCI	0.34 (<0-1.0)	0.34 (<0-1.0)	-0.3	-1.4	0.31 (0.08-0.68)	0.31 (0.08-0.68)	-0.41	2.8	70% ERR, 30% EAR
Bladder	BEIR VII	0.50 (0.18-1.4)	1.65 (0.69-4.0)	-0.3	-1.4	1.2 (0.4-3.7)	0.75 (0.3-1.7)	-0.41	6	70% ERR, 30% EAR
Prostate	BEIR VII	0.12 (<0-0.69)	-	-0.3	-1.4	0.11 (<0-1.0)	-	-0.41	2.8	70% ERR, 30% EAR
Ovary	BEIR VII	-	0.38 (0.1-1.4)	-0.3	-1.4	-	0.70 (0.2-2.1)	-0.41	2.8	70% ERR, 30% EAR
Uterus	BEIR VII	-	0.05 (<0-0.22)	-0.3	-1.4	-	1.2 (<0-2.6)	-0.41	2.8	70% ERR, 30% EAR

(continued)

Leukaemia model

Origin: BEIR VII

Cancer site	ERR model				EAR model				Final selected model
	β males	β females	γ*	δ, φ, θ	β males	β females	γ*	δ, φ, θ	
Leukaemia	1.1 (0.1-2.6)	1.2 (0.1-2.9)	-0.4 (-0.78-0)	-0.48 (-1.1-0.2), 0.42 (0-0.96), 0.87 (0.16-15)	1.62 (0.1-3.6)	0.93 (0.1-2.0)	0.29 (0.0-0.62)	0, 0.56 (0.31-0.85), 0.88 (0.16-15)	70% ERR, 30% EAR

*   Per-decade increase in age at exposure over the range of 0-30 years
**   Exponent of attained age
***   Only for women

5.4.   Paper V

Radiation induced cancer mortality in a cohort of paediatric and adolescent CT scanned patients: results of EPI-CT Spain.

Authors: <u>Bosch de Basea M</u>, Espinosa A, Figuerola J, Cardis E.

Status: Very initial draft.

Cancer mortality in young CT scanned patients: based on the Spanish branch of the EPI-CT study

Authors:

Magda Bosch de Basea[1,2,3*], Ana Espinosa[1,2,3], Jordi Figuerola[1,2,3], E Cardis[1,2,3]

Corresponding author: M. Bosch de Basea
* Institut de Salut Global (ISGlobal), Centre de Recerca en Epidemiologia Ambiental,
Parc de Recerca Biomèdica de Barcelona (PRBB),
Carrer del Dr. Aiguader 88, E-08003 Barcelona, Catalonia, Spain.
Telephone: +34 93 214 7322. Fax: +34 93 214 7302
Corresponding author: magda.boschdebasea@gmail.com

[1] Institut de Salut Global (ISGlobal), Centre de Recerca en Epidemiologia Ambiental,
Parc de Recerca Biomèdica de Barcelona (PRBB),
Carrer del Dr. Aiguader 88, E-08003 Barcelona, Spain.
Telephone: +34 93 214 7322

[2] Universitat Pompeu Fabra (UPF), Barcelona, Spain

[3] CIBER Epidemiología y Salud Pública (CIBERESP)

NUMBER OF:

Words, main text: 3,643
Words, abstract: 264
Tables: 6 (+ 2 supplementary tables)
Figures: 0
References: 29
Running title: Cancer mortality in Spanish CT scanned patients

Key words

CT scan · Cohort study · Mortality · Leukaemia · Brain tumour ·

Cancer

Abbreviations

CT Computed Tomography
LSS Life Span Study
IARC International Agency for Research on Cancer, Lyon, France
INE Instituto Nacional de Estadística (National Statistics Institute)
ICD International Classification of Diseases
WHO World Health Organization
RIS Radiology Information System
DICOM Digital Imaging and Communications in Medicine
MD Maryland
ERR Excess Relative Risk
SMR Standardised mortality ratio (SMR)

Abstract

Background: The use of CT imaging in general population has tripled in Spain over the last two decades, confronting the clear clinical benefits with the concerns related to its potential health risks. We assessed the association between CT scan radiation and leukaemia, hematologic malignancies and cancer risk in the Spanish EPI-CT cohort of young population.

Methods: The Spanish EPI-CT cohort (171,336 individuals) was followed-up for cancer mortality by linkage with the national mortality registries. Technical scan parameters were collected for over 35,000 CT scans to estimate average brain and active bone marrow doses. We estimated the excess relative risk (ERR) of cancer mortality per Gy of radiation using a linear model stratifying by age at the last CT examination. Standardised mortality rates (SMR) for the cohort were calculated using 1999-2013 Spanish cancer mortality rates.

Results: The ERR of non-CLL leukaemia mortality was ERR/Gy = 7.8 (95% CI: -0.49 - 23.39), for haematological malignancy mortality was 6.91 (95% CI: -0.10 – 19.79) and for all brain tumours combined was 7.32 (95% CI: 0.03 - 19.99) . The EPI-CT cohort members experienced higher mortality rates (SMRs) than the general population for most of the causes of death under analysis.

Conclusions: Cancer and non-cancer mortality in cohorts of young scanned patients differ substantially from the general population, suggesting that these patients are selectively more ill than the general population. Dose related increases in the risk of brain tumours as well as leukaemia and haematological malignancies (not statistically significant for the later two) were observed. Confidence intervals were wide however, and compatible both with estimates from atomic bomb survivors.

Background

In Spain the use of computerised tomography (CT) scanning in the general population (including children and young adults) has tripled over the last two decades, rising from 34.9 to 98 CT scans per 1000 population/year between 1996 and 2014 (1). The obvious benefits of this highly informative imaging technique for diagnosis and follow up of diseases have been confronted with mounting concerns regarding its possible relationship with excess lifetime cancer. This is especially worrisome when it is well documented that ionising radiation exposure during childhood results in increased lifetime risks of cancer compared to adult exposure (2–6).

In young people a CT scan may convey organ doses in the scanned area ranging from below 10 mGy to a few tens of mGy (7,8) per examination, which according to the predominant risk model, it may imply a small increase in cancer risks at the population level (3,9). This risk is based on the use of the linear non-threshold model for extrapolating risks from populations with moderate to high doses to the low dose range where individual CT examination doses belongs (10).

Extensive mortality follow-up of the survivors of the Japanese atomic bomb carried out until 2003 indicated elevated mortality rates among those exposed to the ionising radiation from the atomic blast at younger ages (11). A previous publication had estimated that the lifetime risk for all cancer mortality for those exposed in utero or as children were 2.1 (90% Confidence intervals (CI): 0.2 to 6.0) for the in-utero and childhood exposure (12), which for 57% of

the analysis population was below 100 mSv (13). Leukaemia mortality for survivors exposed below the age of 20 are provided in (14), with an ERR/Sv of 6.5 (95% CI 4-10.3) (11).

A number of epidemiological studies have predicted the likely excess lifetime cancer mortality associated with the doses received through CT scanning in children (15–18) using the radiation-associated estimates provided by the US NRC Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation reports (3,19). Although from a public health perspective these estimates are important to weight the benefits of the radiation exposure against the increase of risk of a lifetime fatal cancer, direct risk estimates assessed in population exposed to CT imaging and followed-up for incidence and mortality are needed to fine-tune and complement the risk extrapolations from the Life Span Study (LSS). This is the aim of the European EPI-CT study, a multinational cohort study of about 1.1 million patients who received at least one CT during childhood, adolescence and young adulthood (20).

This paper evaluates the radiation related risk of mortality from cancer in the Spanish branch of the European EPI-CT cohort study. Statistical analyses were conducted to assess the hypothesis that medical exposure to radiation through CT scan imaging is associated with increased death rates of leukaemia, hematopoietic malignancies and brain tumours per unit of radiation dose. A comparison of the mortality rates in the Spanish EPI-CT cohort and in Spain is also included.

Methods

Study population and related data

The methods of this study have been described elsewhere (20). The Spanish EPI-CT cohort is based in a retrospective cohort design including 177,034 individuals who, between 1991 and 2013, received at least 1 CT scan when they were younger than 21 years old in any of the 24 public and state-subsidised private hospitals that participate in the study. These are among the reference hospitals in paediatric assistance within the six participating Spanish Autonomous Communities (Basque country, Catalonia, Valencia Community, Murcia region, Navarre and Madrid Community). Ethical clearance was obtained from all appropriate Spanish authorities as well as from the Ethical Committee of the coordinating centre (IARC). 5698 subjects (3.2%) were discarded from the analysis because they were not residents in Spain or in any of the participating Autonomous Communities and therefore the ascertainment of exposure or vital status could not have been adequately performed. From the 171,336 individuals included in this analysis, the residence was unknown for 26531 subjects (15.5%), and it was assumed that would be in any of the Autonomous Communities were the patients had their last CT scan.

Mortality follow-up up to the year 2014 was obtained from the National Statistics Institute in Spain (Instituto Nacional de Estadística; INE), which provided ascertainment of vital status (whether the patient was living or deceased) and cause of death if deceased, according to the International Classification of Diseases

(ICD) using the 10th revision from 1999 onwards (21). For previous years the ICD-9 revision cause-of-death codes were recoded into ICD-10 using a crosswalk provided from the INE itself. At the INE, the match was done via an iterative deterministic record linkage procedure with probabilistic elements, such as the estimation of the Levenshtein distance as a measure of string matching. All uncertain matches were checked manually by MBB or the INE itself. The outcomes of interest for this analysis were (1) all leukaemias (ICD-10: C91.0, C91.3-C95.9) excluding chronic lymphocytic, all brain tumours (C71.0-C71.9), hematopoietic neoplasms (ICD-10: C91.0, C91.3-C95.9, C82.0-C85.9) excluding chronic lymphocytic and Hodgkin lymphomas. For the standardised mortality rate (SMR) analysis, mortality in the reference population (Spain) for the same ICD codes, as well as for all cancers and all causes, was obtained from the WHO Mortality Database for the 1999 – 2013 period (22). For the unavailable previous years (up to 1993), the 1999 mortality was used assuming that mortality has remained stable over time, and the same was done for 2014 using 2013 mortality (22).

Exposure data and dosimetry at the organ level

Exposure data of each cohort subject was obtained directly from the Radiological Information System (RIS) of the hospital where the CT was received for each CT between the implementation of RIS in the hospital (between 1991 and 2010) until December 2013. The RIS records basic information of the CT examinations performed in the radiology departments, including patient identifying information and basic variables about the examination (including body part

scanned and examination date and, in certain instances, indication for the CT scan and the referring hospital department). CT examinations were classified in 74 categories according to the anatomical area scanned following an existing classification (23).

For the estimation of organ doses, protocol parameters (kvp, mAs and pitch), machine specifications (model and manufacturer), anonymous patient characteristics (age and sex), and the descriptions of the anatomical areas scanned were extracted from the DICOM headers of CT scans, using a dedicated software: PerMoS (Luxembourg Institute of Science and Technology, Luxembourg). The examinations were performed between 2001 and 2015 in the radiology departments of 9 participating hospitals. Additionally, a radiologist determined the start and end of the exposed body region in each type of CT examination in age-specific computational anthropometric models of the human body, which were later validated by an additional paediatric radiologist.

Both the CT start and end landmarks and the CT scan parameters were used in the software for dose estimation; NCICT 2.4 (National Cancer Institute, Bethesda, MD). After discarding the CT scan records with missing parameters, 35,379 examinations could be used with NCICT 2.4, designed to estimate organ doses using hybrid male and female phantoms of different ages (from newborn to adults) (24) that take into account the age- and gender-related differences in anatomy and physiology of reference individuals (25). NCICT uses Monte Carlo simulations of multi-slice CT to estimate absorbed organ doses. For the purpose of the risk analyses in this paper, estimated bone marrow and brain doses were obtained

and a lookup table of estimated doses was compiled using the medians of any combination of examination type, patient age and sex in order to assign doses for all examinations undergone by the cohort members. On average 120 CT scans (median: 32 CT scans) were used to estimate the doses for each combination of CT scan type (74 categories), age (20 categories) and sex (2 categories), although for 25 combinations there were less than 5 CT scans available.

The estimated organ doses by age and sex of the patient, and by examination type were assigned to the 278,345 scans performed in the members of the cohort.

Statistical methods

A basic description of the study cohort was conducted regarding its age distribution at the time of the first CT scan, sex, autonomous community of residence and number of CT scans. The distribution of cumulative doses from CT scans per child was described for the organs of interest in mGy (active bone marrow and brain) by different subgroups of the cohort. The organ-doses used in the present analysis were active bone marrow dose for the leukaemia and hematopoietic neoplasms analysis and brain doses for the brain cancer analysis.

The association between the risk of mortality from leukaemia, haematological malignancies and brain tumours and cumulative radiation dose absorbed in the organ of interest was assessed using the linear excess relative risk (ERR) model fitted with the PEANUTS application included in the EPICURE software package

(26). The ERR is a risk model commonly used in radiation epidemiology. The main analyses included dose as a continuous variable and as a categorical variable in 12 distinct categories (0-,5-,10-,25-,50-,75-,100-,200-,300-,500-,1000- and 1500 mGy). Estimated 90% and 95% profile likelihood confidence intervals were calculated.

Cumulative doses were lagged by 2 years for the leukaemia and hematopoietic malignancies mortality risk analysis and 5 years for the brain tumours mortality risk analysis to take into account a minimum latency period between exposure and a cancer possibly resulting from it. Although the applied lag-times were chosen based on previous publications, alternative lag assumptions were also used in sensitivity analyses.

In order to minimise the inclusion in the study of subjects with undiagnosed cancer at the time of the first CT, or subjects for whom the CT had been used to diagnose the cancer (reverse causation), an exclusion period of 24 months after the first CT scan was applied. Therefore, the date of start of follow-up in the cohort was defined as the date of the first CT scan of the patient plus 24 months, and the exit date was set at the minimum of date of death, if deceased, and date of end of the follow-up (Dec 31, 2014).

The analyses controlled by sex, autonomous community of residence and time period (1991-1999, 2000-2007 and 2008-2013). Testing for confounding by other variables was conducted by introducing the variables and testing for a more than 10% change in the parameter estimates. Only those variables that met that criterion were included in the model. Effect modification by age at the time

of the last scan (0-4, 5-9, 10-14, 15-20) was tested by including interaction terms with dose in the model and testing their significance using the likelihood ratio test.

The number of observed deaths in the Spanish EPI-CT cohort due to "all causes of death", "all leukaemia excluding chronic lymphocytic", "hematopoietic neoplasms" and "brain cancer cases" from 1991 to 2014 was compared to the number of expected deaths based on the mortality rates for these causes in the Spanish population during the same period, using standardised mortality ratios (SMRs), indirectly standardised by age groups ([0,1), [1-5), [5-10), [10-15), [15-20), [20-25), [25-30), [30-35), [35-40), [40-45), [45-50)) and time period. Sex was not used for the standardisation due to the small number of casualties in the study. Two-sided 95% percent confidence intervals for the SMRs were calculated under the assumption that the observed number of deaths followed a Poisson distribution. SMR analyses were performed in Stata 14.

Results

Once the two year exclusion period were applied to the study cohort, the number of included subjects dropped from 171,336 to 152,850 and the number of CT scans from 259,859 to 248,118 CT scans. The distribution of the 152,850 cohort members by age, sex, and vital status is shown in table 1. There were 86,308 males and 66,542 females, with similar median ages at the time of the first CT scan (11.4 years). The median age of individuals still alive at the end of follow-up was 20.0 years (10th-90th percentile: 8.14- 29.01 years) without statistically significant differences between males and females (p-value= 0.181). The median age of death was 17.5 years for males and females, again, without major differences among sexes (p-value=0.052).

The cohort members were followed up for mortality until 2014 for a total of 897,191 person-years, with an average follow-up of 5.9 years (min-max: 5.9 − 22.0 years) from the time of entry into the cohort till censor by death or end of the study (see Web Table 1 for distribution by age at the time of the first CT scan and Autonomous Community). About 99.2% of the cohort (n=151,664) was still alive at the end of the data collection phase of the study in December of 2014 (Table 2). A total of 1186 deceased were ascertained; 481 subjects (40.5%) due to neoplasms, 136 subjects due to diseases of the nervous system (11.5%) and 99 subjects (8.35%) due to congenital malformations (data not shown). Regarding the mortality due to the outcomes of interest in the present analysis, 74 leukaemia cases, 87 brain tumour cases and 85 hematopoietic neoplasms were ascertained (Table 2). Approximately 10% of the all-cause deceased

patients died younger than 6 years (data not shown). 25% of the brain cancer deaths occurred in patients younger than 8 years old, whereas 25% of the leukaemia deaths were observed in patients younger than 14 years old (data not shown).

The most common anatomical areas scanned were the head (55.5%, n=137,784 CT scans), followed by the thorax / chest (13.5%, 33,463 CT scans) and a combination of multiple anatomical areas (8.6%, n=21,281 CT scans). Once the 2 and 5 years lag periods were applied to allow for the induction of the disease, only 239,613 and 161,071 out of the initial 248,118 CT scans were included in the quantification of mortality risks respectively. The main determinants of the organ-dose distribution were the age of the patient and the anatomical area scanned. Web Table 2 presents the 10 CT scan types that contribute to the highest sex-averaged active bone marrow and brain doses, by age groups. In general terms, the active bone marrow doses increased with increasing age at the time of the exposure for those CT scan types that covered most bone marrow locations (mainly the spinal column). Similarly, for those CTs that involved higher doses to the brain, a positive correlation between age and exposure and brain doses was observed.

The overall crude mortality rate in the Spanish EPI-CT cohort was 775.9 deaths per 100,000 population with a SMR of 3.33 (95% CI: 3.14 −3.52), based on 1186 cases (Table 3). The EPI-CT cohort members experienced higher mortality rates than the general population for most of the causes of death included in the present analysis. SMRs were significantly different from 1.0 for all the death causes under study.

Table 4 displays the distribution of the cohort members by categories of individual cumulative doses to the active marrow and to the brain. 43.3% (n= 66,189) and 50.6% (n= 77,359) of the entire cohort had cumulative doses to the active marrow and to the brain in the lowest category of exposure (0 – 4.9 mGy). The distribution was similar for both sexes, although a higher proportion of women belonged to the less exposed category.

Additionally, 79.1% of the cohort had cumulative active bone marrow doses below 10.0 mGy and 50.7% of the cohort had cumulative brain doses below 10 mGy.

A notable difference in the cumulative bone marrow dose distribution was observed by vital status of the patients, where although in both groups of individuals cumulative marrow doses below 5 mGy were abundant, they were more prevalent in the group who was alive at the end of the follow-up than in that of deceased members. Specifically, 43.4% of those alive had cumulative marrow doses in the lowest category (below 5 mGy), whereas only 26.0% of those deceased accumulated similar doses. The median bone marrow cumulative dose among those alive was 2.9 mGy (IR: 2.2 – 4.0 mGy) compared to the 4.02 mGy (IR: 2.3 – 9.7 mGy) among the deceased ones. On the contrary, a higher proportion of deceased individuals (72.3%) was observed in the lowest cumulative brain dose category compared to those alive (50.44%). Additionally, those alive received a higher proportion of head CTs (56.2%) and lower proportion of chest CTs (12.7) compared to the deceased group that received a higher proportion of chest CT (31.9%) and a lower proportion of head CTs (41.2%) (data not

shown). Additionally, 0.19% of those alive had cumulative bone marrow doses above 100 mGy compared to 1.27% of those deceased. Similarly, among those subjects alive 1.81% accumulated brain doses above 100 mGy compared to the 3.29% of the deceased group of subjects.

The excess dose-related mortality associated with CT scanning performed in young patients from the Spanish EPI-CT cohort is shown in the Table 5. The estimated association between non-CLL leukaemia mortality and CT scan doses with a lag assumption of two years let to an excess relative risk (ERR) per unit of dose (Gy) of ERR/Gy = 7.8 (97.5% CI: -0.49 - 23.39). For all hematologic malignancies mortality, excluding CLL and Hodgkin lymphoma the ERR at 1 Gy was = 6.91 (97.5% CI: -0.10 – 19.79). For mortality due to all brain tumours combined the ERR at 1 Gy was = 7.32 (97.5% CI: 0.03 - 19.99) assuming a 5-year lag time, pointing out that the risk of dying from brain cancer was not significantly associated with CT scan doses. For brain cancer mortality there was no evidence of effect modification when including 'age at the time of the last CT scan' as interaction factor.

Discussion

These are the first results of the Spanish study of paediatric and adolescent CT scans based in one of the largest cohorts assembled to date. Analyses show a clear increased mortality in this cohort compared to the general population, overall as well as for all cancers, leukaemia, haematological malignancies and brain cancer. The total number of deaths from leukaemia, haematological malignancies and brain tumours were relatively low, as the follow-up was short on average (5.9 years).

Our results suggest, nevertheless, an association between the radiation dose from CT imaging and mortality from non-CLL leukaemia, haematological malignancies and brain cancer, in this population of patients exposed below 21 years of age. The observed risk estimates have wide confidence intervals and are similar to the mortality estimates from the atomic bomb survivors and lower but statistically compatible with estimates based on incidence data from the Pearce (27) and Mathews (28) studies of paediatric CTs (Table 6). However, this association was statistically significant only for brain cancer. To our knowledge there is no other published study directly quantifying the cancer mortality risks of CT imaging in young population.

A relevant strength of this study and an important advantage compared to previous published studies of cancer risk in relation to CT scanning (Pearce *et al.* (27) and in particular of Matthews *et al.* (28) is the estimation of doses based on a sizeable amount of relevant technical parameters that were used for CT imaging in nine participating Spanish hospitals. It is noted, however, that the

estimated average brain and active marrow doses are similar to those obtained in studies of CT scanned young population (27,29), although slightly lower.

The brain was the most exposed vital organ in the patients of the Spanish EPI-CT cohort, accounting for over half of all the CT scans undergone by the patients. In several publications CT scan radiation exposure to the brain has been related with increased risks of brain cancer. Our findings for brain cancer are aligned with those of Brenner *et al.* who projected increased CT scan-related fatal risks in paediatric and young population (18).

The increased mortality rates in the Spanish EPI-CT study compared with the general population, are of note. They suggest that the population that undergoes CTs is at greater risk of cancer (even after removing subjects with less than 2 years of follow-up) and non-cancer diseases than the general population. While this was suspected, similar analyses in other national cohorts would be valuable.

There are several caveats in this analysis that are worth commenting. First, the reference mortality data used for the SMR corresponds to statistics from 1999 to 2013, and the first and last available mortality records were used to impute mortality for the unavailable years. Although there is some potential for imprecision in the rates used, no major changes in the mortality rates have been observed for Spain and it has been assumed that it would not substantially affect the results.

Completeness of data, defined as the collection of RIS data from the start of CT scanning at the hospital, was only attained in one

hospital and therefore some members of the cohort may have an incomplete exposure history, resulting in exposure misclassification.

By the end of the study the cohort was relatively young (the oldest member of the cohort was 47 years old in 2014), with less than 1% of deceased patients. An extended follow-up would provide a key chance to test the association of CT scan radiation exposure with the mortality risk of other cancer and non-cancer outcomes which the current study would not allow because of insufficient follow-up. Despite these limitations, this study, the first in Spain and one of the largest to date, provides important information both in terms of the mortality of the patient population and in terms of radiation induced risks, with estimates that, though still uncertain, are similar to those seen among atomic bomb survivors exposed below the age of 20, and lower – though statistically compatible – than recent results from other national CT cohorts. Further follow-up of this cohort and, in the meantime, combined analysis of the data from this and other EPI-CT national cohorts will provide invaluable information about risks from CT scanning in young people.

Funding

Acknowledgements

Disclosure of interests: The authors declare that they have no competing financial interests.

Human Participant Protection

The Ethics Committee of the International Agency for Research on Cancer approved the study protocol (IARC IEC 12-35). The protocol has also been approved by all appropriate hospital ethics committees, prior to commencing the epidemiological study.

References

1. Ministerio de Sanidad, Servicios Sociales e Igualdad. Indicadores clave del SNS [Internet]. 2014 [cited 2014 Aug 8]. Available from: http://www.msssi.gob.es/estadEstudios/estadisticas/sisInfSanSNS/in clasSNS_DB.htm

2. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiation research. 2007 Jul;168(1):1–64.

3. Committee on the Biological Effects of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation. BEIR, VII Report, phase II. Washington: US National Research Council; 2006.

4. Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci USA. 2003 Nov 25;100(24):13761–6.

5. Jacob P, Kenigsberg Y, Zvonova I, Goulko G, Buglova E, Heidenreich WF, et al. Childhood exposure due to the Chernobyl accident and thyroid cancer risk in contaminated areas of Belarus and Russia. Br J Cancer. 1999 Jul;80(9):1461–9.

6. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res. 1994 Feb;137(2 Suppl):S68-97.

7. Huda W, Vance A. Patient Radiation Doses from Adult and Pediatric CT. American Journal of Roentgenology. 2007 Feb 1;188(2):540–6.

8. Lee C, Kim KP, Long DJ, Bolch WE. Organ doses for reference pediatric and adolescent patients undergoing computed tomography estimated by Monte Carlo simulation. Med Phys. 2012 Apr;39(4):2129–46.

9. ICRP (International Commission on Radiological Protection). The 2007 recommendations of the International Commission for Radiation Protection. Publication 103 [Internet]. 2007 p. 2–4. (Ann. ICRP). Report No.: ICRP Publication 103. Available from:

http://www.icrp.org/docs/ICRP_Publication_103-Annals_of_the_ICRP_37%282-4%29-Free_extract.pdf

10. International Commission on Radiological Protection. Low-dose Extrapolation of Radiation-related Cancer Risk. 2005. (Ann ICRP 35 (4)). Report No.: Publication 99.

11. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. Radiat Res. 2012 Mar;177(3):229–43.

12. Delongchamp RR, Mabuchi K, Yoshimoto Y, Preston DL. Cancer mortality among atomic bomb survivors exposed in utero or as young children, October 1950-May 1992. Radiat Res. 1997 Mar;147(3):385–95.

13. Preston DL, Cullings H, Suyama A, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. J Natl Cancer Inst. 2008 Mar 19;100(6):428–36.

14. UNSCEAR. Sources, effects and risks of ionising radiation. Vol. II, Annex B - Effects of radiation exposure in children [Internet]. United Nations, New York; 2013. (UNSCEAR 2013 Report). Available from: http://www.unscear.org/docs/reports/2013/UNSCEAR2013Report_AnnexB_Children_13-87320_Ebook_web.pdf

15. Chodick G, Ronckers CM, Shalev V, Ron E. Excess lifetime cancer mortality risk attributable to radiation exposure from computed tomography examinations in children. The Israel Medical Association journal : IMAJ. 2007 Aug;9(8):584–7.

16. de Jong PA, Mayo JR, Golmohammadi K, Nakano Y, Lequin MH, Tiddens HAWM, et al. Estimation of cancer mortality associated with repetitive computed tomography scanning. Am J Respir Crit Care Med. 2006 Jan 15;173(2):199–203.

17. Koral K, Blackburn T, Bailey AA, Koral KM, Anderson J. Strengthening the argument for rapid brain MR imaging: estimation of reduction in lifetime attributable risk of developing fatal cancer in children with shunted hydrocephalus by instituting a rapid brain MR imaging protocol in lieu of Head CT. AJNR Am J Neuroradiol. 2012 Nov;33(10):1851–4.

18. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. AJR Am J Roentgenol. 2001 Feb;176(2):289–96.

19. Nuclear Regulatory Commission. Health effects of exposure to low levels of ionizing radiation: BEIR V. Washington, DC: National Academy Press; 1990.

20. Bosch de Basea M, Pearce MS, Kesminiene A, Bernier M-O, Dabin J, Engels H, et al. EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT. J Radiol Prot. 2015 Jul 30;35(3):611–28.

21. World Health Organisation. International statistical classification of diseases and related health problems (ICD) - 10th revision [Internet]. WHO. 2011 [cited 2013 Sep 18]. Available from: http://www.who.int/classifications/icd/en/

22. World Health Organization. Mortality Database [Internet]. Available from: http://www.who.int/healthinfo/mortality_data/en/

23. European Commission. Directorate-General for Mobility and Transport, Directorate-General for Energy. European Guidance on Estimating Population Doses from Medical X-Ray Procedures [Internet]. 2008 [cited 2016 Mar 11]. Report No.: Radiation protection n° 154. Available from: http://ddmed.eu/_media/background_of_ddm1:rp154.pdf

24. Lee C, Williams JL, Lee C, Bolch WE. The UF series of tomographic computational phantoms of pediatric patients. Med Phys. 2005 Dec;32(12):3537–48.

25. ICRP Publication 89: Basic anatomical and physiological data for use in radiological protection: reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. Ann ICRP. 2002;32(3–4):5–265.

26. Preston DL, Shilnikova NS. EPICURE [Internet]. Ottawa, ON, Canada: Risk Sciences International; Available from: http://www.risksciences.com/app/wa/mediaEntry?mediaEntryId=1421

27. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk

of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012 Aug 4;380(9840):499–505.

28. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;346:f2360.

29. Journy N, Ancelet S, Rehel J-L, Mezzarobba M, Aubert B, Laurier D, et al. Predicted cancer risks induced by computed tomography examinations during childhood, by a quantitative risk assessment approach. Radiat Environ Biophys. 2013 Oct 9;

Table 1 Description of the EPI-CT population in Spain (N = 152,850)

Characteristics	Males N	(%)	Females N	(%)	p-value
Age at the time of the first scan					
<1	7426	(8.6 %)	544	(8.2 %)	<0.001 [1]
1 - 4	1292	(15.0 %)	967	(14.5 %)	
5 - 9	1400	(16.2 %)	112	(16.9 %)	
10 - 14	1871	(21.7 %)	148	(22.4 %)	
15 - 19	2769	(32.1 %)	207	(31.2 %)	
≥ 20	5550	(6.4 %)	454	(6.8 %)	
Age at the time of the first scan - Median (IQR)*					
All (deceased + alive)	12.6	(1.3 - 19.5)	12.6	(1.3 - 19.5)	0.201 [2]
Alive	12.6	(1.3 - 19.5)	12.6	(1.4 - 19.5)	0.153 [2]
Decesead (all)	12.3	(1.4 - 19.3)	10.9	(0.9 - 19.1)	0.067 [2]
Deaths due to leukaemia	10.1	(3.4 - 19.1)	9.3	(2.2 - 18.6)	0.358 [2]
Deaths due to hem. malign.	10.1	(2.6 - 19.1)	9.6	(2.2 - 18.6)	0.468 [2]
Deaths due to brain t.	7.6	(2.1 - 18.1)	8.2	(3.1 - 16.7)	0.975 [2]
Sex	86308	(56.5 %)	66542	(43.5 %)	<0.001 [3]
Residence by Autonomous Community (% patients)					
Catalonia	3136	(36.3 %)	241	(36.4 %)	0.020 [1]
Madrid Community	1513	(17.5 %)	119	(18.0 %)	
Murcia region	2114	(2.5 %)	161	(2.4 %)	
Navarre	4741	(5.5 %)	375	(5.7 %)	
Basque country	9925	(11.5 %)	772	(11.6 %)	
Valencian Community	9228	(10.7 %)	706	(10.6 %)	
Missing residence	1379	(16.0 %)	102	(15.4 %)	
Number CT scans per patient - Median (p10 - p90)*	1	(1 - 1)	1	(1 - 1)	<0.001 [2]
Number of patients having CT scans					
1	6206	(71.9 %)	496	(74.6 %)	<0.001 [1]
2 - 5	2149	(24.9 %)	151	(22.7 %)	
6 - 10	2082	(2.4 %)	128	(1.9 %)	
11 -20	594	(0.7 %)	411	(0.6 %)	
> 20	73	(0.1 %)	74	(0.1 %)	

 **p10 - p90: Percentile 10th - Percentile 90th
 [1] Chi-square test | [2] Wilcoxon-Mann-Whitney test | [3] Binomial test

Table 2 Distribution of CT scanned individuals, observed person-years at risk, total number of deaths, number of deaths due to brain tumor and leukemia by age at the time of the first CT scan and sex, in the Spanish EPI-CT Spain cohort, once the exclusion period (24 months) after the first CT is applied

Age at the time of the first scan	Number of subjects	Observed person-years	Total number of deaths	Number of deaths due to leukemia	Number of deaths due to hematopoietic malignancies	Number of deaths due to brain tumors	Alive
Males							
0 to 0.9 years old	7,426	42840.20	58	2	2	2	7,368
1 to 4 years old	12,920	76757.77	112	3	6	17	12,808
5 to 9 years old	14,001	84154.76	124	13	14	12	13,877
10 to 14 years old	18,716	110924.48	148	10	12	10	18,568
15 - 19 years	27,695	160028.34	238	9	12	14	27,457
≥ 20 years	5,550	30961.54	28	1	1	1	5,522
Females							
0 to 0.9 years old	5,446	32193.72	51	-	-	2	5,395
1 to 4 years old	9,670	57288.02	80	11	11	8	9,590
5 to 9 years old	11,274	66828.81	94	9	9	8	11,180
10 to 14 years old	14,880	88984.06	101	7	9	4	14,779
15 - 19 years	20,730	120392.77	124	8	8	6	20,606
≥ 20 years	4,542	25836.57	28	1	1	3	4514

Table 3 Standardised mortality rates in EPI-CT cohort members per 100 000 population aged 0 – 45 years, 1993 – 2014

Cause-of-death	ICD-10 code	N	SMR	(95 % CI)
All	All ICD-codes*	1186	3.33	(3.14 - 3.52)
All except neoplasms and external causes	All ICD-codes except neoplasms and external causes**	556	4.30	(3.96 - 4.67)
All cancers	C00 - D48	448	10.48	(9.55 - 11.50)
Leukaemia ***	C91.0, C91.3 -C95.9	74	8.09	(6.44 - 10.18)
Haematological malignances****	C91.0, C91.3 -C95.9, C82.0-C85.9	85	6.62	(5.35 - 8.19)
Brain cancer	C71.0-C71.9	87	13.94	(11.30 - 17.20)

*   ICD-10 codes: A00-B99,C00-D48,D50-D89,E00-E88,F01-F99,G00-G98,H00-H59,H60-H93,I00-I99,J00-J98,K00-K92,L00-L98,M00-M99,N00-N98,O00-O99,P00-P96,Q00-Q99,R00-R99,V01-Y98,U04

**   ICD-10 codes: A00-B99,D50-D89,E00-E88,F01-F99,G00-G98,H00-H59,H60-H93,I00-I99,J00-J98,K00-K92,L00-L98,M00-M99,N00-N98,O00-O99, P00-P96,Q00-Q99,R00-R99,U04

***   excluding chronic lymphocytic

**** excluding chronic lymphocytic leukaemia and Hodgkin lymphoma

Abbreviations: ICD-10 International Classification of Diseases revision 10th, N observed number of deaths, SMR standardized mortality rate, CI confidence interval

Table 4 Number of patients by cumulative exposure categories (in mGy) in the EPI-CT Spain cohort

	Total number of subjects	Cumulative exposure categories (in mGy)										
		0 - 4.9	5.0 - 9.9	10.0 - 24.9	25.0 - 49.9	50.0 - 74.9	75.0 - 99.9	100 - 199.9	200 - 299.9	300.0 - 499.9	500.0 - 999.9	1000.0 - 1500.0
Bone marrow doses												
Total population	152,850	66189	5477	2461	5570	1049	345	291	16	3	1	
Sex:												
Males	86,308	35632	3199	1423	3429	641	214	151	12	2	1	
Females	66,542	30557	2278	1038	2141	408	131	140	4	1		
Age at the first CT scan:												
<1 year	12,872	2269	7234	2496	611	149	52	58	2	1		
1 - 4 years	22,590	4897	1279	3341	1178	208	87	73	6	2	1	
5 - 9 years	25,275	4564	1570	3862	870	181	54	40	3			
10 - 14 years	33,596	17309	9702	5204	1088	194	57	38	4			
15 - 19 years	48,425	29982	8146	8157	1661	302	94	82	1			
≥ 20 years	10,092	7168	1193	1553	162	15	1					
Vital status												
Alive	151,664	65881	5444	2430	5423	987	320	278	14	3	1	
Deceased (total)	1,186	308	324	305	147	62	25	13	2			
Causes of death:												
Leukaemia	74	17	21	22	11	3	0	0	0			
Hematopoietic m.	85	20	23	23	15	3	1					

(continued)

	Total number of subjects	Cumulative exposure categories (in mGy)										
		0 - 4.9	5.0 - 9.9	10.0 - 24.9	25.0 - 49.9	50.0 - 74.9	75.0 - 99.9	100 - 199.9	200 - 299.9	300.0 - 499.9	500.0 - 999.9	1000.0 - 1500.0
Brain doses												
Total population	152,850	77359	82	10066	52555	7811	2188	2195	404	161	28	1
Sex:												
Males	86,308	42978	54	5840	29558	4833	1282	1395	267	83	18	
Females	66,542	34381	28	4226	22997	2978	906	800	137	78	10	1
Age at the first CT scan:												
<1 year	12,872	6111	2	4950	1027	344	177	178	54	25	4	
1 - 4 years	22,590	11110	9	5106	4705	951	300	316	53	31	9	
5 - 9 years	25,275	12268	23	5	10523	1524	458	364	75	30	5	
10 - 14 years	33,596	17330	26	4	13092	1991	572	445	92	37	7	
15 - 20 years	48,425	25264	20	1	18965	2604	592	816	122	37	3	1
≥ 20 years	10,092	5276	2	4243	397	89	76	8	1			
Vital status												
Alive	151,664	76502	81	10025	52376	7763	2167	2173	392	157	27	1
Deceased	1,186	857	1	41	179	48	21	22	12	4		1
Causes of death:												
Brain tumors	87	66	1	5	6	2	4	2	1			

Table 5 Excess relative risk per Gy (ERR/ Gy) of cumulative active bone marrow and brain dose

Cause-of-death	ICD-10 code	N	ERR	(90% CI)	(95% CI)
Leukaemia *	C91.0, C91.3 -C95.9	74	7.83	(0.48 - 20.18)	(-0.49 - 23.39)
Haematological malignancies**	C91.0, C91.3 -C95.9, C82.0-C85.9	85	6.91	(0.73 - 17.20)	(-0.10 - 19.79)
Brain cancer	C71.0-C71.9	87	7.32	(0.90 - 17.49)	(1.99 - 19.99)

* excluding Chronic lymphocytic leukaemia
** excluding Chronic lymphocytic leukaemia and Hodgkin lymphoma

Abbreviations: ICD-10 International Classification of Diseases revision 10th, N observed number of deaths, ERR excess relative risk, CI confidence interval.

Table 6 Comparison of risk estimates with those of other published studies

	Average follow-up period (years)	Leukaemia ERR (95% CI) and **number of cases/deaths**		Brain cancer ERR (95% CI) and **number of cases/deaths**	
A-bomb survivors < 20 years					
Mortality	-	6.6 (4.2, 10.3)		1.2 (0.3, 2.9)	
Incidence	-	6.5 (4.0, 10.3)		5.7 (1.6, 17)	
UK CT study	-	36 (5, 120)	74 cases	23 (10, 49)	135 cases
Australian CT study	9.5	39 (14, 70)		21 (14, 29)	
French study	4.4	57 (-7.9, 193)	15 cases	22 (-16, 1)	12 cases
This study	5.9	7.8 (-0.5, 24)	74 deaths	7.3 (2, 20)	87 deaths

Supplementary material of paper V

Radiation induced cancer mortality in a cohort of paediatric and adolescent CT scanned patients: results of EPI-CT Spain.

Web Table 1 Follow-up of the Spanish EPI-CT cohort (n=152,850 subjects) by Autonomous Community and age at the time of the first CT scan

		Time at risk (person-years)	Per subject			
			Mean	Min	Median	Max
Overall cohort		897,191.04	5.87	0.00	4.85	21.98

By Autonomous Community of residence and age (y) at the time of first CT scan:

		Time at risk (person-years)	Mean	Min	Median	Max
Catalonia	0 to 0.9	47,381.65	7.30	0.01	6.51	20.47
	1 to 4	84,238.33	7.45	0.00	6.60	21.20
	5 to 9	89,596.79	7.81	0.00	7.03	21.59
	10 to 14	113,491.18	7.90	0.00	7.18	21.76
	15 - 19	147,488.03	7.84	0.00	6.95	21.98
	≥ 20	25,840.05	7.82	0.00	7.07	21.83
Madrid C.	0 to 0.9	11,532.89	4.19	0.01	3.75	12.32
	1 to 4	18,671.51	4.07	0.01	3.72	16.49
	5 to 9	22,981.76	4.25	0.00	3.75	14.44
	10 to 14	30,766.19	4.52	0.00	4.07	13.37
	15 - 19	45,359.94	4.66	0.00	4.46	13.68
	≥ 20	10,593.38	4.58	0.01	4.23	13.44
Murcia R.	0 to 0.9	1,204.74	2.72	0.02	2.51	12.20
	1 to 4	2,182.38	3.02	0.03	2.80	12.14
	5 to 9	1,973.31	2.73	0.01	2.38	17.72
	10 to 14	2,328.74	2.37	0.01	1.84	17.17
	15 - 19	3,288.44	2.38	0.01	1.92	18.26
	≥ 20	377.41	2.27	0.01	2.03	6.05
Navarre	0 to 0.9	1,717.29	5.61	0.07	5.79	11.67
	1 to 4	5,473.73	5.93	0.02	6.15	14.71
	5 to 9	8,911.88	5.63	0.03	5.41	13.52
	10 to 14	11,293.32	5.53	0.02	5.12	12.11
	15 - 19	19,152.65	5.76	0.00	5.51	15.81
	≥ 20	5,026.89	6.04	0.01	5.84	12.36
Basque country	0 to 0.9	2,868.92	3.25	0.02	3.11	20.79
	1 to 4	5,614.35	3.51	0.01	3.38	20.52
	5 to 9	8,324.50	3.70	0.00	3.64	21.92
	10 to 14	15,386.82	3.68	0.01	3.45	21.92
	15 - 19	27,780.35	3.59	0.00	3.24	21.21
	≥ 20	6,388.91	3.61	0.01	3.33	21.86
Valencian C.	0 to 0.9	10,328.43	5.17	0.01	4.80	18.33
	1 to 4	17,865.49	5.16	0.00	4.69	20.67
	5 to 9	19,195.34	5.00	0.00	4.45	17.10
	10 to 14	26,642.29	5.10	0.00	4.63	20.29
	15 - 19	37,351.69	5.02	0.00	4.58	18.46
	≥ 20	8,571.48	5.02	0.00	4.53	13.16

Web Table 2 Selected CT scan types and related active marrow and brain doses by age group

CT type	Age groups				
	<1 year	1 - 4 y	5 - 9 y	10 - 14 y	15 - 20 y
Sex-age-averaged median active bone marrow doses (mGy)					
Supra-aortic trunks	3.17	3.63	5.82	14.66	13.10
Neck + chest	3.22	3.55	6.09	13.82	12.64
Abdomen + pelvis	3.19	3.37	5.52	13.47	13.05
Other combinations	3.21	3.41	5.91	13.13	12.68
Head + Neck	3.20	3.50	5.56	12.96	13.09
Whole spine	3.21	3.46	5.57	13.02	13.03
Trunk	3.19	3.51	5.43	13.09	12.60
Chest + abdomen	3.19	3.47	5.12	13.53	12.51
Whole body	3.25	3.80	5.30	12.37	12.32
Thoracic-lumbar spine	3.23	6.62	14.36	12.82	-
Sex-age-averaged median brain doses (mGy)					
Head	22.99	25.49	27.90	29.45	33.83
Sella turcica	23.25	26.26	27.99	29.38	32.54
Brain vascular	22.82	25.55	27.98	29.53	32.28
Dental	22.74	25.38	28.07	29.24	32.51
Brain	22.96	25.27	28.00	29.17	32.35
Head soft tissues	22.88	25.68	27.99	29.10	31.96
Sinus	22.87	25.26	28.02	29.15	32.23
Face	22.74	25.37	28.01	29.17	32.21
Temporal bone / petrous b.	22.82	25.10	27.92	29.20	32.06
Skull & facial bones	22.79	25.02	27.94	29.28	31.88

6. DISCUSSION

This chapter is aimed to complement and expand the discussion included in each of the constituent papers and draft manuscripts of the present thesis.

6.1 Main findings

Since the US National Academy of Sciences highlighted in its 2006 Report on the BEIR VII the need for "follow-up studies of cohorts of persons receiving CT scans, including children", several studies have attempted to directly estimate the risk of cancer resulting from exposure to ionising radiation during CT scans. These studies have been largely criticised due to the potential effects of cancer-prone syndromes, reverse causation, dosimetric flaws and residual confounding due to unmeasured factors (e.g. SES).

The aim of Paper I was to identify the main epidemiological factors that could challenge the validity and adequacy of a study of the health effects of CT imaging on paediatric and young adult patients and the resulting protocol used in the European EPI-CT cohort. It also described the potential impact of these factors and the measures that the EPI-CT protocol had foreseen to overcome them.

The potential main factors that could lead to an incorrect assessment of the association between ionising radiation exposure from CT scans and cancer are:

Table 12. Factors which could distort the association between ionising radiation exposure and cancer, and impact on the association estimate.

Factor	Potential effect	Potential impact on the association estimate*
Lack of information on emigration (most countries)	Incident cases will be lost, while person-years at risk will be overestimated	Underestimation of the true effect of ionising radiation exposure
Lack of information on mortality (partially in France and Germany)	Person-years at risk will be overestimated	Underestimation of the true effect of ionising radiation exposure

Factor	Potential effect	Potential impact on the association estimate*
Incomplete ionising radiation exposure history (missing CT scans or other irradiating procedures)	Cumulative exposure will be non-differentially underestimated	Bias towards the null or away of the null of the estimate of the true effect of ionising radiation exposure
Poor dose reconstruction due to lack of imaging parameters	Expected for earlier time periods – Non differential misclassification of the true exposure. Also, Berkson error due to the use of mean dose to assign doses for all subjects	Bias towards the null or away of the null of the estimate of the true effect of ionising radiation exposure. Underestimation of uncertainty due to Berkson error
Lack of information on socioeconomic status	SES may be responsible for a part (or all) of the apparent association	Bias of the estimate of the true effect of ionising radiation exposure. The direction of the bias depends on the direction of association between CTs and SES and SES and the health outcome
Lack of information on cancer-prone disorders	Potential confounding by indication	Overestimation or underestimation of the true effect
Including CT scans related to the cancer diagnosis / underlying cancer symptoms on the analysis	Potential reverse causation	Overestimation of the true effect

* Under the alternative hypothesis

Given the potential impact of the results of the international EPI-CT study on clinical practice and public health in terms of patient protection, it is imperative that the results of the EPI-CT study are corrected for the factors which may invalidate them. As discussed in Paper I, these issues are being assessed through sub-studies. In this sense, simulation studies, where a synthetic population with similar attributes to the international EPI-CT cohort is created, are being used to assess the impact of many of the distorting factors listed in Table 12.

Information bias due to lack of emigration data may occur in most participating countries given the fact that this information is not

available at the individual level, allowing its consideration in the EPI-CT analyses. Countries where emigration data of the cohort members is available (Denmark, Norway, Sweden and part of the UK) will provide information on the magnitude and direction of the possible bias related to lack of emigration data. However, it is expected that the lack of migratory data will minimally impact the association estimate due to limited emigration in most countries.

The lack of information on mortality will affect only two of the nine participating countries (France and Germany), potentially leading to an underestimation of the true effect of ionising radiation exposure. The use of lifetables as a surrogate of mortality data could bias the estimate of the association in both directions, depending on whether the mortality in the French and German EPI-CT cohorts is higher or lower to that described in the lifetables. The potential impact of the missing information will be tested in the rest of participating countries to assess the magnitude and impact of missing mortality data.

Regarding the potential incomplete exposure history of some of the international EPI-CT cohort members it is important to bear in mind that, *a priori*, there are no specific reasons to expect a differential frequency of incomplete radiation accounts between those who will develop cancer at the end of the follow-up and those who will not. As Rothman states (206), when nondifferential misclassification affects a non dichotomous exposure variable, as in the case of CT scan radiation exposure, "nondifferential misclassification may bias the estimate either towards the null or away from it, depending on the categories into which subjects are misclassified" (206). Therefore, the bias of the estimate of the true effect of ionising radiation exposure may be in either direction.

Another important factor when assessing issues in exposure estimation is the effect of the unavailability of imaging parameters (e.g. mAs, Kvp, pitch) in earlier years. The EPI-CT study was designed to improve upon earlier CT risk studies by, among other things, using a more comprehensive approach in terms of dosimetry. In particular, the EPI-CT study takes advantage of new strategies to collect scanner- and patient-specific data, and it concentrates efforts in the uncertainty analysis. Therefore, although there is potential for uncertainty in dose reconstruction, it is

expected that it would be adequately characterized as well as the magnitude of its impact on the risk estimates. Additionally, it is important to take into account that in earlier years radiological clinical practice was less variable due to the use of standard CT imaging protocols and the limited adaptability of the scanning settings to the patient characteristics.

Reverse causation is not expected to pose a problem in the leukaemia risk assessment because CT imaging is not used for the diagnosis of the disease but for the follow-up of the abnormal enlargement of some organs (organomegaly) related to leukaemia in later stages. Excluding scans in the year before the diagnosis should effectively avoid the problem of reverse causation for leukaemia or under-diagnosed leukaemia. For brain cancer (and all solid tumours, in general) reverse causation could clearly threaten the validity of the results, though data from the International Mobi-Kids study show that most brain tumors in young people are diagnosed rapidly after the appearance of the initial symptoms and a very small proportion after more than 1 year after the first symptoms (Cardis, Zumel, personal communication). Thus, excluding scans in the previous two years should minimise the problem of reverse causation.

Paper II of this thesis focuses on describing the patterns of use of CT imaging over time in Catalonia, the Autonomous Community that accounts for approximately half (42%) of the Spanish EPI-CT cohort.

In general, an average annual increase of 4.5% in the total number of CT scans was observed from 1991 to 2013, in parallel with an increase on the availability of CT scanners, as reported from 1996 onwards.

During the 23-year study period, 25% of the cohort members received 2 to 5 CT scans, whereas a small but non-negligible proportion of the cohort (4.2 %) underwent more than 5 CT examinations before turning 21 years old. This last group could have accrued cumulative organ doses in the range for which there is direct uncontroversial evidence of radiation-induced cancer risks (above 100 mGy) in studies of atomic bombs survivors and other exposed populations. The results of the previously published studies

about CT scanning suggest that cumulative organ-doses of the order of 50 and 60 mGy might almost triple the leukaemia and brain cancer risks, respectively (82). In addition, it is important to mention that the great majority of the Spanish EPI-CT cohort members accrued lower doses, and hence presumably lower radiation-related cancer risks, as they underwent only one CT examination during the study period.

We also found increasing annual rates of CT imaging in the same patient which may be the result of new CT scan indications or of the gradual superseding of other imaging techniques by the CT, as the preferred modality of imaging in the clinical practice.

Although an increase in the absolute number of CTs was observed over the last two decades, the available data did not allow discerning what proportion of the increase was attributable to a higher availability of CT scans, a greater number of patients attended at the participating hospitals, an increase in the number of scans per patient, or to new CT scanning indications.

Paper III assesses the potential differences in CT imaging by SES, a potential confounder of the relationship between exposure to ionising radiation during a CT scan and cancer risk.

The Urban Vulnerability Synthetic Index, the main SES measure used in the analysis, was chosen due to its high correlation with the Spanish deprivation index MEDEA (Spearman rho= 0.95), which was constructed using analogous socioeconomic components and had a similar performance to other contextual indicators used worldwide (207,208).

The descriptive analyses showed some evidence of socioeconomic variation in the CT scanned individuals, and in particular, a higher rate of scans of multiple body parts was observed in the less affluent categories. This possibly reflects a higher rate of accidents and injuries among the less privileged groups. On the other hand, a lower proportion of repeated CT scans per patient (category of "above 11 CTs") was observed among the less affluent quintiles. A more in-depth analysis (controlling for sex and age of the patient at the time of the last CT) in which the rate of CT scans per person was modelled by SES quintile suggested that, when all the

Autonomous Communities were combined, there were no SES differences in the chance to receive a CT scan for the diagnosis and follow-up of medical conditions.

When the different Autonomous Communities were independently analysed, no relationship between SES and number of CT scans per patient was found for Navarre, Murcia and Madrid Community. On the other hand, in Catalonia, a slightly lower CT scan rate per patient was observed in the lowest socioeconomic categories compared to the more accommodated quintiles. A similar relationship was observed for the Valencian Community, except for the least socioeconomically favored group, which showed the opposite.

Between 2001 and 2011, unemployment was the the SES component that varied the most, in large part due to the 2007/2008 financial crisis. Unemployment has been considered in previous published studies as one of the socioeconomic dimensions with higher correlation with several deprivation indexes such as the Jarman and Townsend indexes. It is also regarded as an effective indicator to predict both the health variation and the use of health care of a community (209). Using the 2001 census, a significant decrease in the number of CT scans per patient was observed with decreasing SES. However, using a more updated measure (2011 census) suggested that those belonging to lower SES categories (compared to the reference category) received a higher number of CT scans per patient, although no statistically significant.

When performing analyses, the influence of selecting one SES indicator over another was evident in the results. Different SES indicators collected in different time points led to divergent associations between SES and frequency of CT scans, highlighting the difficulty to adequately capture a rapidly changing socioeconomic reality.

Paper IV estimates the frequency of CT scans performed in children and young adults in Spain in 2013 and predicts the related increase in the lifetime (up to 110 years) burden of cancer that could be related to the current intensity of use of CT scans in Spain.

The extrapolation of the age, sex and body part scanned frequencies of CT scans from Catalonia to the whole Spanish population resulted in the estimation that over 105,000 CT scans were performed in 2013 among young people aged 0-20 years nationally. 11,000 CT scans of the spine, lumbar spine, sacrum, whole body, arms and 'unknown anatomical area' were not included in the risk projection exercise due to the lack of PACS-recorded CT scans in these locations to be used for dose estimation. Head CT and abdomen CT were the most prevalent anatomic areas and, of the 94.000 CT scans eventually included in the risk projection study, 57.0% were received by those in the 15-20 years age group.

In general, the organ doses were similar to the doses quoted in other studies. Prostate, breast, colon and lung cancer were the dominant baseline risks reflecting the current cancer site-specific incidence in Spain, whereas the highest lifetime attributable risks related to ionising radiation exposure from CT were found for breast, lung and urinary bladder. Breast and lung cancer are radiosensitive tissues/organs, in particular after exposures at young ages. The evidence for bladder cancer is not so clear as for lung and breast cancer, in fact both the excess relative risk and excess absolute risk for those below age 20 in the LSS cohort study are below 0.

When taking all the cancer sites into account, the CT scan types that provided the overall highest lifetime risk were trunk, thoracic spine and thorax CT scan. When the cancer-site radiation-related lifetime attributable risks (LARs) were multiplied by the 2013 estimated distribution of CT scans the dominating neoplasms were oral cavity and pharynx, brain, colon and lung cancer, followed by leukaemia. All in all, 81 future cancers were projected to arise from the 94.000 CT scans corresponding to the Spanish 2013 CT imaging practice in young people. This corresponds to 0.2 % all of cancers expected to occur over the same time period in this population due to other causes, if current mortality rates and cancer incidence rates do not change in the population in the next decades. Taking into account the uncertainties related to the Paper IV dose estimation, it was predicted that using the first quartile (25th percentile) of the organ-doses distribution for the estimation of doses 46 future cancer cases instead of 81 would be expected in the lifetime of those exposed to ionising radiation through a CT scan in 2013. Similarly, using the 3rd quartile of the organ-doses distribution (75th percentile) for the

estimation of doses, 107 future cancer cases instead of 81 would be expected in the lifetime of those exposed.

Further analyses are underway to quantify uncertainties in these estimates of population risk from current CT scanning practices in young people. It is important to bear in mind that the current risk projection is mainly based on risk estimates from the atomic bomb survivors and other populations. Therefore, it is reasonable to think that the use of the risk estimates from Pearce *et al.* (82) would result in a larger estimated cancer burden. Regardless of the limitations and implicit assumptions of the analysis, the risk projection is a rich assessment tool to help visualise the detrimental future effects of current exposures. It provides evidence in a quantitative and tangible way that helps raise awareness in the imaging community of the possible need to optimise practice, in order to minimise the radiation exposure of young population.

Finally, the preliminary draft paper (Paper V) included in this thesis assessed the radiation related risk of mortality from leukaemia, haematological malignances and brain cancer in the Spanish branch of the European EPI-CT cohort.

The 152,850 cohort members were followed up for mortality until 2014 for a total of 897,191 person-years, with an average follow-up of 5.9 years (min-max: 5.9 – 22.0 years) from the time of entry into the cohort till censor by death or end of the study. About 99.2% of the cohort (n=151,664) was still alive at the end of the study in December of 2014. 79.1% of the cohort had cumulative active bone marrow doses below 10.0 mGy and 50.7% of the cohort had cumulative brain doses below 10 mGy.

In light of the results of these analyses, the radiation received from CT imaging appeared associated to brain cancer, non-CLL leukaemia and haematological malignancy mortality risk, in population exposed below 21 years of age, suggesting a potential relationship with low-dose ionising radiation exposure from CT imaging. However, this association was statistically significant only for brain cancer. These results are based on 74 deaths by leukaemia, 85 deaths by haematological malignancies and 87 brain tumour deaths ascertained in one of the largest cohorts to date of CT scan irradiated children.

We also observed that the all-cause mortality risk in the Spanish EPI-CT study is increased compared with the general population, suggesting poorer health among the members of the Spanish cohort. The all cancer, non-CLL leukaemia, haematological malignancies and brain cancer age-standardised mortality rates are also increased compared with the general population.

6.2. Methodological considerations: strengths and limitations

6.2.1. Study design and analytical considerations

The set-up of a large cohort study of subjects who underwent CT scanning in childhood and adolescence, such as the international EPI-CT, is particularly advantageous to carry out precise direct estimations of small risks such as those resulting from exposure to low-doses of ionising radiation during pediatric CT scans. This design is specially indicated also for exposures that are relatively rare in the general population (about 1% of children and adolescents receive CT scans annually) for which general population based studies would have limited power. Cohort studies have proved to be valid to assess causality given their temporal sequence, where exposure is typically identified before the outcome. Even for retrospective cohort studies the same rationale is applied allowing for causality assessment (210). The quality of the evidence resulting from well-designed cohort studies has been compared to that of the randomized clinical trials (210). Despite the clear benefits of retrospective cohort studies such as this one, its design is susceptible to the effects of bias, as it has been discussed in Paper I.

In the case of the Spanish branch of the EPI-CT study, the early availability of exposure data for Catalonia allowed us to describe the patterns of CT scan use over time before the end of the study. The nine participating hospitals are among the reference hospitals in the Autonomous Community. According to the 2011 age-specific official data on healthcare delivery (211), these hospitals were the health care providers to 37.5% of all Catalan population in the 0-20 years old range and the percentage is likely to be higher for CT scanning. Hence, we can confidently assume that the conclusions drawn from the analyses are not based on anecdotal evidence.

The assessment of the relationship between the number of CT scans per person and socioeconomic status in a large population (n= 123,729) is one of the main strengths of the analysis in Paper III. The two previous studies on CT scan distribution in the young population over the SES spectrum (Pearce *et al.* (212), and Miller *et al.* (213) were based on substantially smaller populations (n=21,257

and n=19,063 patients, respectively). Additionally, the similarity of the constituent indicators of the deprivation indexes used in one of the studies (Townsend index) allowed comparability between Paper III and the Pearce *et al.* study. The availability of several socioeconomic indicators allowed capturing different dimensions that configure the environment in which the patients reside.

Given the time required to set-up and collect the data from a large cohort, the projection of probabilities of organ-specific cancer incidence is a great tool to perform an early assessment of the health effects related to the ionising radiation exposure received during CT imaging. Risk projection of site-specific solid cancer incidence has generally higher statistical uncertainties due to the use of tissue/organ-specific cancer incidence data, which has lower counts compared to fitting aggregated data as in all solid cancer projections. Nevertheless, the risk projection models used in Paper IV were based on solid in-depth analyses of human epidemiology data by the BEIR VII Committee. In particular, the Committee models for site-specific solid cancer were based on LSS cancer incidence data with a long follow-up (1958-1998), supplemented, mainly for breast and thyroid cancer, with data from Caucasian populations exposed in medical settings. For leukaemia, the models were based on the Life Span Study deaths occurring between 1950 and 2000 due to the higher quality of the data. For the cancer-sites not covered by the BEIR VII, we used the models developed by Berrington de Gonzalez using the LSS cohort, which were developed applying a similar methodology.

Paper V is the first published study directly quantifying the cancer mortality risks of CT imaging in Spanish young population. It is based in one of the largest cohorts assembled to date of paediatric and adolescent CT scanned subjects. Mortality follow-up was performed until 2014 with varying lengths of follow-up depending on the Autonomous Community of residence, ranging from 2.7 to 7 years of mean follow-up. This correlates with the implementation of the RIS (the electronic recording of CT scans) at the hospitals of each Autonomous Community. Therefore, the subjects residing in those Communities where the RIS was implemented earlier, would have a longer follow-up (they would enter the study earlier).

6.2.2. Exposure assessment limitations

In this section the potential limitations on the exposure estimation and their related uncertainties are reviewed. The subsequent implications in terms of the potential induced error will be discussed in the section "6.2.4. Confounding, effect modification and other sources of error".

Due to its methodological nature, Paper I is not discussed in this section.

Exposure misclassification in Paper II is an unavoidable study limitation because of incomplete ionising radiation exposure history. As mentioned in said paper, the implementation of electronic records did not occur in parallel at participating hospitals and not all the hospitals providing CT imaging services to the young population were included in the Spanish EPI-CT study.

Paper III defines the contextual socioeconomic status of an individual (socioeconomic status at the census tract level) as a possible explanatory factor of the CT scan rate per patient (outcome).

The validity of using contextual measures to ascertain the socioeconomic reality of the patients included in the Spanish EPI-CT study, remains open to question. Nevertheless, some studies highlight that both, the individual and the contextual socioeconomic variables, are useful for capturing health inequalities (214,215).

The use of the Urban Vulnerability Synthetic Index (UVSI) based on the 2001 census to assign a SES level to each individual presumes that the UVSI provides a reasonable SES approximation for the years before and after the 2001 census. As of today, the use of a single SES time-point estimation is the dominant approach used in epidemiological studies to control for the distorting effect that unmeasured lifestyle factors (including smoking and diet) captured by 'socioeconomic status' may introduce in the assessment of any exposure - health outcome relationship. On a wide scale, SES is considered generally stable over time. Nevertheless, substantial changes derived from the 2007/2008 financial crisis may have had a

profound effect on SES category relations, reshaping the socioeconomic spectrum and, potentially, the health care access. Therefore, it seems reasonable to assume that the use of the 2001 census Urban Vulnerability Synthetic Index could have resulted in exposure misclassification in the study. This was the motivation for studying other measures of SES, including measures based on more recent time points and measures focusing on specific determinants of the Urban Vulnerability Synthetic Index, including unemployment and schooling.

The use of census tracts, the geographic areas defined for the purpose of taking a census, as socioeconomic boundaries may not be ideal if they do not overlap with the geographical distribution of the factors that relate the socioeconomic environment with the outcome (health care access and usability). The lack of individual SES measures prevented us from assessing the potential impact of this misclassification. Additionally, if the selection of the contextual socioeconomic variables used in the analyses failed to reflect the individual SES and neither provided complementary information of the contextual socioeconomic circumstances of the individual, the results of the analysis in Paper III may be incorrect due to exposure misclassification.

The use of contextual SES measures (census tract SES measures) for exposure ascertainment may suggest the potential presence of an 'ecological fallacy', which is considered to occur when making causal inferences from aggregated data to the individual level. However, the fact that the individual is the unit of observation both in the exposure (living in a census tract with specific SES contextual features) and the outcome (number of CT scans per patient) renders the aggregation bias irrelevant to this analysis (215).

For Papers IV and V the organ dose (mGy) is the preferred quantity for risk estimation given the fact that dose absorbed in a given organ is thought to determine the cancer risk to that organ from radiation.

The estimated organ doses used in the risk projection analysis (Paper IV) and cancer mortality risks (Paper V) are average doses for the relevant organs taking into account the body part scanned,

and the age and sex of the patient. As explained in the methods section of both papers, the estimated organ-doses were calculated using the extracted machine parameters of a considerable amount of real CT scans performed between 2010 and 2013 for the risk projections paper (Paper IV) and 2001 and 2015 in the cancer mortality risks paper (Paper V). The use of contemporary CT scan parameters for the Paper IV and the use of machine parameters covering a broad period of time for Paper V allows for the dose estimates to adequately reflect dose distributions that have changed over time.

In the risk projection analyses (paper IV), an additional benefit of averaging the individual doses is the reduction of the effect of the variability present among standard clinical practice in the different hospitals where the machine parameters were obtained.

Exposure misclassification is a critical factor limiting the validity of epidemiological studies. In the Spanish EPI-CT study, the cohort inclusion criteria specifies that the accrued subjects had to have, at least, one recorded CT scan in a participating hospital before turning 21. As the participating hospitals are among the largest hospitals attending a substantial fraction of all the paediatric and adult population in each of the six participating Autonomous Communities, no severe exposure misclassification is expected, as the vast majority of CT scans in the study age range will have been carried out in these hospitals. Nevertheless, the design of the study is likely to miss (i) some CTs that took place before the electronic record was implemented at the participating hospitals, and (ii) CTs performed in non-participating hospitals or abroad.

The cohort members could have also accumulated ionising radiation doses from other medical procedures, such as nuclear medicine or certain interventional procedures. As observed in the Table 2 of the section "1.1.3.Medical radiation procedures" of the present thesis, it is worth highlighting that in Spain, medical radiation procedures other than CTs represented 36.82% of the per caput dose due to medical procedures (11) mainly related to "higher dose" procedures such as interventional cardiology which, though delivering sizeable doses to patients, are much less frequent than CTs. Therefore it is unlikely that these procedures may introduce any systematic error in our estimates of radiation doses to the study participants.

Another important consideration regarding exposure assessment is the absence of records of repeated scans as a consequence of the movement of the patient during image acquisition. In the scope of this thesis, we were not able to assess the magnitude of this phenomenon in the participating hospitals or how repeated CT scans were recorded at each hospital. Although there is a minimal risk of exposure misclassification due to repeated scans and, therefore, of having imprecise number of CTs/dose estimates in Paper II, III, IV and V, the evolution of technology towards faster image acquisition reduced the likelihood of motion artifacts in the CT examinations.

6.2.3. Outcome assessment limitations

In this section the potential limitations related to outcome assessment are reviewed. The subsequent implications in terms of the potential induced error will be discussed in the section "6.2.4. Confounding, effect modification and other sources of error".

Theoretically, the design of cohort studies reduces the possibility of the results being affected by selection bias at the enrolment. This is because at baseline, when exposure status is established, the outcome is yet to be determined. Even in studies of retrospective nature, such as the EPI-CT, the exposure and outcome ascertainment are not performed simultaneously and therefore, the possibility of selection bias is negligible.

Paper I and II will not be discussed in this section due to their methodological and descriptive nature.

In the case of paper III, the outcome under study is the exposure to ionising radiation during a CT examination in terms of number of CT scans per patient. The potential limiations regarding the CT scan exposure ascertainment have already been discussed in the previous section.

In the risk projections (Paper IV), the lifetime risks for 17 site-specific solid cancers were developed based on the available published risk models (1,216). It is clear that as a result of the

estimated 2013 CT imaging practice, additional sites were exposed to irradiation, although their lifetime risks were not included in the present analysis.

Another aspect to note is that Spanish EPI-CT could have had a differential loss to follow up between those with higher cumulative exposures and those with lower cumulative exposures. This could be the case if those who had higher cumulative exposures (and therefore poorer health or more complex conditions that required specific medical expertise) were referred to hospitals located in non-participating Autonomous Communities.

A critical aspect in the outcome assessment in Paper V is the adequacy of using the cause of death as a measure of radiation-related disease risk given the fact that advances in the therapeutic options provide an increasingly favourable long-term prognosis for cancer patients. Given that the oldest followed-up patient in Paper V was 44.7 years old, the use of the 2008 SEER (217) estimates of 5-year survival rates for leukaemia and brain cancer in the population under 50 years of age seems adequate. Figure 9 presents the 5 year-relative survival by diagnostic year and cancer site confirming the improvement of the diagnostic outlook for brain cancer and leukaemia patients.

As observed, the survival rates have increased substantially between 1975 and 2008 for lymphoblastic leukaemia, myeloid leukaemia and brain cancer. Within the framework of this thesis it was not possible to conduct cancer incidence analyses as the cancer diagnosis data are still being validated for part of the cohort. However, assuming that survival is not related to CT scan radiation dose, the results of the mortality analysis in which careful adjustment for time period is made should not be biased by these trends.

Figure 9. 1975 -2008 5-Year relative survival by year of diagnosis by cancer site in population under 50 years of age, including both sexes.
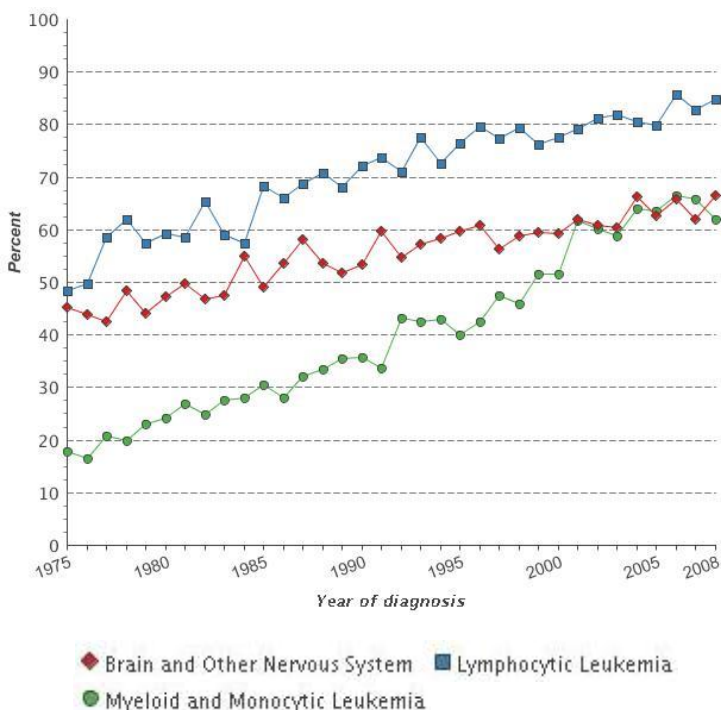
In Paper V, it is important to take into account the use of mortality registry data which rely on death certificates for the classification of the health outcomes of interest. Validation studies have reported conflicting findings on the sensitivity and imperfect specificity of death certificates which may question the use of death registry data to measure deaths due to cancer and non-cancer outcomes (218). The reliability of death certificates is typically lower when coding the death cause in more specific subcategories than when using general categories such as "leukaemia", "brain tumours" or "all neoplasms".

However, it is important to mention that the provider of the cause of death, the Spanish National Statistics Institute (INE) has a long-track record as a mortality registry as it has been in operations since 1975. Additionally, in 2005 they adhered to the Code of Practice for European statistics, a set of quality guidelines and a system of internal quality control and validation procedures developed by the European Statistical System Committee. All in all, outcome

misclassification is unlikely to occur in the more recent years due to the more exhaustive quality control mechanisms. Nevertheless, it should not be discarded for the earlier years of follow-up.

6.2.4. Confounding, effect modification and other sources of error

Paper I deals explicitly with the potential confounding and sources of error and bias that may affect the validity of a study on the health effects of paediatric and young adult CT imaging.

In Paper II, the primary source of error is the incompleteness of the time series used because most of the participating hospitals started their CT scan activity before the gradual digitalization of this procedure. An important aspect to consider when measuring the impact of this potential error is that from 2004 onwards all but one participating hospital had the Radiology Information System implemented and therefore the records of their radiology practice reliably reflected the CT scan use until the last year of the study (2013). This could have led to wrong conclusions regarding the increase in the use of CT scans for the earlier study period but it is not regarded as an issue after 2004.

Additionally, due to the study design, it is likely that some individuals would have been assigned an exposure lower than their true cumulative exposure. This is because not all the Spanish hospitals attending the young population are participating in the study. Given that the reference pediatric hospitals are participating in the Spanish EPI-CT study this is expected to be less of a problem for the young people than it would be for adults. In case that the true exposure of the cohort was higher than ascertained, Paper II conclusions regarding the absolute increase of CT scans over time would remain in the same direction but perhaps an increase in the number of CT scans per patient would appear with clearer definition.

Also, it is expected that the non-recorded repeated scans due to patient movement mainly affected the scan practice at the beginning of the follow-up time (around 1991) and have had an small overall

effect due to a lower CT scan frequency in that time period. This is also of relevance for Papers III, IV and V, as they also deal with exposure to ionising radiation during a CT examination.

In Paper III, as explained in the section "6.2.3. Exposure assessment limitations", the primary bias stems from the potential exposure misclassification in terms of SES categorisation, of the subjects included in the analysis. Given the fact that, overall, the probability of exposure misclassification (SES category) seems unrelated with the outcome of interest (cumulative number of CT scans) and that the socioeconomic status is a multi-level categorical variable, if there was an exposure-response trend it would be disrupted by misclassification. However, in the absence of a relationship as in Paper III, it should not introduce bias.

In accordance with Paper II, Paper III might also be affected by the incomplete radiation history of some of the cohort members, affecting the validity of the results if the missing exposure responds to a differential pattern and it is not distributed homogeneously among all the SES strata.

In Paper IV, several assumptions were made in order to perform the risk projection analysis. First of all, the estimates of the 2013 CT scan practice in Spain among children and adolescents were based on the interpolations of the relative frequencies of Catalonia. Differences between the real Spanish CT scan frequencies and the age-sex and anatomic area CT scan distribution in Catalonia could cause a major distortion in the predicted cancer cases. The fact that in Catalonia 15% of the Spanish population resides, reduces the probability of an erroneous CT scan distribution estimation. Nevertheless, the results of the study are vulnerable to any change in the age, sex and body part scanned distributions of CTs at the national level.

Secondly, in Paper IV, EPI-CT Spanish data was used to determine and discard the fraction of CT scans performed in patients that would not live long enough after having a CT scan to develop a malignancy. It is likely that the EPI-CT population differs in health status with the general population, being the former in poorer health than the latter. Therefore, the mortality rates in this cohort may not be comparable with the mortality rates of the general population. If

this is confirmed (as the very initial analyses in Paper V suggest), it would imply that a proportion of the discarded CT scans were received by patients who would remain alive and at risk of developing a future malignancy at any point of their lives. Therefore, the current results of the risk projection analyses would be conservative and, consequently, a slightly higher number of cancer cases should be expected.

Moreover, the EPI-CT Spanish data was also used to estimate and discard the fraction of CT scans that in the span of one year had an associated cancer code, because it is unlikely that these CT scans are related to future second cancers. Therefore, there exists a risk of not reflecting the real proportion of Spanish CTs related to cancer. In favour of the data used to estimate the cancer-related CT scan proportion it should be clarified that the hospital that provided the data is the largest hospital of Catalonia and among the largest in the rest of Spain. Again, in case the proportion of cancer-related CT scan codes was not correct, a slight variation would be observed in the predicted number of cancer cases.

Additionally, the lack of risk projection models covering all the anatomic sites that were exposed during the estimated 2013 CT scan practice may have resulted again in conservative results. The risk projection models use an age-sex specific incidence function fitting the 2007 Spanish cancer-site incidence available at the CI5 initiative (140). Due to the fact that the following cancer-sites not included in the analysis (namely: bone, larynx, skin and eye cancer, as well as myelomas and lymphomas) represent 15% of the total Spanish cancer incidence (219), it is not expected that the number of projected cancer cases would change substantially. Therefore, this issue is not expected to severely bias the estimates of the cancer burden in Spain from current CT scanning practices in young people, since the organs for which risk models were not available are those for which both cancer incidence rates and radiation induced cancer risk are low.

Again, Paper V may be affected by the potentially incomplete exposure history of the cohort members. The yet unpublished EPI-CT results from part of the UK and Belgium where information on all scans is available suggest that the unaccounted CT scan doses are unlikely to be an important source of error. However, their main

effect would be a small overestimation in our estimates of the fatal cancer risks from CT scans.

A possibly important source of bias in any cohort study such as the EPI-CT is losses to follow-up. Cohort members may have migrated, changed residence to a non-participating Autonomous Community or changed hospitals during the development of the study, unbeknownst to us due to the lack of data on their migratory status. This could have affected the validity of Paper V and the potential inferences drawn from the study, if patients lost to follow-up present a different prognosis than those who completed the study until 2014. Given the fact that the follow-up of the cohort is performed passively, through cancer and mortality registries, we lack the means to measure its potential magnitude, although it is typically assumed that a loss of follow-up inferior to 5% leads to little bias whereas a loss superior to 20% may endanger the reliability of the results (220). A recent work on economics (221) described how the aggregate migration outflows in Spain could be considered negligible for the period 2000-2007 (and presumably for before the year 2000) (221). The paper describes how the international financial crisis and the great recession that Spain endured increased the emigration rates to the 0.4% of the total domestic population in the period 2008-2010. According to the same publication, the migration outflows rose to 1.2% of the domestic population in 2012 (221). Therefore, losses to follow-up due to migration could be discarded for earlier years and could have impacted the follow-up of the cohort members in more recent times.

As introduced earlier, Paper V may have been affected in earlier years from outcome misclassification due to a potentially poorer classification of the causes of death. In any case, an *a priori* argument to expect differential misclassification among those with higher and lower exposure to ionising radiation does not exist and therefore we could expect a potential bias towards the null.

In addition to this, other potential confounder of the association under study in paper V that could bias the results would be the unmeasured presence of cancer predisposing syndromes. The prevalence of diseases related to a higher risk of cancer were only available for 3 Autonomous Communities: Valencian Community, Murcia Region and Navarre. Significant heterogeneity among the

three registries was found in the disease codification, recorded diseases and year of registry activity commencement. Although some registries were active earlier, none of the registries could provide complete coverage at the population level before 2010, and even then, their exhaustivity was questionable.

Table 13 summarises the cancer predisposing syndromes that are registred at the rare disease registries in 3 Autonomous Communities and the (non-exhaustive) prevalence of the diseases among the Spanish EPI-CT cohort.

Table 13. Summary table with cancer predisposing syndromes potentially distorting the association between ionising radiation exposure and cancer mortality risks, their ICD-9 code and absolute frequency in the 3 registries.

Rare disease	ICD-9	N (total for the 3 registries)
Neurofibromatosis	237.7	51
Neurofibromatosis (type 1)	237.71	49
Neurofibromatosis (type 2)	237.72	1
Werner syndrome	259.8	2
Cystic fibrosis	277	231
Fanconi anemia	284.09	33
Ataxia telangiectasia	334.8	27
Cardiofaciocutaneous syndrome	756	167
Bloom Syndrome	757.39	5
Mosaic trisomy 8	758	42
Down Syndrome	758.0	32
Turner syndrome	758.6	7
Klinefelter Syndrome	758.7	3
Tuberous sclerosis	759.5	41
Sturge-Weber/ von Hippel Lindau /cowden syndrome	759.6	23
Rubinstein Taybi/ Sotos /Dubowitz / Silver-Russell / Noonan syndrome	759.89	77
Fetal alcohol syndrome	760.71	1
Common variable immunodeficiency	279.06	40
Severe combined immunodeficiency	279.2	40
Organ transplantation	996.8	12

As discussed earlier in this thesis, the theoretical paper by Meulepas *et al.* (222) estimating the confounding bias of relative risks (RR) for categories of CT radiation exposure among cancer predisposing syndrome patients further supports the conclusion of no significant confounding for leukemia and brain tumors by these diseases (191).

This is evidenced by the weak association with leukemia and brain tumors and the rare incidence of the predisposing syndromes (180,192).

In paper V, the unaccounted effect of socioeconomic status could bias the association between ionising radiation exposure during CT scans and cancer mortality risks if there was a significant association between the socioeconomic status of the patient and the likelihood of receiving a CT scan and a strong association between socioeconomic circumstances and the malignancy distribution. In the light of the results obtained in Paper III, we are able to rule out the potential confounding effect of SES in the estimate of the association under study.

6.3. Contribution to the current knowledge

The comprehensive analysis of the potential factors invalidating a low-dose radiation cohort study may serve as a guiding checklist of all the factors to take into account in low-dose studies, increasing the validity and accuracy of their results. The impact of solid evidence regarding low-dose risk estimates strengths the radiation epidemiology base upon which population dose guidelines are developed.

The assessment over time of the medical CT radiation exposure in Spanish children and young adults is, to our knowledge, the first study tackling the use of the CT imaging over the years. It is very informative confirming the increase of CT scan use comparable to other industrialised countries. It is an important addition to the current body of knowledge regarding the growth in the rate of pediatric CT imaging worldwide.

This thesis also investigates the relationship between socioeconomic status (SES) and CT ionising radiation exposure, an issue that still remains unclear, and with different results in different countries (212,223). This is an important issue given the fact that SES is a potential confounding factor of the relation between radiation doses from CT and risk of cancer as it has demonstrated its influence in the distribution of cancer. In the absence of extensive evidence regarding this topic, these analysis are informative to support the argument that the results of studies assessing the risks of low-dose medical imaging radiation are unlikely to be substantially confounded by unmeasured socioeconomic position. Additionally, the results of the analysis may help inform health care access in a publicly funded system where the possibility of SES influencing diagnostic imaging utilisation should not exist.

Considering the amount of time needed to implement a large cohort such as the EPI-CT, and to follow-up the population over time (the current follow-up in most of the EPI-CT countries is of the order of 4-10 years) the projection of risks included in this thesis provides timely theoretical estimates of the radiation effects in the Spanish young population. This data may support discussions regarding the

need to implement stricter guidelines to reduce the radiation exposure among young population and puts the radiation related risk of cancer in perspective when taking into account the naturally occurring cancers.

Finally, this research adds to the scarce body of knowledge evaluating directly the relation between exposure to low-doses of ionising radiation and increase in mortality rates of cancer in both children and young adults. Results are comparable with the estimates from the atomic bomb survivors, and statistically compatible with estimates from the UK study from Pearce *et al* (82). Results of the full European EPI-CT study are needed to obtain more precise estimates of risk.

6.4. Public health implications

The research findings included in the present thesis have strong public health implications when viewed together with earlier scientific evidence.

The confirmation of the increasing rates of CT scan use in Catalonia (Spain) over time argues for active surveillance of the adequacy of its use and of its diagnostic reference levels, in particular, among radiation-sensitive population such as children and adolescents. As explicitly stated in the 2013 European directive on the health protection standards against the dangers of ionising radiation exposure for the general public (224), the recording and reporting of doses from medical procedures, the use of diagnostic reference levels and the availability of dose-indicating devices needs to be strengthened. In Spain, and in countries with a similar scenario, the lack of consistent monitoring data on low dose exposure makes it difficult to assess the extent of individual exposure and limits any attempt of evaluating policy initiatives for exposure reduction. The multiple health benefits of the radiological medical procedures are unquestionable but an accurate control on the doses and the appropriateness of the examinations warrants the minimal risks for patients.

Based on the projected risk assessment we demonstrated that although the risks for the individual patient are minimal, the annual imaging practice supposed a small but not negligible additional number of cancer cases expected to occur in the next decades.

The cancer mortality risk estimates presented in this thesis also provide guidance for prioritizing regulatory intervention activities to reduce cumulative exposure particularly among the young people. The uncertainties inherent in this analysis require a more in-depth analysis, using pooled data from all European EPI-CT countries before reaching final conclusions regarding the increased risk of fatal cancer related to this procedure.

However, in light of the results of the risk projection analysis and of the cancer mortality risks, as well as of the increasing awareness of the general population about the potential risks related to radiation

exposure it is crucial from a public-health standpoint to promote a risk-benefit discussion of the use of CT scan for each clinical case in the context of a shared medical decision making.

While most of the discussions and data presented in these papers focus on the Spanish experience, similar circumstances are emerging in other industrialised countries as the use of CT scan remains at growth. The fundamental precept *primum non nocere* must prevail against skeptical attitudes regarding the health effects of this exposure.

At the moment, the radiation doses from procedures used by physicians in diagnosis and treatment of disease are not limited by regulations, but follow recommendations and guidelines that are periodically updated as more information on risks becomes available. As the EPI-CT study research progresses, more will become known about the health effects of exposure related to CT scan radiation exposure at young age. However, enough scientific information is now available to warrant preventive actions in the form of strict justification and dose optimisation carried out by health care providers (referring physicians and radiologists) and promoted by public health officials.

6.5. Future research

After decades of research, the radiogenic cancer risk of exposures to ionising radiation below 100 mSv remains the subject of continuing discussion among scientist. The long follow-up of large cohorts of exposed population may allow for precise estimates of cancer risk given the statistical power reached.

The results of the analyses on the international EPI-CT cohort study are expected to represent a substantial addition to the scientific basis defining the shape of the dose-response relationship for radiation induced health effects at low doses/dose-rates. If the combination of the previous literature with the results of the international EPI-CT cohort were to show higher cancer incidence associated to low-dose exposure, then the presumption of an error-free repair mechanism in mammalian cells and of a safe dose threshold would be untenable. The subsequent implications of such findings would affect not only the radiation protection field but would resonate in occupational, power production, research, industrial and military settings.

Similarly, the available epidemiologic evidence falls short on the strength and consistency required to conclude about the non-cancer effects related to radiation exposure below 500 mSv. This is another critical area requiring answers for appropriate decision making in patient protection (and in radiation protection in general) given the increasing use of medical ionising radiation. As of today, cardiovascular and neurological conditions are the focus of several studies underway relying both on epidemiological and biological approaches. Should these effects be demonstrated following low dose and low dose-rate exposure, this would have important implications for radiological protection given the high prevalence of these diseases in the general population.

The continuation of the follow-up of large cohorts such as the international EPI-CT cohort during the next decades is essential to allow the assessment of non-cancer conditions potentially induced by radiation that are more common in the aging population. Further updates on the dose exposure information over time of the cohort members will also increase the number of subjects with more

substantial average cumulative doses, which will strengthen the dose-response analysis.

In Spain, a nested-case control of leukaemia and brain cancer is under preparation. This study, which is an important complement to the cohort study, will allow the collection of individual data on other sources of radiation exposure not included in the current exposure assessment, such as other CT scans received in other hospitals as well as interventional radiology, conventional radiography and nuclear medicine. Additionally it will allow the collection of individual information on syndromes and diseases that could be related to both the risk of cancer and the frequency of CT and thus potentially confound any association observed in the international EPI-CT cohort. It is, therefore, expected that the case-control nested will produce improved estimates of the radiation induced risk. The study will also allow the collection of biological samples in order to study potential markers of radiation sensitivity using, in particular, exome sequencing and methylation profiling.

The latter is an important aspect given the current paucity of data on individual variability in radiation-related cancer risk. Differences in cancer risk among subjects may be related to several factors such as health status, genetic and epigenetic make-up, and may be modified by individual lifestyle. If confirmed, the public health implications are important and question the potential inadequacy of the present radiation protection system if specific individuals do not fit into such general regulations.

Also for consideration is the fact that rare disease syndromes are slowly starting to be systematically recorded in Spain. Recent initiatives, such as the Spanish Rare Diseases Registries Research Network-SpainRDR, which is aimed to build the Spanish National Rare Diseases Registry based on patient registries and population-based registries, may provide the tools to assess the genetic susceptibility to radiogenic cancer. Up to now, the absence of an exhaustive record of rare diseases incidence has precluded any research on this topic. As for the case on individual variability in radiogenic cancer risk there is some potential for inadequated radiation protection of this vulnerable group of patients.

The combination of the existing aggregated evidence on radiogenic risks at low-dose exposure with the results of the international EPI-CT cohort may represent a turning point in radiation epidemiology.

7. CONCLUSIONS

- Epidemiological studies of diagnostic radiation exposures aim to impact on patient protection and clinical practice. The lack of information on the subjects of study regarding migratory and vital status, and socioeconomic position may bias the estimate of the association under study. Additionally, a misestimation of the true exposure, confounding by indication and reverse confounding may pose a threat to the validity of the study results.

- Within the Spanish EPI-CT study, an average annual increase in the total number of CT scans in population under 21 years of age was observed from 1991 to 2013 in Catalonia. However, the available data did not allow discerning what proportion of the increase was attributable to a higher availability of CT scans, a greater number of patients attended at the participating hospitals, an increase in the number of scans per patient, or to new CT scanning indications.

- Within the Spanish EPI-CT study, the socioeconomic status of the patient, as measured by the Urban Vulnerability Synthetic Index, was unrelated to the frequency of CT scans per patient, based on the 2001 census.

- Within the Spanish EPI-CT study, the use of different indicators and of SES data collected at different time points led to different relations between SES and frequency of CT scans, outlining the difficulty of adequately capturing the social and economic dimensions which may affect health and healthcare utilisation.

- The projection of cancer risks of over 94.000 CT scans in young Spanish population estimated that 81 future cancers would arise from one year of CT imaging. This represents an additional 0.2% of cancer cases over the 39,000 cancer cases expected to occur spontaneously in the lifespan of the exposed individuals.

- The analysis highlighted that the frequency of CT scans of the head and the elevated lifetime attributable risks of the organs exposed during abdomen CT examinations notably contributed to the total projected cancer risks.

- Preliminary results of the analysis of the mortality of the Spanish EPI-CT cohort indicate an increased risk of both brain tumours, haematological malignancies and leukaemia (non-significant for the later), similar to the atomic bomb survivors studies and statistically compatible with those from the CT scan studies.

8. SCIENTIFIC WORK RELATED TO THIS THESIS

8.1. Peer-reviewed publications (published & submitted)

Bosch de Basea M, Espinosa A, Gil M, Figuerola J, Pardina M, Vilar J, Cardis E. CT scan exposure in Spanish children and young adults by socioeconomic status. Submitted to: BMC Health Services Research (1st of January 2016).

Bosch de Basea M, Salotti JA, Pearce MS, Muchart J, Riera L, Barber I, Pedraza
S, Pardina M, Capdevila A, Espinosa A, Cardis E. Trends and patterns in the use of computed tomography in children and young adults in Catalonia - results from the EPI-CT study. Pediatr Radiol. 2016 Jan;46(1):119-29. doi: 10.1007/s00247-015-3434-5.

Cardis E, Bosch de Basea M. Comment on 'Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France'--Evidence of confounding by predisposing factors unclear. Br J Cancer. 2015 Dec 1;113(11):1641. doi: 10.1038/bjc.2015.393.

Bosch de Basea M, Pearce MS, Kesminiene A, Bernier MO, Dabin J, Engels H, Hauptmann M, Krille L, Meulepas JM, Struelens L, Baatout S, Kaijser M, Maccia C, Jahnen A, Thierry-Chef I, Blettner M, Johansen C, Kjaerheim K, Nordenskjöld A, Olerud H, Salotti JA, Andersen TV, Vrijheid M, Cardis E. EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT. J Radiol Prot. 2015 Sep;35(3):611-28. doi: 10.1088/0952-4746/35/3/611.

8.2. Conference presentations

Bosch de Basea M, Cardis E. New projects on epidemiology of pediatric radio-diagnostic. Conference on "The radiation protection of the patient in the 2011 year". April 2011. Madrid, Spain. *Oral presentation.*

Bosch de Basea M, Cardis E. on behalf of the EPI-CT consortium members. EPI-CT: cohort study in young population with radiologic exposure to CT scan. Spanish conference of the Spanish Society of Medical Physics and the Spanish Society of Radiologic Protection. June 2011. Seville. *Scientific poster.*

Bosch de Basea M, Sadetzki S., Armstrong B, et al. Medical exposure to ionising radiation and brain tumour risk - analyses of data from five interphone countries. International Society of Environmental Epidemiology 2011. Sept 2011. Barcelona. *Scientific poster.*

Bosch de Basea M, Pearce MS, Kesminiene A, Bernier MO, Dabin J, Engels H, Hauptmann M, Krille L, Meulepas JM, Struelens L, Baatout S, Kaijser M, Maccia C, Jahnen A, Thierry-Chef I, Blettner M, Johansen C, Kjaerheim K, Nordenskjöld A, Olerud H, Salotti JA, Andersen TV, Vrijheid M, Cardis E. EPI – CT: Design and epidemiological methods of an international study on cancer risks after paediatric CT. May 2013. European Child Conference. Dublin, Ireland. *Scientific poster.*

Bosch de Basea M, Pearce MS, Kesminiene A, Bernier MO, Dabin J, Engels H, Hauptmann M, Krille L, Meulepas JM, Struelens L, Baatout S, Kaijser M, Maccia C, Jahnen A, Thierry-Chef I, Blettner M, Johansen C, Kjaerheim K, Nordenskjöld A, Olerud H, Salotti JA, Andersen TV, Vrijheid M, Cardis E. EPI – CT: Design and epidemiological methods of an international study on cancer risks after paediatric CT. August 2013. Basel, Switzerland. *Oral presentation.*

Bosch de Basea M, Muchart J, Riera Ll, Barber I, Figuerola J, Albert A, Gil M, Cardis E. CT Scan use in Catalonia - Socioeconomic variation and descriptive patterns from 1991-2013. MELODI General Assembly meeting.

Bosch de Basea M. Quantification of the risks associated to the ionising radiation exposure during a CT scan in children and young population. Cancer registry of Girona. May 2015. Girona, Spain. *Oral presentation.*

8.3. Thesis - related work

The Ph.D. candidate started working at IS Global (formerly known as CREAL) in 2010 and was involved from day one in the EPI-CT study when it kicked-off in 2011. She has been part of the EPI-CT Work Package 2 (WP2), responsible of the epidemiological methods of the study where all the potential methodological factors threatening the validity of the EPI-CT results were discussed in depth.

A relevant task was the compilation of the "Country-specific procedures" in a report that was the first deliverable of the WP2 for the European Commission, which was the main financial supporter of the study. She was involved, as well, in the organisation and the definition of the agenda for the WP2 periodical meetings (web based or phone conferencing) with the rest of the members.

Another relevant task was her contribution in a Research funding application for the Consejo de Seguridad Nuclear, which successfully granted 472.000 euros to the study.

As mentioned earlier, the Ph.D. candidate was responsible for the set-up, coordination and cohort management of the Spanish branch of the EPI-CT study. That meant the initial contact with the radiologist, enrollment of 24 hospitals in six different Autonomous Communities, gaining ethical clearance for hospital (which included the preparation of the required paperwork, responses to the Ethics board additional requests and, sometimes, oral presentations for the different Ethics interlocutor). It also involved the coordination of the installation of the PerMoS software in nine hospitals in two Autonomous Communities in order to extract the technical parameters of 113,589 CT examinations performed in 58,819 patients, which would be later used for dose estimation. The initial visits to some of the IT departments at the hospital for the installation of the software were also performed by the present candidate, after being trained by the Luxembourg EPI-CT team.

She also was in charged of the linkage with the mortality registry (National Statistics Institute), cancer registries (Valencian C., Murcia R., Navarre, Basque country, Girona, Tarragona, and

Oficina Regional de Coordinación Oncológica), inpatient database registries or Conjunto Mínimo Básico de Datos (Catalonia, Valencian C., Murcia R., Navarre, Basque country and Madrid C.) and rare diseases registry (Valencian C., Murcia R. and Navarre). This included the initial contacts, contract management, the coordination of the pilot linkage (generally of 1,000 patients) with the mortality, cancer and inpatient registries and the validation of results in the case of the National Statistics Institute twice (Madrid 2013 and Madrid 2014).

9. References

1.	National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation : BEIR VII Phase 2. Washington, D.C.: National Academies Press; 2006.

2.	UNSCEAR. UNSCEAR 2008 Report Vol. I Sources and effects of ionising radiation. Annex A: Medical radiation exposures [Internet]. United Nations, Vienna; 2010 Oct. (UNSCEAR 2008 Report). Available from: http://www.unscear.org/unscear/en/publications/2008_1.html

3.	WHO | What is Ionizing Radiation? [Internet]. WHO. [cited 2016 Jan 21]. Available from: http://www.who.int/ionizing_radiation/about/what_is_ir/en/

4.	Podgorsak EB, International Atomic Energy Agency. Radiation Oncology Physics: A Handbook for Teachers and Students [Internet]. 2005 [cited 2016 Aug 20]. Available from: http://www-pub.iaea.org/books/IAEABooks/7086/Radiation-Oncology-Physics

5.	(ARPANSA) ARP and NSA. ARPANSA - Ionising and Non Ionising Radiation [Internet]. Australian Radiation Protection and Nuclear Safety Agency (ARPANSA); Available from: http://www.arpansa.gov.au/radiationprotection/basics/ion_nonion.cfm

6.	UNSCEAR. Sources and effects of ionizing radiation, Vol. I, Annex B - Exposures of the public and workers from various sources of radiation [Internet]. United Nations, New York; 2010 Oct. (UNSCEAR 2008 Report). Available from: http://www.unscear.org/docs/reports/2008/09-86753_Report_2008_Annex_B.pdf

7.	UNSCEAR. Sources and effects. Annex B: Exposures from natural radiation sources [Internet]. 2000. (UNSCEAR 2000 Report). Available from: http://www.unscear.org/docs/reports/annexb.pdf

8.	ICRP. ICRP publication 119: Compendium of Dose Coefficients based on ICRP Publication 60. Ann ICRP [Internet]. 2012;41

http://www.icrp.org/docs/P%20119%20JAICRP%2041(s)%20Co
mpendium%20of%20Dose%20Coefficients%20based%20on%20I
CRP%20Publication%2060.pdf

9. Monty C. UNSCEAR Report 2000 Report: Sources and Effects of
    Ionizing Radiation. J Radiol Prot. 2001;21(1):83.

10. Bliss JD. Radioactivity in Selected Mineral Extraction Industries :
    A Literature Review [Internet]. U.S. Environmental Protection
    Agency;   1978   p.   64.   Available   from:
    http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=93000XY2.txt

11. European Commission. Directorate-General for Mobility and
    Transport, Directorate-General for Energy. Medical Radiation
    Exposure of the European Population [Internet]. 2014 [cited 2016
    Mar 11]. Report No.: Radiation protection no 180. Available
    from:
    https://ec.europa.eu/energy/sites/ener/files/documents/RP180.pdf

12. National Council on Radiation Protection and Measurements.
    Ionizing radiation exposure of the population of the United States.
    2009. Report No.: NCRP Report No 160.

13. Hounsfield GN. Computed medical imaging. Science. 1980 Oct
    3;210(4465):22–8.

14. Ulzheimer S, Flohr T. Multislice CT: Current Technology and
    Future Developments. In: Reiser MF, Becker CR, Nikolaou K,
    Glazer G, editors. Multislice CT [Internet]. Springer Berlin
    Heidelberg; 2009 [cited 2016 Aug 20]. p. 3–23. (Medical
    Radiology). Available from:
    http://link.springer.com/chapter/10.1007/978-3-540-33125-4_1

15. Consulta Interactiva del Sistema Nacional de Salud (SNS).
    Sistema de información de atención especializada. Dotación.
    [Internet]. Available from:
    http://pestadistico.inteligenciadegestion.msssi.es/publicoSNS/com
    un/DefaultPublico.aspx

16. European Commission. Eurostat. Database. Population and social
    conditions. Health. Operations, procedures, and treatments
    [Internet]. 2016. Available from:
    http://ec.europa.eu/eurostat/data/database

17. Consulta Interactiva del Sistema Nacional de Salud (SNS). Sistema de información de atención especializada. Actividad asistencial. Actividad diagnóstica. [Internet]. [cited 2016 Mar 21]. Available from: http://pestadistico.inteligenciadegestion.msssi.es/publicoSNS/comun/DefaultPublico.aspx

18. Almohiy H. Paediatric computed tomography radiation dose: A review of the global dilemma. World J Radiol. 2014 Jan 28;6(1):1–6.

19. Bosch de Basea M, Salotti JA, Pearce MS, Muchart J, Riera L, Barber I, et al. Trends and patterns in the use of computed tomography in children and young adults in Catalonia - results from the EPI-CT study. Pediatr Radiol. 2016 Jan;46(1):119–29.

20. Pearce MS, Salotti JA, Howe NL, McHugh K, Kim KP, Lee C, et al. CT Scans in Young People in Great Britain: Temporal and Descriptive Patterns, 1993-2002. Radiol Res Pract. 2012;2012:594278.

21. Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013 Aug 1;167(8):700–7.

22. Servicios generales de información sanitaria e innovación. Ministerio de sanidad, servicios sociales e igualdad [Ministry of health, social services and equality]. Indicadores Clave Sistema Nacional de Salud Versión 1.0 [Internet]. Available from: http://inclasns.msssi.es/?show=true

23. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med. 2007 Nov 29;357(22):2277–84.

24. Brady Z, Cain TM, Johnston PN. Paediatric CT imaging trends in Australia. J Med Imaging Radiat Oncol. 2011 Apr;55(2):132–42.

25. Zacharias C, Alessio AM, Otto RK, Iyer RS, Philips GS, Swanson JO, et al. Pediatric CT: strategies to lower radiation dose. AJR Am J Roentgenol. 2013 May;200(5):950–6.

26. Honnef D, Wildberger JE, Stargardt A, Hohl C, Barker M, Günther RW, et al. [Multislice spiral CT (MSCT) in pediatric

radiology: dose reduction for chest and abdomen examinations]. Rofo. 2004 Jul;176(7):1021–30.

27.   Smith-Bindman R, Miglioretti DL, Johnson E, Lee C, Feigelson HS, Flynn M, et al. Use of Diagnostic Imaging Studies and Associated Radiation Exposure For Patients Enrolled in Large Integrated Healthcare Systems, 1996–2010. JAMA [Internet]. 2012 Jun 13 [cited 2016 Apr 11];307(22). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3859870/

28.   European Commission. Directorate-General for Mobility and Transport, Directorate-General for Energy. European Guidance on Estimating Population Doses from Medical X-Ray Procedures [Internet]. 2008 [cited 2016 Mar 11]. Report No.: Radiation protection no 154. Available from: http://ddmed.eu/_media/background_of_ddm1:rp154.pdf

29.   UNSCEAR. Sources, effects and risks of ionising radiation. Vol. II, Annex B - Effects of radiation exposure in children [Internet]. United Nations, New York; 2013. (UNSCEAR 2013 Report). Available from: http://www.unscear.org/docs/reports/2013/UNSCEAR2013Report _AnnexB_Children_13-87320_Ebook_web.pdf

30.   UNSCEAR. UNSCEAR 2006 Report, Scientific Report: Effects of Ionising Radiation, Vol. 1: Scientific Annex A - Epidemiological studies of radiation and cancer. United Nations, Vienna; 2008.

31.   Merzenich H, Krille L, Hammer G, Kaiser M, Yamashita S, Zeeb H. Paediatric CT scan usage and referrals of children to computed tomography in Germany--a cross-sectional survey of medical practice and awareness of radiation related health risks among physicians. BMC Health Serv Res. 2012;12:47.

32.   Bernier M-O, Rehel J-L, Brisse HJ, Wu-Zhou X, Caer-Lorho S, Jacob S, et al. Radiation exposure from CT in early childhood: a French large-scale multicentre study. Br J Radiol. 2012 Jan;85(1009):53–60.

33.   Dorfman AL, Fazel R, Einstein AJ, Applegate KE, Krumholz HM, Wang Y, et al. Use of medical imaging procedures with ionizing radiation in children: a population-based study. Arch Pediatr Adolesc Med. 2011 May;165(5):458–64.

34. Krille L, Dreger S, Schindel R, Albrecht T, Asmussen M, Barkhausen J, et al. Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study. Radiat Environ Biophys. 2015 Jan 8;

35. International Atomic Energy Agency. Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards [Internet]. 2014 Jul. (Series No. General Safety Requirements Part 3). Available from: http://www-pub.iaea.org/MTCD/publications/PDF/Pub1578_web-57265295.pdf

36. Lee C, Kim KP, Long DJ, Bolch WE. Organ doses for reference pediatric and adolescent patients undergoing computed tomography estimated by Monte Carlo simulation. Med Phys. 2012 Apr;39(4):2129–46.

37. Linet MS, Kim KP, Rajaraman P. Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations. Pediatr Radiol. 2009 Feb;39 Suppl 1:S4-26.

38. Mahesh M. MDCT Physics: The Basics: Technology, Image Quality and Radiation Dose. Philadelphia: Wolters Kluwer Health; 2009.

39. Lee C, Pearce MS, Salotti JA, Harbron RW, Little MP, McHugh K, et al. Reduction in radiation doses from paediatric CT scans in Great Britain. BJR. 2016 Feb 11;89(1060):20150305.

40. European Commission. Directorate-General for Energy and Transport. Directorate-General for Nuclear Energy. Referral Guidelines For Imaging [Internet]. 2014 [cited 2016 Mar 11]. Report No.: Radiation protection no 118. Available from: https://ec.europa.eu/energy/sites/ener/files/documents/RP180.pdf

41. Goske MJ, Applegate KE, Boylan J, Butler PF, Callahan MJ, Coley BD, et al. The Image Gently campaign: working together to change practice. AJR Am J Roentgenol. 2008 Feb;190(2):273–4.

42. Singh S, Kalra MK, Moore MA, Shailam R, Liu B, Toth TL, et al. Dose Reduction and Compliance with Pediatric CT Protocols Adapted to Patient Size, Clinical Indication, and Number of Prior Studies. Radiology. 2009 Jul 1;252(1):200–8.

43. Saxena AK, Kochhar R. Inadvertent High Radiation Dose to Pediatric Patients During CT: Whose Responsibility Is It? American Journal of Roentgenology. 2006 Feb 1;186(2):583–4.

44. Fricke BL, Donnelly LF, Frush DP, Yoshizumi T, Varchena V, Poe SA, et al. In-Plane Bismuth Breast Shields for Pediatric CT: Effects on Radiation Dose and Image Quality Using Experimental and Clinical Data. American Journal of Roentgenology. 2003 Feb 1;180(2):407–11.

45. Almén A, Leitz W, Richter S. National Survey on Justification of CT-examinations in Sweden [Internet]. 2009. Report No.: 2009:03. Available from: www.stralsakerhetsmyndigheten.se

46. ¿Hay control de las pruebas de imagen ionizantes en urgencias pediátricas? [Is there any control on the ionising radiation imaging in the pediatric emergency ward?]. In Anales de Pediatría; p. 177–94. Available from: http://www.analesdepediatria.org/es/x-reunion-anual-sociedad-espanola/articulo/13091495/

47. Han W, Ngok Yu K. Chapter 6: Response of cells to ionizing radiation. In: Advances in biomedical sciences and engineering. Bentham science publishers; 2009.

48. Basic Clinical Radiobiology Fourth Edition [Internet]. CRC Press. 2009. Available from: https://www.crcpress.com/Basic-Clinical-Radiobiology-Fourth-Edition/Joiner-van-der-Kogel/9780340929667

49. Shah DJ, Sachs RK, Wilson DJ. Radiation-induced cancer: a modern view. Br J Radiol. 2012 Dec;85(1020):e1166-1173.

50. Suntharalingam N, Podgorsak EB, Hendry JH. Basic radiobiology. In: Review of Radiation Oncology Physics: A Handbook for Teachers and Students [Internet]. Available from: http://www.irsn.fr/FR/professionnels_sante/documentation/Documents/syllabus_chapitre_14.pdf

51. Morgan WF, Sowa MB. Effects of ionizing radiation in nonirradiated cells. PNAS. 2005 Oct 4;102(40):14127–8.

52. Bower M, Waxman J. Lecture Notes: Oncology. John Wiley & Sons; 2015. 363 p.

53. Lomax ME, Folkes LK, O'Neill P. Biological Consequences of Radiation-induced DNA Damage: Relevance to Radiotherapy. Clinical Oncology. 2013 Oct;25(10):578–85.

54. Clark TA, Spittle KE, Turner SW, Korlach J. Direct Detection and Sequencing of Damaged DNA Bases. Genome Integrity. 2011;2:10.

55. Mullenders L, Atkinson M, Paretzke H, Sabatier L, Bouffler S. Assessing cancer risks of low-dose radiation. Nat Rev Cancer. 2009 Aug;9(8):596–604.

56. Caldecott KW. Single-strand break repair and genetic disease. Nat Rev Genet. 2008 Aug;9(8):619–31.

57. Barker S, Weinfeld M, Zheng J, Li L, Murray D. Identification of mammalian proteins cross-linked to DNA by ionizing radiation. J Biol Chem. 2005 Oct 7;280(40):33826–38.

58. Dextraze M-E, Gantchev T, Girouard S, Hunting D. DNA interstrand cross-links induced by ionizing radiation: An unsung lesion. Mutation Research/Reviews in Mutation Research. 2010 Apr;704(1–3):101–7.

59. Roots R, Kraft G, Gosschalk E. The formation of radiation-induced dna breaks: The ratio of double-strand breaks to single-strand breaks. International Journal of Radiation Oncology*Biology*Physics. 1985 Feb 1;11(2):259–65.

60. Little JB. Radiation carcinogenesis. Carcinogenesis. 2000 Mar 1;21(3):397–404.

61. Armstrong B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular Biology of the Cell. In: 4th edition. Garland Science; 2002.

62. Clancy S. DNA damage & repair: mechanisms for maintaining DNA integrity. Nature Education. 2008;1(1):103.

63. Gospodinov A, Herceg Z. Chromatin structure in double strand break repair. DNA Repair (Amst). 2013 Oct;12(10):800–10.

64. Vignard J, Mirey G, Salles B. Ionizing-radiation induced DNA double-strand breaks: A direct and indirect lighting up. Radiotherapy and Oncology. 2013 Sep;108(3):362–9.

65. Dexheimer TS. DNA Repair Pathways and Mechanisms. In: Mathews LA, Cabarcas SM, Hurt EM, editors. DNA Repair of Cancer Stem Cells [Internet]. Springer Netherlands; 2013 [cited 2016 Apr 7]. p. 19–32. Available from: http://link.springer.com/chapter/10.1007/978-94-007-4590-2_2

66. Harper JW, Elledge SJ. The DNA damage response: ten years after. Mol Cell. 2007 Dec 14;28(5):739–45.

67. Nosel I, Vaurijoux A, Barquinero J-F, Gruel G. Characterization of gene expression profiles at low and very low doses of ionizing radiation. DNA Repair (Amst). 2013 Jul;12(7):508–17.

68. Taylor AM, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. Blood. 1996 Jan 15;87(2):423–38.

69. Stieglitz E, Loh ML. Genetic predispositions to childhood leukemia. Ther Adv Hematol. 2013 Aug;4(4):270–90.

70. Pfeiffer P, Goedecke W, Obe G. Mechanisms of DNA double-strand break repair and their potential to induce chromosomal aberrations. Mutagenesis. 2000 Jul 1;15(4):289–302.

71. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. Lippincott Williams & Wilkins; 2006. 566 p.

72. Greenberger JS. Radioprotection. In Vivo. 2009;23(2):323–36.

73. UNSCEAR. Biological mechanisms of radiation actions at low dose [Internet]. United Nations, New York; 2013. (UNSCEAR 2012 Report). Available from: http://www.unscear.org/docs/reports/2013/UNSCEAR2013Report_AnnexB_Children_13-87320_Ebook_web.pdf

74. Ruddon RW. Cancer Biology. Oxford University Press, USA; 2007. 570 p.

75. Barcellos-Hoff MH, Park C, Wright EG. Radiation and the microenvironment – tumorigenesis and therapy. Nat Rev Cancer. 2005 Nov;5(11):867–75.

76. Barcellos-Hoff MH, Nguyen DH. Radiation carcinogenesis in context: how do irradiated tissues become tumors? Health Phys. 2009 Nov;97(5):446–57.

77. ICRP. ICRP publication 99: low-dose extrapolation of radiation-related cancer risk. Ann ICRP. 2005 Dec;35(4):1–142.

78. WHO International, Expert Working Group, WHO International. Health risk assessment from the nuclear accident after the 2011 Great East Japan earthquake and tsunami, based on a preliminary dose estimation [Internet]. WHO Library; Available from: http://www.who.int/ionizing_radiation/pub_meet/fukushima_risk_assessment_2013/en/

79. Baysson H, Journy N, Roué T, Ducou-Lepointe H, Etard C, Bernier M-O. [Exposure to CT scans in childhood and long-term cancer risk: A review of epidemiological studies]. Bull Cancer. 2016 Feb;103(2):190–8.

80. IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 75. Ionizing radiation, part 1: X- and Gamma- Radiation, and Neutrons [Internet]. Lyon: IARC (International Agency for Research on Cancer); 2000. Available from: http://monographs.iarc.fr/ENG/Monographs/vol75/

81. National Toxicology Program. Report on Carcinogens, Eleventh Edition. Research Triangle Park, NC: U.S.: Department of Health and Human Services, Public Health Service.; 2004.

82. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012 Aug 4;380(9840):499–505.

83. Journy N, Rouée T, Cardis E, Ducou Le Pointe H, Brisse H, Chateil JF, et al. Predisposing factors for cancer: effect modifiers of the potential association between childhood CT scans and cancer risk. submitted.

84. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. Radiat Res. 2005 Apr;163(4):424–32.

85. Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, et al. Risk of Thyroid Cancer After Exposure to 131I in Childhood. JNCI J Natl Cancer Inst. 2005 May 18;97(10):724–32.

86. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. Radiat Res. 2007 Apr;167(4):396–416.

87. Little MP, Wakeford R, Tawn EJ, Bouffler SD, Berrington de Gonzalez A. Risks Associated with Low Doses and Low Dose Rates of Ionizing Radiation: Why Linearity May Be (Almost) the Best We Can Do. Radiology. 2009 Apr;251(1):6–12.

88. ICRP. ICRP Publication 103: The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann ICRP. 2007;37(2–4):1–332.

89. Tubiana M, Feinendegen LE, Yang C, Kaminski JM. The Linear No-Threshold Relationship Is Inconsistent with Radiation Biologic and Experimental Data. Radiology. 2009 Apr;251(1):13–22.

90. Wakeford R. The risk of childhood leukaemia following exposure to ionising radiation--a review. J Radiol Prot. 2013 Mar;33(1):1–25.

91. Ichimaru M, Asmussen M, Tan K. A review of forty-five years study of Hiroshima and Nagasaki atomic bomb survivors. Atomic bomb and Leukaemia. J Radiat Res. 1991 Mar;32 Suppl:162–7.

92. Hsu W-L, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, et al. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiat Res. 2013 Mar;179(3):361–82.

93. Richardson D, Sugiyama H, Nishi N, Sakata R, Shimizu Y, Grant EJ, et al. Ionizing Radiation and Leukemia Mortality among Japanese Atomic Bomb Survivors, 1950–2000. Radiation Research. 2009 Aug 26;172(3):368–82.

94. Little MP. Cancer and non-cancer effects in Japanese atomic bomb survivors. J Radiol Prot. 2009 Jun;29(2A):A43-59.

95. Russ A. Ionizing Radiation and Childhood Leukemia. Environ Health Perspect. 2007 Aug;115(8):A395–6.

96. Wakeford R. The cancer epidemiology of radiation. Oncogene. 2004;23(38):6404–28.

97.   Laurier D, Grosche B, Auvinen A, Clavel J, Cobaleda C, Dehos A, et al. Childhood leukaemia risks: from unexplained findings near nuclear installations to recommendations for future research. J Radiol Prot. 2014 Sep;34(3):R53-68.

98.   Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res. 1994 Feb;137(2 Suppl):S68-97.

99.   Linet MS, Slovis TL, Miller DL, Kleinerman R, Lee C, Rajaraman P, et al. Cancer Risks Associated with External Radiation From Diagnostic Imaging Procedures. CA Cancer J Clin. 2012;62(2):75–100.

100.   Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 2007 Jul;168(1):1–64.

101.   United Nations Scientific Committee on the Effects of Atomic Radiation. UNSCEAR 2006 report - Vol. I: Effects of Ionizing radiation. Annex A: Epidemiological studies of radiation and cancer. [Internet]. [cited 2016 Aug 23]. Available from: http://www.unscear.org/docs/publications/2006/UNSCEAR_2006 _Annex-A-CORR.pdf

102.   Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. Radiat Res. 2012 Mar;177(3):229–43.

103.   Cardis E, Hatch M. The Chernobyl accident--an epidemiological perspective. Clin Oncol (R Coll Radiol). 2011 May;23(4):251–60.

104.   Parkin DM, Cardis E, Masuyer E, Friedl HP, Hansluwka H, Bobev D, et al. Childhood leukaemia following the Chernobyl accident: the European Childhood Leukaemia-Lymphoma Incidence Study (ECLIS). Eur J Cancer. 1992;29A(1):87–95.

105.   Laurier D, Jacob S, Bernier MO, Leuraud K, Metz C, Samson E, et al. Epidemiological studies of leukaemia in children and young adults around nuclear facilities: a critical review. Radiat Prot Dosimetry. 2008;132(2):182–90.

106. Tsuda T, Tokinobu A, Yamamoto E, Suzuki E. Thyroid Cancer Detection by Ultrasound Among Residents Ages 18 Years and Younger in Fukushima, Japan: 2011 to 2014. Epidemiology. 2015 Oct;1.

107. Fukushima Study Links Children's Cancer To Nuclear Accident [Internet]. NPR.org. [cited 2016 Sep 8]. Available from: http://www.npr.org/sections/thetwo-way/2015/10/08/446873871/fukushima-study-links-childrens-cancer-to-nuclear-accident

108. Stevens W, Thomas DC, Lyon JL, Till JE, Kerber RA, Simon SL, et al. Leukemia in Utah and radioactive fallout from the Nevada test site. A case-control study. JAMA. 1990 Aug 1;264(5):585–91.

109. Little MP. Comparison of the risks of cancer incidence and mortality following radiation therapy for benign and malignant disease with the cancer risks observed in the Japanese A-bomb survivors. Int J Radiat Biol. 2001 Apr;77(4):431–64.

110. Brenner DJ. What we know and what we don't know about cancer risks associated with radiation doses from radiological imaging. Br J Radiol. 2014 Mar;87(1035):20130629.

111. Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. Int J Cancer. 1994 Nov 1;59(3):327–38.

112. Weiss HA, Darby SC, Fearn T, Doll R. Leukemia Mortality after X-Ray Treatment for Ankylosing Spondylitis. Radiation Research. 1995;142(1):1–11.

113. Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice John D. Thyroid Neoplasia Following Low-Dose Radiation in Childhood. Radiation Research. 1989 Dec 1;120(3):516–31.

114. Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. Radiat Res. 1998 Jun;149(6):625–30.

115. Schneider AB, Ron E, Lubin J, Stovall M, Shore-Freedman E, Tolentino J, et al. Acoustic neuromas following childhood

radiation treatment for benign conditions of the head and neck. Neuro Oncol. 2008 Jan;10(1):73–8.

116. Bithell JF, Stewart AM. Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey. Br J Cancer. 1975 Mar;31(3):271–87.

117. Harvey EB, Boice JDJ, Honeyman M, Flannery JT. Prenatal X-Ray Exposure and Childhood Cancer in Twins. New England Journal of Medicine. 1985 Feb 28;312(9):541–5.

118. Wakeford R, Little MP. Risk coefficients for childhood cancer after intrauterine irradiation: a review. Int J Radiat Biol. 2003 May;79(5):293–309.

119. Meinert R, Kaletsch U, Kaatsch P, Schüz J, Michaelis J. Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. Cancer Epidemiol Biomarkers Prev. 1999 Sep;8(9):793–9.

120. Hammer GP, Seidenbusch MC, Schneider K, Regulla DF, Zeeb H, Spix C, et al. A cohort study of childhood cancer incidence after postnatal diagnostic X-ray exposure. Radiat Res. 2009 Apr;171(4):504–12.

121. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;346:f2360.

122. Huang W-Y, Muo C-H, Lin C-Y, Jen Y-M, Yang M-H, Lin J-C, et al. Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. Br J Cancer. 2014 Apr 29;110(9):2354–60.

123. Journy N, Rehel J-L, Ducou Le Pointe H, Lee C, Brisse H, Chateil J-F, et al. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br J Cancer. 2015 Jan 6;112(1):185–93.

124. Cardis, E., Bosch de Basea M. Commentary to Journy et al – Evidence of confounding by predisposing factors unclear. Br J Cancer. in press;

125. Hauptmann M, Meulepas JM. CT scans in childhood and risk of leukaemia and brain tumours. The Lancet. 2012 Nov;380(9855):1736.

126. Walsh L, Shore R, Auvinen A, Jung T, Wakeford R. Risks from CT scans—what do recent studies tell us? J Radiol Prot. 2014;34(1):E1.

127. International Agency for Research on Cancer. ACCIS: Automated Childhood Cancer Information System [Internet]. 2016. Available from: http://accis.iarc.fr/

128. Wiemels J. Perspectives on the causes of childhood leukemia. Chem Biol Interact. 2012 Apr 5;196(3):59–67.

129. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-oncology. 2002 Oct;4(4):278–99.

130. Kennedy JA, Barabé F. Investigating human leukemogenesis: from cell lines to in vivo models of human leukemia. Leukemia. 2008 Aug 7;22(11):2029–40.

131. Rubin P, Casarett GW. Clinical radiation pathology as applied to curative radiotherapy. Cancer. 1968 Oct;22(4):767–78.

132. Cristy M. Active bone marrow distribution as a function of age in humans. Phys Med Biol. 1981 May;26(3):389–400.

133. Domen J, Wagers A, Weissman IL. Regenerative Medicine. Chapter 2: Bone marrow (Hematopoietic) stem cells. (2006): 13. [Internet]. Department of Health and Human Services. National Institutes of Health; 2006 Aug. Available from: http://stemcells.nih.gov/info/scireport/pages/2006report.aspx

134. Stewart BW, Kleihues P, editors. Human cancers by organ site. In: World Cancer Report 2003. Lyon, France: International Agency for Research on Cancer; 2003. p. 181–265.

135. Ferlay J, Parkin DM, Curado MP, Bray F, Edwards B, Shin HR and Forman D. Cancer Incidence in Five Continents, Volumes I to IX: IARC CancerBase No. 9. Lyon, France: International Agency for Research on Cancer; 2010 [Internet].Available from: http://ci5.iarc.fr/CI5plus/references.htm

136. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013 [Internet]. GLOBOCAN 2012 v1.0. 2013 [cited 2016 Aug 2]. Available from: http://globocan.iarc.fr

137. European Environment and health information system (ENHIS). World health organization (WHO). Incidence of childhood leukaemia. Fact sheet 4.1 [Internet]. 2009. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/97016/4.1.-Incidence-of-childhood-leukaemia-EDITED_layouted.pdf

138. Kaatsch P. Epidemiology of childhood cancer. Cancer Treatment Reviews. 2010 Jun;36(4):277–85.

139. Marcos-Gragera R, Cervantes-Amat M, Vicente ML, de Sanjosé S, Guallar E, Godoy C, et al. Population-based incidence of childhood leukaemias and lymphomas in Spain (1993-2002). Eur J Cancer Prev. 2010 Jul;19(4):247–55.

140. Curado MP, Edwards B, Shin HR, Ferlay J, Heanue M, Boyle P, et al. Cancer Incidence in Five Continents Vol. IX. Lyon: IARC; 2007. (IARC Scientific publications). Report No.: No 160.

141. Bertuccio P, Bosetti C, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. Trends in mortality from leukemia in Europe: An update to 2009 and a projection to 2012. Int J Cancer. 2013 Jan 15;132(2):427–36.

142. Bosetti C, Bertuccio P, Chatenoud L, Negri E, Levi F, La Vecchia C. Childhood cancer mortality in Europe, 1970–2007. European Journal of Cancer. 2010 Jan;46(2):384–94.

143. International Agency for Research on Cancer. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Volume 2. Fourth Edition [Internet]. Lyon, France; 2008 Available from: http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=70&codcch=4002

144. UK CR. Leukaemia [Internet]. 2014 [cited 2016 Aug 24]. Available from: http://www.cancerresearchuk.org/about-cancer/type/leukaemia/

145. Marcos-Gragera R, Galceran J, Felipe S, Peris-Bonet R. Incidence and survival time trends for spanish children and adolescents with leukaemia from 1983 to 2007 (Conference paper). In 2015.

146. ICRP. ICRP Publication 118: ICRP Statement on Tissue Reactions / Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context. Ann ICRP. 2012;41((1/2)).

147. Ghaffari S. Oxidative Stress in the Regulation of Normal and Neoplastic Hematopoiesis. Antioxid Redox Signal. 2008 Nov;10(11):1923–40.

148. Richardson C, Yan S, Vestal CG. Oxidative stress, bone marrow failure, and genome instability in hematopoietic stem cells. Int J Mol Sci. 2015;16(2):2366–85.

149. Owusu-Ansah E, Banerjee U. Reactive Oxygen Species prime Drosophila haematopoietic progenitors for differentiation. Nature. 2009 Sep 24;461(7263):537–41.

150. Mullighan CG. The molecular genetic makeup of acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2012;2012:389–96.

151. Richardson DB, Wing S, Schroeder J, Schmitz-Feuerhake I, Hoffmann W. Ionizing radiation and chronic lymphocytic leukemia. Environ Health Perspect. 2005 Jan;113(1):1–5.

152. Daniels RD, Schubauer-Berigan MK. A meta-analysis of leukaemia risk from protracted exposure to low-dose gamma radiation. Occup Environ Med. 2011 Jun;68(6):457–64.

153. Galceran J, Ameijide A, Carulla M, Mateos A, Quirós J. Estimaciones de la incidencia y la supervivencia del cáncer en España y su situación en Europa [Internet]. Red Española de Registros de Cáncer (REDECAN); 2014 Oct.

154. Sociedad Española de Oncología Médica (SEOM). Información sobre el cáncer. Información tipos de cáncer. Tumores cerebrales. [Internet]. Available from: http://www.seom.org/es/informacion-sobre-el-cancer/info-tipos-cancer/tumores-cerebrales?start=2#content

155. Rickert CH, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst. 2001 Sep;17(9):503–11.

156. Arora RS, Alston RD, Eden TOB, Estlin EJ, Moran A, Birch JM. Age–incidence patterns of primary CNS tumors in children, adolescents, and adults in England. Neuro Oncol. 2009 Aug;11(4):403–13.

157. Johnson KJ, Cullen J, Barnholtz-Sloan JS, Ostrom QT, Langer CE, Turner MC, et al. Childhood Brain Tumor Epidemiology: A Brain Tumor Epidemiology Consortium Review. Cancer Epidemiol Biomarkers Prev. 2014 Dec 1;23(12):2716–36.

158. Kaatsch P, Steliarova-Foucher E, Crocetti E, Magnani C, Spix C, Zambon P. Time trends of cancer incidence in European children (1978–1997): Report from the Automated Childhood Cancer Information System project. European Journal of Cancer. 2006 Sep;42(13):1961–71.

159. Karalexi MA, Papathoma P, Thomopoulos TP, Ryzhov A, Zborovskaya A, Dimitrova N, et al. Childhood central nervous system tumour mortality and survival in Southern and Eastern Europe (1983–2014): Gaps persist across 14 cancer registries. European Journal of Cancer. 2015 Nov;51(17):2665–77.

160. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. The Lancet Oncology. 2014 Jan;15(1):35–47.

161. Vescovi AL, Galli R, Reynolds BA. Brain tumour stem cells. Nat Rev Cancer. 2006 Jun;6(6):425–36.

162. Kazanis I, Lathia J, Moss L, ffrench-Constant C. The neural stem cell microenvironment. In: StemBook [Internet]. Cambridge (MA): Harvard Stem Cell Institute; 2008 [cited 2016 Aug 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK27023/

163. Picano E, Vano E, Domenici L, Bottai M, Thierry-Chef I. Cancer and non-cancer brain and eye effects of chronic low-dose ionizing radiation exposure. BMC Cancer. 2012;12:157.

164. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001 Nov 1;414(6859):105–11.

165. Visvader JE. Cells of origin in cancer. Nature. 2011 Jan 20;469(7330):314–22.

166. Guo C-Y, Luo L, Urata Y, Goto S, Huang W-J, Takamura S, et al. Sensitivity and dose dependency of radiation-induced injury in hematopoietic stem/progenitor cells in mice. Sci Rep. 2015;5:8055.

167. Umansky F, Shoshan Y, Rosenthal G, Fraifeld S, Spektor S. Radiation-induced meningioma. Neurosurgical Focus. 2008 Apr 30;24(5):E7.

168. Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. Journal of the National Cancer Institute. 2002 Oct;94(20):1555–63.

169. Longstreth WT, Phillips LE, Drangsholt M, Koepsell TD, Custer BS, Gehrels J-A, et al. Dental X-rays and the risk of intracranial meningioma: a population-based case-control study. Cancer. 2004 Mar 1;100(5):1026–34.

170. Prasad G, Haas-Kogan DA. Radiation-induced gliomas. Expert Rev Neurother [Internet]. 2009 Oct [cited 2016 Aug 3];9(10). Available from:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830919/

171. Yonehara S, Brenner AV, Kishikawa M, Inskip PD, Preston DL, Ron E, et al. Clinical and epidemiologic characteristics of first primary tumors of the central nervous system and related organs among atomic bomb survivors in Hiroshima and Nagasaki, 1958-1995. Cancer. 2004 Oct 1;101(7):1644–54.

172. Davis F, Il'yasova D, Rankin K, McCarthy B, Bigner DD. Medical diagnostic radiation exposures and risk of gliomas. Radiat Res. 2011 Jun;175(6):790–6.

173. Braganza MZ, Kitahara CM, Berrington de González A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. Neuro-oncology. 2012 Nov;14(11):1316–24.

174. Hodgson S. Mechanisms of inherited cancer susceptibility. J Zhejiang Univ Sci B. 2008 Jan;9(1):1–4.

175. Tidyman WE, Rauen KA. The RASopathies: Developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev. 2009 Jun;19(3):230–6.

176. Kleinerman RA. Radiation-sensitive genetically susceptible pediatric sub-populations. Pediatr Radiol. 2009 Feb;39 Suppl 1:S27-31.

177. Saletta F, Dalla Pozza L, Byrne JA. Genetic causes of cancer predisposition in children and adolescents. Transl Pediatr. 2015 Apr;4(2):67–75.

178. Nižetić D, Groet J. Tumorigenesis in Down's syndrome: big lessons from a small chromosome. Nat Rev Cancer. 2012 Oct;12(10):721–32.

179. Maisonneuve P, Marshall BC, Knapp EA, Lowenfels AB. Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States. J Natl Cancer Inst. 2013 Jan 16;105(2):122–9.

180. Meulepas, Johanna M, Ronckers CM, Merks JH., Weijerman ME, Lubin JH, Hauptmann M. Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes. Submitted; 2015.

181. Pollard JM, Gatti RA. Clinical Radiation Sensitivity with DNA Repair Disorders: An Overview. Int J Radiat Oncol Biol Phys. 2009 Aug 1;74(5):1323–31.

182. Evans DGR, Birch JM, Ramsden RT, Sharif S, Baser ME. Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. J Med Genet. 2006 Apr;43(4):289–94.

183. Streffer C. An update on the mechanisms and pathophysiological consequences of genomic instability with a focus on ionizing radiation. Research and Reports in Biology. 2015 Dec;225.

184. Harbour JW. Molecular basis of low-penetrance retinoblastoma. Arch Ophthalmol. 2001 Nov;119(11):1699–704.

185. Friedman JM. Neurofibromatosis 1. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJ, et al., editors. GeneReviews(®) [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2016 Jan 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1109/

186. Carlson ML, Babovic-Vuksanovic D, Messiaen L, Scheithauer BW, Scheithauer BB, Neff BA, et al. Radiation-induced rhabdomyosarcoma of the brainstem in a patient with neurofibromatosis type 2. J Neurosurg. 2010 Jan;112(1):81–7.

187. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene. 2004;23(38):6445–70.

188. Denicola C. Rare ATM Gene Mutations, Plus Radiation, May Increase Risk of a Second Breast Cancer. JNCI Journal of the National Cancer Institute. 2010 Apr 7;102(7):NP-NP.

189. Dumon-Jones V, Frappart P-O, Tong W-M, Sajithlal G, Hulla W, Schmid G, et al. Nbn heterozygosity renders mice susceptible to tumor formation and ionizing radiation-induced tumorigenesis. Cancer Res. 2003 Nov 1;63(21):7263–9.

190. Muirhead CR. Response to "Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France." Br J Cancer. 2015 May 26;112(11):1841–2.

191. Journy N, Roué T, Cardis E, Le Pointe HD, Brisse H, Chateil J-F, et al. Childhood CT scans and cancer risk: impact of predisposing factors for cancer on the risk estimates. J Radiol Prot. 2016 Mar;36(1):N1-7.

192. Retraction: Confounding of the Association between Radiation Exposure from CT Scans and Risk of Leukemia and Brain Tumors by Cancer Susceptibility Syndromes. Cancer Epidemiol Biomarkers Prev. 2016 Jul 1;25(7):1192–1192.

193. Bhayana R, Vermeulen MJ, Li Q, Hellings CR, Berdahl C, Schull MJ. Socioeconomic status and the use of computed tomography in the emergency department. CJEM. 2014 Jul;16(4):288–95.

194. Ribeiro A de A, Nardocci AC. Desigualdades socioeconômicas na incidência e mortalidade por câncer: revisão de estudos ecológicos, 1998-2008. Saude soc. 2013;22(3):878–91.

195. Kroll ME, Stiller CA, Murphy MFG, Carpenter LM. Childhood leukaemia and socioeconomic status in England and Wales 1976–2005: evidence of higher incidence in relatively affluent communities persists over time. Br J Cancer. 2011 Nov 22;105(11):1783–7.

196. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: a review. Int J Epidemiol. 2006 Apr;35(2):370–84.

197. Adam M, Rebholz CE, Egger M, Zwahlen M, Kuehni CE. Childhood leukaemia and socioeconomic status: what is the evidence? Radiat Prot Dosimetry. 2008;132(2):246–54.

198. Inskip PD, Tarone RE, Hatch EE, Wilcosky TC, Fine HA, Black PM, et al. Sociodemographic indicators and risk of brain tumours. Int J Epidemiol. 2003 Apr 1;32(2):225–33.

199. Plascak JJ, Fisher JL. Area-Based Socioeconomic Position and Adult Glioma: A Hierarchical Analysis of Surveillance Epidemiology and End Results Data. PLoS ONE. 2013 Apr 9;8(4):e60910.

200. Carozza SE, Puumala SE, Chow EJ, Fox EE, Horel S, Johnson KJ, et al. Parental educational attainment as an indicator of socioeconomic status and risk of childhood cancers. Br J Cancer. 2010 Jun 29;103(1):136–42.

201. Krille L, Dreger S, Schindel R, Albrecht T, Asmussen M, Barkhausen J, et al. Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study. Radiat Environ Biophys. 2015 Mar;54(1):1–12.

202. VISC+: más valor a la información de salud de Cataluña [Internet]. Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS). [cited 2016 Aug 29]. Available from: http://aquas.gencat.cat/es/projectes/visc/index.html

203. Thierry-Chef I, Dabin J, Friberg EG, Hermen J, Istad TS, Jahnen A, et al. Assessing organ doses from paediatric CT scans--a novel approach for an epidemiology study (the EPI-CT study). Int J Environ Res Public Health. 2013 Feb;10(2):717–28.

204. Jahnen A, Kohler S, Hermen J, Tack D, Back C. Automatic computed tomography patient dose calculation using DICOM header metadata. Radiat Prot Dosimetry. 2011 Sep;147(1–2):317–20.

205. Lee C, Kim KP, Bolch WE, Moroz BE, Folio L. NCICT: a computational solution to estimate organ doses for pediatric and adult patients undergoing CT scans. J Radiol Prot. 2015 Dec;35(4):891–909.

206. Rothman K. Epidemiology - An Introduction. New York, New York: Oxford University Press, Inc.; 2002.

207. Diez-Roux AV, Kiefe CI, Jacobs DR, Haan M, Jackson SA, Nieto FJ, et al. Area characteristics and individual-level socioeconomic position indicators in three population-based epidemiologic studies. Ann Epidemiol. 2001 Aug;11(6):395–405.

208. Kölegård Stjärne M, Diderichsen F, Reuterwall C, Hallqvist J, Sheep Study Group. Socioeconomic context in area of living and risk of myocardial infarction: results from Stockholm Heart Epidemiology Program (SHEEP). J Epidemiol Community Health. 2002 Jan;56(1):29–35.

209. Campbell DA, Radford JM, Burton P. Unemployment rates: an alternative to the Jarman index? BMJ. 1991 Sep 28;303(6805):750–5.

210. Song JW, Chung KC. Observational Studies: Cohort and Case-Control Studies. Plast Reconstr Surg. 2010 Dec;126(6):2234–42.

211. Instituto Nacional de Estadística. INE base. Censos de Población y Viviendas 2011. Resultados Nacionales, por Comunidades Autónomas y Provincias. Población por sexo, edad (año a año) y nacionalidad (española/extranjera). [Internet]. [cited 2016 Jun 15]. Available from: http://www.ine.es/jaxi/Datos.htm?path=/t20/e244/avance/p01/l0/&file=04001.px

212. Pearce MS, Salotti JA, McHugh K, Kim KP, Craft AW, Lubin J, et al. Socio-economic variation in CT scanning in Northern England, 1990-2002. BMC Health Serv Res. 2012;12:24.

213.	Miller TS. Impact of Socioeconomic Status on Ionizing Radiation Exposure from Medical Imaging in Children. J Am Coll Radiol. 2012 Nov;9(11):799–807.

214.	Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992 May;82(5):703–10.

215.	Domínguez-Berjón F, Borrell C, Rodríguez-Sanz M, Pastor V. The usefulness of area-based socioeconomic measures to monitor social inequalities in health in Southern Europe. Eur J Public Health. 2006 Feb;16(1):54–61.

216.	Berrington de Gonzalez A, Iulian Apostoaei a, Veiga LHS, Rajaraman P, Thomas B a, Owen Hoffman F, et al. RadRAT: a radiation risk assessment tool for lifetime cancer risk projection. Journal of radiological protection : official journal of the Society for Radiological Protection. 2012 Sep;32(3):205–22.

217.	Surveillance Research Program, NCI's Division of Cancer Control and Population Sciences. Fast Stats - Surveillance, Epidemiology, and End Results Program. [Internet]. Available from: http://seer.cancer.gov/faststats/selections.php?run=runit&output= 2&data=4&statistic=6&year=201607&race=1&sex=1&age=9&se ries=cancer&cancer=76;91;95

218.	Lund JL, Harlan LC, Yabroff KR, Warren JL. Should Cause of Death From the Death Certificate Be Used to Examine Cancer-Specific Survival? A Study of Patients With Distant Stage Disease. Cancer Invest. 2010 Aug;28(7):758–64.

219.	Forman D, Bray F, Brewster D, Gombe Mbalawa C, Kohler B, Piñeros M, et al. Cancer Incidence in Spain (2007) [Internet]. Cancer Incidence in Five Continents, Vol. X (electronic version). Lyon: International Agency for Research on Cancer. [cited 2016 Jun 15]. Available from: http://ci5.iarc.fr

220.	Dettori JR. Loss to follow-up. Evid Based Spine Care J. 2011 Feb;2(1):7–10.

221.	Izquierdo M, Jimeno JF, Lacuesta A. Spain: from immigration to emigration? BANCO DE ESPAÑA, Madrid [Internet]. 2015; Available from:

http://www.bde.es/f/webbde/SES/Secciones/Publicaciones/Public
acionesSeriadas/DocumentosTrabajo/15/Fich/dt1503e.pdf

222. Meulepas JM, Ronckers CM, Merks J, Weijerman ME, Lubin JH, Hauptmann M. Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes. Cancer Epidemiol Biomarkers Prev. 2015 Nov 23;cebp.0636.2015.

223. Meulepas JM, Ronckers CM, Smets AMJB, Nievelstein RAJ, Jahnen A, Lee C, et al. Leukemia and brain tumors among children after radiation exposure from CT scans: design and methodological opportunities of the Dutch Pediatric CT Study. Eur J Epidemiol. 2014 Apr;29(4):293–301.

224. Official Journal of the European Union. Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom [Internet]. Available from: https://ec.europa.eu/energy/sites/ener/files/documents/CELEX-32013L0059-EN-TXT.pdf