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Arvid Nordenskjöld

Karolinska Institutet

From DEPARTMENT OF MEDICINE, SOLNA
CLINICAL EPIDEMIOLOGICAL UNIT
Karolinska Institutet, Stockholm, Sweden

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# Long-term health hazards from diagnostic X-ray exposure
# THESIS FOR DOCTORAL DEGREE (Ph.D.)

By


## Arvid Nordenskjöld

*Principal Supervisor:*
Dr Magnus Kaijser
Karolinska Institutet
Department of Medicine, Solna
Division of Clinical Epidemiology Unit

*Co-supervisor(s):*
Fredrik Granath
Karolinska Institutet
Department of Medicine, Solna
Division of Clinical Epidemiology Unit

Peter Aspellin
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Radiology

*Opponent:*
Joachim Schüz
International Agency for Research on Cancer,
Lyon, France
Section of Environment and Radiation

*Examination Board:*
Lars Holmberg
Uppsala Universitet
Department of Surgical Sciences
King's College, London, United Kingdom
Faculty of Life Sciences and Medicine

Marie Lundell
Karolinska Institutet
Department of Oncology-Pathology

Johan Wikström
Uppsala Universitet
Department of Surgical Sciences, Radiology


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For Science!

# ABSTRACT

Medical imaging is an important function in the diagnosis and management of disease and its use have been increasing with technological advancements. A large part of medical imaging uses ionizing radiation as medium for imaging although it does pose potential risks to the patient. Computed Tomography (CT) uses a larger radiation dose than conventional X-rays and technological advances has led to more complex examinations increasing radiation doses even higher. The increased availability of CT machines has also facilitated the increased usage. This means that the population as a whole receives an increasing radiation dose and CT is now the most important contributor to radiation dose from medical examinations. The potential damage from ionizing radiation concerns long-term risks and includes cancer but other effects are known and includes cognitive difficulties amongst children.

In study I we investigated the relationship between pelvimetry and negative effects from ionizing radiation on cognitive function expressed as changes in school grades. We examined 1 536 children exposed to pelvimetry in utero and compared them to 44 530 unexposed children. We found no negative effect on school grades when controlling for sex, birth order, mother's education and birth position.

In study II and III we examined the risk of ionizing radiation from CT of the head. We gathered data from a radiological archive in Sweden and collected 26 370 patients. Patients were then matched on age, sex and residence to 4 controls, both cohorts were then linked to national registries in order to gather outcome data. The outcome in study II was meningioma and in study III glioma. We found no evidence of increased risk for neither meningioma nor glioma after CT examinations. However, information in national registries were not enough for exclusion of prevalent tumor at time of first CT or radiotherapy, referral notes were necessary in order to minimize bias.

Study IV is a method article and is a description of the international EPI-CT study that aims to investigate children who have had a CT examination. As part of EPI-CT we have collected RIS and PACS data from hospitals in order to assemble the Swedish cohort. This data will then be linked to national registries in order to investigate adverse effects from CT examinations.

In conclusion we have not found any negative result on school performance after pelvimetry nor have we found any increased risk for meningioma or glial tumors after CT examination of the head.

# LIST OF SCIENTIFIC PAPERS

This thesis is based on the following publications referred to in the text by Roman numerals.

I. Nordenskjöld AC, Palme M, Kaijser M. X-ray exposure in utero and school performance: a population-based study of X-ray pelvimetry. Clinical Radiology. 2015;70(8):830-4.

II. Nordenskjold AC, Bujila R, Aspelin P, Flodmark O, Kaijser M. Risk of Meningioma after CT of the Head. Radiology. 2017;285(2):568-75.

III. Nordenskjold AC, Bujila R, Aspelin P, Flodmark O, Kaijser M. Computed Tomography and Brain tumors- a population based matched cohort study (manuscript)

IV. Magda Bosch de B, Mark SP, Ausrele K, et al. EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT. Journal of Radiological Protection. 2015;35(3):611.

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ALARA | As Low As Reasonably Possible |
| CT | Computed tomography |
| DNA | Deoxyribonucleic acid |
| DSB | Double Stranded Break |
| DT | Datortomografi |
| eV | Electron volt |
| Gy | Gray |
| HR | Hazard Ratio |
| ICRP | International Commission on Radiological Protection |
| LSS | Life Span Study |
| LNT | Linear no-threshold |
| PACS | Picture Archiving and Communicating System |
| PIN | Personal Identification Number |
| RIS | Radiological Information System |
| SI | The international system of units |
| SSB | Single Stranded Break |
| Sv | Sievert |
| WR | Weighting Factor |

# 1 INTRODUCTION

As a radiologist on call, the question “How dangerous is this examination?” may be a dreaded one to get from a patient during lonely nights. The answer to the question is complex and depends not only on the nature of the examination, but also on the patient, the patient’s illness, as well as his or her understanding and perception of risks. An often used short and easy answer is that a single Computed Tomography (CT) scan is not very dangerous and that one can compare it to the risk from the increase in background radiation received from a flight over the Atlantic Ocean. Another way to answer the question is to put the examination in context with the risks from the disease under investigation. A more thorough discussion about what we know of the risks associated with radiation from diagnostic X-rays would have to bring up the atomic bombs over Hiroshima and Nagasaki – bad topics of discussion for any radiologist who wants to comfort his patients before an examination. The aim with the present thesis is to add new insight into risks conveyed though radiation from diagnostic radiology, and, hopefully, to make it more easy to give relevant advice to patients and referring doctors when deciding about x-ray examinations.

# 2 BACKGROUND

Medical X-ray imaging is an indispensable tool in the diagnosis and management of disease, and its importance has grown with technological advancement in particular with the arrival of CT-scanners in 1973.[1] However, since CT uses substantially larger amounts of ionizing radiation than are conveyed with conventional X-ray imaging, concerns over radiation related risks have been growing.[2] There are now serious concerns about the accompanied risks of exposing patients to large doses of ionizing radiation in medical imaging.

### 2.1.1 X-ray imaging

X-rays were first discovered by Wilhelm Röntgen in November 1895.[3, 4] While striving for brevity in writing, Röntgen named his discovery X-rays, and in the initial article he had already found a use for X-rays since he had managed to take an image of the bones in the hand of his wife (Image 1). X-rays were quickly adapted by the medical community and used for imaging of the body, primarily in projection radiography or conventional X-rays which produced two-dimensional images. When X-rays pass through the body different amounts of X-rays are absorbed depending on the composition of the body part. Bones absorbs more X-rays than softer tissues, and soft tissues absorb different amounts of radiation depending on fat and water content, and, finally, as in the lungs, air absorbs, very few X-rays. In radiography, the x-rays are captured by a film after having passed through the body. Another way of visualizing x-rays are with fluoroscopy. In fluoroscopy, the x-rays strike a fluorescent material after passing through the body, and the difference in attenuation can be visualized in real time on a screen.[5]

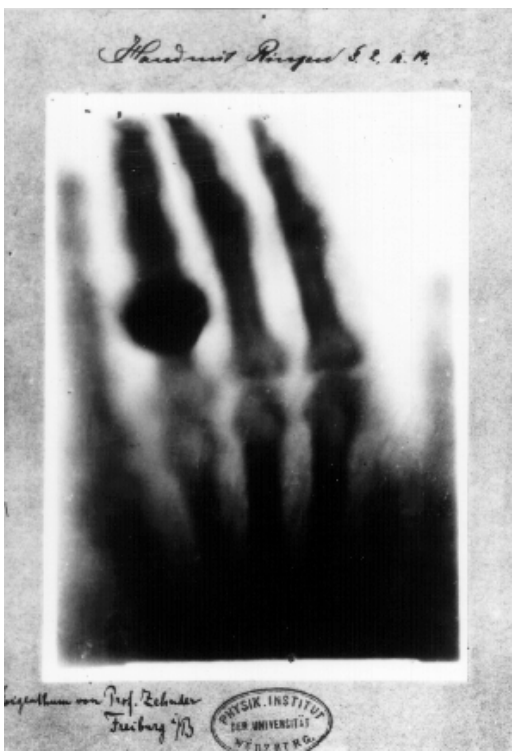


*Image 1- X-ray image of Anna Bertha Röntgen's hand*

Shortly after the discovery of X-rays, the dangers of ionizing radiation became apparent. Initially, skin erythema and loss of hair were the most apparent adverse effects from X-ray exposure while increased risks of cancer became visible among researchers investigating the properties of other sources of ionizing radiation.[6] Relatively early, it was speculated that an increased mortality among diagnostic radiologists could be attributed to exposure to X-rays.[7]

### 2.1.2 Invention of the CT scanner

The invention of CT in 1972 was a significant milestone for the medical community, and today CT-examinations are one of the cornerstones of a radiological department, both in managing emergency as well as elective diagnostics.[8, 9] The first commercially available CT scanner was the EMI-scanner developed by Hounsfield which became available for sale 1973. The EMI-scanner was limited to only examining the head and it was operated by positioning the patient's head in the center of the machine with the head surrounded by a water-filled plastic cap. The possibility of creating images of the brain was an important clinical innovation, even though each rotation of the X-ray tube creating just one slice of the head took more than 5 minutes to complete and the computer had to spend hours post processing in order to create the actual images.[9] Sweden in particular was an early adopter with the first EMI scanner installed in October 1973 at the Department of Neuroradiology at Karolinska Hospital.[10]

### 2.1.3 CT Technology

When performing a CT examination, the patient lies positioned on a bed with the X-ray tube and the detectors rotating around the patient, thus taking scans of one slice of the body from multiple angles. By combining data from the scans at different angles, it is possible to compute the attenuation coefficient – hence the term computed – of each part of the investigated slice, and cross-sectional images can be created that enable physicians to look at organs inside the body.[11]

CT technology was initially limited by the rotating X-ray tube and detectors being attached to the cables that supplied electricity. This changed in 1987 with the invention of the slip ring scanners which enabled continuously supplying electricity to tube and detectors, regardless of number of rotations. This allowed for the development of the helical, or spiral, CT technique.[12] In a helical CT, the patient is being moved through the CT gantry while the X-ray tube and detectors within the gantry rotate continuously. The technique has been developed with an increasing number of detectors and today, CT scanners with 64 detectors or more are able to capture the attenuation of the entire volume scanned, and to depict it in isometric cubes, or voxels, of 0.6 mm in length, thus allowing for creating images not only along the axial (head to feet) direction but also coronal (front to back) and sagittal (right to left) directions. Further improvements of the CT technique include use of intravenous contrast material[13], stereotaxic CT[14] and use of dynamic CT scanning[15] to mention just a few techniques developed at the Neuroradiologic Clinic at Karolinska Hospital.

The development of CT scanners and techniques has meant that CT examinations can be used to diagnose an increasing variety of diseases.[1] This translates not only into patients being exposed to an increasing number of examinations, but also to an increasing complexity of the examinations used for imaging of pathological processes. Both factors have led to increased radiation doses to patients from diagnostic X-rays.[2] Because of the known dangers X-rays pose to humans – most notably in form of an increased risk of cancer – this is a cause for concern. The number of CT scans performed each year have increased greatly throughout the world, with number of scans increasing 12-fold in the UK and more than 20-fold in the USA from the 1980s to 2007 and there more than 60 million scans in the USA in 2007.[16] The

estimated effective dose of ionizing radiation per individual in the US population increased from 3,6 mSv in the early 1980s to 6,2 mSv in 2006, and the majority of this increase was attributable to radiation from medical examinations.[17] Whereas medical radiation only attributed to 15% of the total radiation exposure in 1980, it had increased to nearly the half in 2006.[17, 18] In addition CT was attributed to half of the medical exposure to the patients.[17] Given the current usage of CT examinations, the proportion of radiation attributable to CT has likely increased even further. In Sweden a report on the usage of radiological examinations in 2005 found CT examinations contributing to 55-60% of the total radiation dose to the population, even though only about 12% of the total number of all radiological examinations were CT examinations (650 000 examinations out of 5,4 millions).[19] The report concludes that the total amount of CT examinations has doubled from 1995 to 2005.

## 2.2 RADIATION

Electromagnetic radiation covers a broad spectrum of different types of radiation and it can both be described as waves (with frequencies and wavelengths) and as photons with different energy content.[20] In the lower end of the electromagnetic spectrum there are radio waves and low frequency waves (wavelengths with up to 100 000 km). Microwaves have higher frequencies than radio waves. Light, (infrared, visible light and ultraviolet light) have higher frequencies than microwaves and visible light detectable by the human eye have wavelength between 380 and 760 nm.[21] X-rays and gamma rays have even higher frequencies with X-rays between 0.01 and 10 nm (corresponding to about 100 eV to 100 keV) and gamma rays from about 1 pm and smaller (corresponding to a few keV and up to several MeV).[20] The energy content of the radiation increases with decreasing wavelength, and the definition of ionizing radiation is that it carries enough energy to liberate electrons from atoms. As it passes through matter, ionizing radiation can interact with the atoms and it is through this interaction it can have adverse effects.

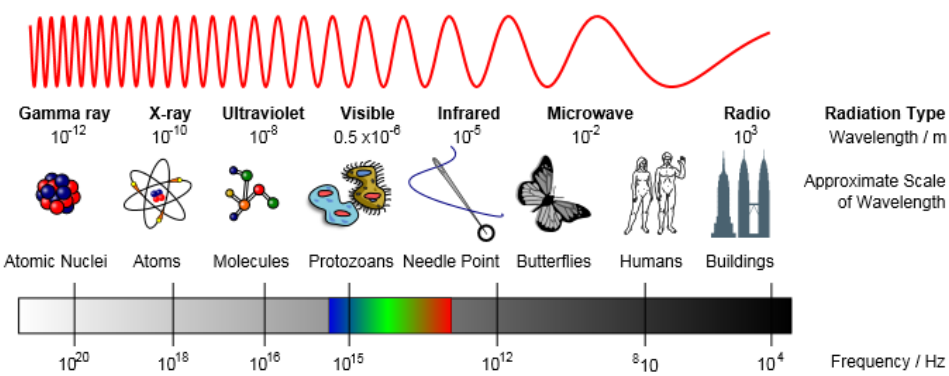


*Image 2-Electromagnetic spectrum*

### 2.2.1 Particle Radiation

Ionizing particle radiation consists of subatomic or atomic particles traveling with enough speed to be ionizing.[20] Common types of particle radiation are alpha (2 protons and 2 neutrons), beta (electrons or positrons) and single protons or neutrons. Particle radiation usually results from the radioactive decay of radioactive material. In the case of alpha and

beta radiation, it is highly ionizing but does not penetrate far into tissue. Alpha particles, for example, can be shielded from by a sheet of paper. Positrons, being the antiparticle of electrons, can interact directly with electrons and when they do, they annihilate each other and produce two gamma rays. This is the basis for Positron Emission Tomography (PET) examinations. Particle radiation is rarely a concern in the clinical setting as a source of ionizing radiation, but need to be considered in the case of research since many studies of ionizing radiation may not only be dealing with electromagnetic radiation but also particle radiation.

### 2.2.2 Electromagnetic radiation

The difference between X-rays and gamma rays are dependent not on the energy content of the photons but rather their source of origin. X-rays originate when electrons are rearranged within an atom or when an electron strikes a target (for example when an electrical current goes from anode to cathode in an X-ray tube) and gamma rays are emitted from radioactive decay of atomic nuclei. This means that there is some overlap in frequencies and thus energy between X-rays and gamma rays. Both X-rays and gamma rays have photons with enough energy to indirectly ionize molecules and atoms. The mechanism through which photons ionize differs depending on its energy content. Lower energetic photons ionize through photoelectric absorption while higher photons interact through the Compton effect and high energy photons, above, 5 MeV, ionize through the so called pair production.

The photoelectric effect occurs when a photon at energies below 100 keV ejects an electron from the shield of an atom and the photon is extinguished with most of its energy transferred to the electron as kinetic energy. The Compton effect occurs at photon energies higher than 100 keV where, once again, a photon ejects an electron, but when the photon has enough energy, it may also create a new secondary "scattered" photon with the energy left after having ejected the electron. This scattered photon can then also interact with other atoms and further ionize atoms through the Compton effect until a final photon is absorbed through photoelectric effect. The final ionizing type of interaction is the pair-production and is not used in medical imaging. It occurs when a photon above 1 MeV interacts with an atomic nucleus creating a pair consisting of one positron and one electron. These particles can then further ionize nearby molecules through other interactions.[22, 23]

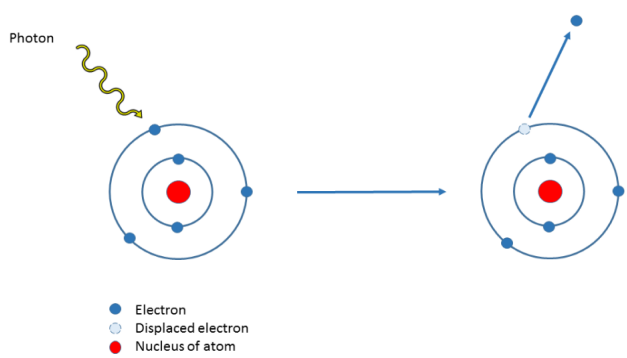


*Image 3- Photoelectric effect. Photon ejects electron from the atom and the photon is extinguished.*

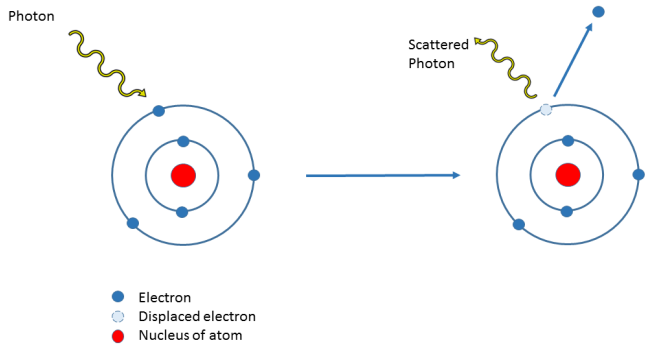


*Image 4- Compton effect. Photon ejects electron from atom along with a secondary scattered photon*

## 2.3 DOSIMETRY

There are several ways of measuring dose from ionizing radiation. The most commons are absorbed dose, equivalent dose and effective dose.

### 2.3.1 Absorbed dose

Absorbed dose is the amount of energy deposited by ionizing radiation into matter. The SI unit for absorbed dose is Gray (Gy) and 1 Gy is equal to 1 joule per kilogram. Absorbed dose is a physical quantity and does not take into consideration the sensitivity to radiation of different organs in the body. A legacy unit occasionally used is rad (rad), 1 rad is equal to 0.01 Gy.

### 2.3.2 Equivalent dose

In order to account of the different degrees to which radiation can ionize molecules, equivalent dose is used. Equivalent dose is calculated by multiplying the absorbed dose by a radiation weighting factor (WR) that depends on the type of ionizing radiation. In the case of X-rays, gamma and beta radiation the radiation weighting factor is 1. For particle radiation the WR is higher with alpha particles at 20, protons at 2 and neutrons at different values depending on the kinetic energy of the neutron.[24] For equivalent dose, the unit of measure is Sievert (Sv). An older non-SI unit is “roentgen equivalent of man” (rem) with 1 rem equal to 0.01 Sv.

### 2.3.3 Effective dose

Effective dose is a measurement of the stochastic risk of cancer and genetic effects from radiation. It is calculated by taking the equivalent dose (which takes different types of radiation into account) and multiplying this with an organ weighting factor. To calculate the effective dose for one radiation event like a CT examination, the effective doses for all exposed organs separate are summed into one estimate. Unfortunately, effective dose uses the same unit of measure as absorbed dose, Sv, adding extra confusion to the field of dosimetry.

The effective dose is greatly dependent on the organ weighting factor. The organ weighting factor is calculated by taking into account studies of adverse effects of radiation. Since the International Commission on Radiological Protection (ICRP) first started using effective dose in 1977,[25] the organ weighting factors have been updated, both by several organs initially not included in the list having been added and organ weighting factors being revised as new studies are incorporated into the calculations. The most radiosensitive organs are considered to be colon, lung and red bone marrow.[24]

## 2.4 BIOLOGICAL EFFECTS FROM IONIZING RADIATION

The biological effects from ionizing radiation can be divided into two groups, deterministic and stochastic. The deterministic effects have a direct effect and a threshold dose that needs to be exceeded for the damage to occur. Acute radiation sickness is deterministic and occurs at whole body radiation at more than 1 Gy. There are less severe deterministic effects like hair loss and skin erythema that can occur at lower doses, and although there are a few reported such incidents that have occurred in radiology departments today, these were more common early in the 1900s.[6]

When considering the risk of exposing a patient to a medical examination, it is most often the stochastic risks that are a concern. There is no threshold for stochastic effects and the effects are induction of cancer or other genetic effects. It is important to consider that even though the risk increases with dose, the severity of the effect does not, since a cancer either develops or it does not.

The damage from ionizing radiation can be caused through direct interaction with molecules in the cell, proteins, or DNA, but the most likely pathway of damage is through radiolysis where free radicals are created from water molecules ($H_2O$).[23] Water is the major component of cells (~80%), thus, a photon is more likely to hit a water molecule than anything else when traversing through tissue.[26] When a photon from an X-ray strikes a water molecule, it can create a multitude of various free radicals that are highly reactive and that cause negative effects when interacting with other nearby molecules in the cells. The higher the energy of the photon, the more free radicals are created. The damage to the cells is greatly dependent on where in the cell the free radicals are created.[27] If the photon traverse the nucleus of the cell, there is a possibility that changes occur in the DNA. Damage to DNA may take the form of either a damaged base, or single (SSB) or double (DSB) strand breaks as well as several of these together.[28] The cell have mechanisms to repair DNA damage, but these repair mechanisms are more efficient at repairing the damage in the case of base damage or a SSB, since in both these cases they have the second DNA strand as template when repairing. Cells also have different sensitivity to mutations depending on the phase of the cell cycle, with mitosis being the most sensitive. This is partly dependent on the amount of DNA accessible for interaction with ionizing radiation and partly dependent on the efficiency of the repair mechanisms during the cell cycle.[29]

Oxidative stress with the creation of free radicals is a normal occurrence in a cell, and it is usually associated with only minimal damage. When the free radicals are created from ionizing radiation, however, the pattern is slightly different. Free radicals created from ionizing radiation tend to be clustered with a lot of free radicals occurring tightly together.[23]

When this happens close to DNA, the damage may be much more severe compared to the same amount of free radicals created from other processes.

Histones are a group of proteins that package the DNA in the cell, when a DSB occurs in the DNA, the histone protein H2AX is phosphorylated and called γ-H2AX.[30] The effects of DNA damage after irradiation by CT examinations can be seen in an increase of γ-H2AX foci.[31] The formation of γ-H2AX foci makes it possible to assess DNA damage as well as their repair as the foci disappears. Furthermore it seems that the use of intravenous contrast media could further magnify the damage from ionizing radiation.[32]

### 2.4.1 Cancer

Cancer is considered a stochastic effect of radiation and it is the most dangerous somatic effect after exposure to doses below 1 Gy. Most of the data on cancer risks after radiation exposure is, however, gathered from studies of radiation doses above 100 mGy.[17, 24, 33] For lower doses, below 100 mGy, estimates are insecure.[34, 35] Carcinogenesis is a multistep process that can generally be divided into 4 steps, tumor initiation, tumor promotion, malignant conversion and tumor progression.[36] The changes necessary for cancer initiation usually occurs in just a few groups of regulatory genes that govern specific functions in the cell. That means that even though ionizing radiation may affect DNA, unless damage occurs in these specific groups of genes, cancer is unlikely to be initiated. An explanatory concept of these groups of genes is to divide them into gatekeeper and caretaker genes.[37] Gatekeeper genes can be said to protect the cell from cancer and if these genes are inactivated or their function removed in other ways, this often removes the normal function of cell growth. This, in turn, can increase the growth rate of the cell and thus increase the times DNA is copied, potentially increasing the risk of further errors in the DNA code. The caretaker group of genes deal with safeguarding the integrity of the genome such as repairing DNA, segregating the chromosomes properly, controlling the cell cycle and initiating apoptosis.

### 2.4.2 Cognition

Radiation has the potential to damage cells causing other adverse effects than cancer. The damage to the cell may cause impairment of function rather than unlimited growth or deterministic effects. If the cell DNA is damaged in such a way that some of its function is impaired this may have effects on the function of entire the organ. This concern is more important when considering growing cells since any DNA damage may be passed on to clones of the original cell and the damage to the organ may not be apparent until much later. Children are considered to be particularly vulnerable to this types of damages, and the sensitivity to radiation increases with lower age.[35]

### 2.4.3 Linear No-Threshold model

The linear no-threshold model (LNT) is a model used in radiation protection for modeling risks from ionizing radiation. The idea became wide-spread in the 1950s and it has since been the basis for thinking of radiation risk. LNT states that the risk for cancer from low dose radiation decreases linearly with the radiation dose. Furthermore, there is no threshold where the ionizing radiation does not pose any risk at all. The model is robust at higher doses above 1 Gy and even down to lower doses to about 100 mGy. At doses below 100 mGy, there is,

however, some debate. The model is still considered the most likely to correctly describe the dose-risk association, but due to the large studies needed to assess the risk after exposure to small doses of radiation, the data is more uncertain, and other possible models have been suggested.[38, 39] Alternative models of the dose risk association below 100 mGy include that risks could be disproportionally higher than the same risk increase at higher doses, supra-linearity. Alternatively, there could be biological mechanisms that are more effective at protecting the organism from radiation at lower doses, thus making risk lower than expected from the LNT model, linear-quadratic model. There is also the possibility that there could be a dose threshold below which there is no cancer risk at all. It has even been suggested that a low dose of radiation could trigger biological responses that are so beneficial that the radiation exposure leads not to an increase but to a decrease in the risk of cancer (also known as hormesis).[40]

A consequence of LNT as current model for risk from ionizing radiation is the concept of "As Low As Reasonable Achievable" (ALARA) in medical imaging, meaning that the goal is to use as little radiation as possible to still achieve diagnostic images.

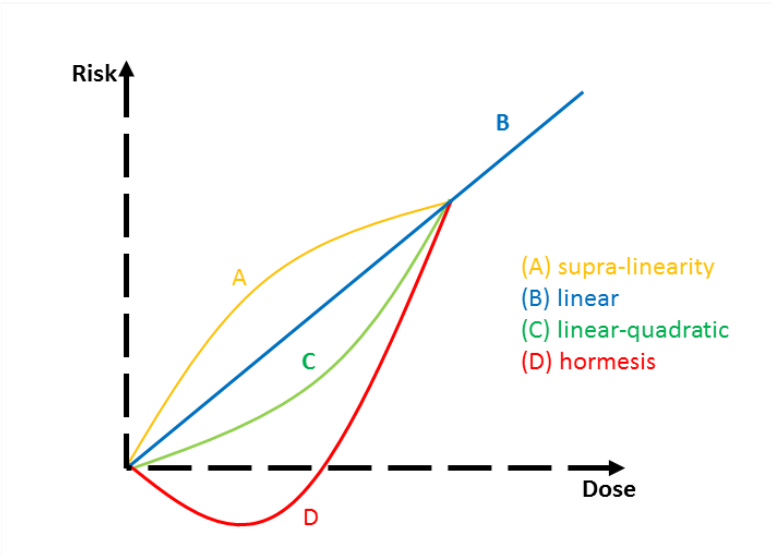


*Image 5- Different assumptions on the extrapolation of the cancer risk vs. radiation dose to low-dose levels, given a known risk at a high dose: (A) supra-linearity, (B) linear, (C) linear-quadratic, (D) hormesis*

## 2.5 EPIDEMIOLOGICAL STUDIES

Studies of the risk from ionizing radiation started fairly early in the 1900s when early health effects became apparent among radiation researchers and health personnel. Most of the early health effects were different types of deterministic effects, predominantly skin erythema and hair loss, but more severe damages were also reported.[6] The carcinogenic effects of ionizing radiation among radiation workers also became apparent rather early.[7] The knowledge of the risks of ionizing radiation increased after the second world war with a large number of animal studies[41] as well as studies appearing from the LSS cohort of the atomic bomb survivors in Hiroshima and Nagasaki.[42, 43] Although experimental studies have been performed on

animals and human cells, most of the studies on human individuals have been epidemiological studies on exposure related to medical exposure, work or accidental exposure (atomic bombs or nuclear accidents). Medical exposure studies can be divided into either exposure from radiotherapy or from diagnostic imaging, where radiotherapy uses higher doses than diagnostic imaging. Recently, there have been a few studies where cancer risks after exposure to radiation from CT examination has been assessed through various patient registries.[44-46]

### 2.5.1 Life Span Study

The Life Span Study (LSS) of the Japanese Atomic Bomb survivor cohort [34, 47-49] still remains the largest contributor to our understanding of the risk of ionizing radiation to humans.

Hiroshima was attacked by atomic bombs on August 6 and Nagasaki on August 9, 1945. In the immediate attack approximately 300 000 persons died, and the survivors received ionizing radiation in the form of gamma rays and neutrons. Shortly thereafter, in November 26, 1946, the ABCC (Atomic Bomb Casualty Commission) was established by President Truman in order to study the effect of radiation on the survivors of the atomic bombs. The ABCC was later reorganized into the RERF (Radiation Effects Research Foundation) in 1975. The initial of these investigative bodies were primarily focused on direct radiation damages as well as potential genetic effects from the radiation on the survivors and their descendants. It was also evident that it was possible to study cancer and mortality effects from the radiation exposure. Therefore, the LSS was established in 1950 with about 120 000 survivors. There were other cohorts established as well, notably the "in utero" cohort of 3 600 subjects, as well as the children cohort of 77 000 individuals, with overlap between the cohorts. The LSS cohort has multiple strengths. Apart from its large size, it contains individuals of both sexes as well as from all age groups. The population was also basically healthy at time of inclusion, and it was not selected based on any risk factors for cancer. Furthermore, the dosimetry of the cohort is extensive and has been updated several times with further improvements. Thus, the cohort exhibits a large variety of doses. Follow-up is virtually complete with regard to mortality, and it has very good coverage for cancer incidence. Finally, it has more than 60 years of follow-up time. Data on cancer are gathered by the cancer registries in Hiroshima and Nagasaki and includes data on non-fatal cancers as well as some benign tumors, and it contains histology data on the tumors. There are some limitations of the cohort, though, since data wasn't collected for leukemia before 1950 and for solid cancers before 1958. Cancer data is also limited to residents of the Hiroshima and Nagasaki areas, and thus lacking information on cancer on those who moved out of the catchment area.[47]

The primary endpoint from the LSS cohort has been mortality and cancer incidence, but some other health effects have also been studied. A subset of the LSS cohort known as the Adult Health Study (AHS) comprising 22 000 subjects have been used to evaluate the effects of ionizing radiation on both specific diseases as well as organs.[50, 51] Children in utero as well as children born to atomic survivors have been studied for both mental and physical development, and genetic studies have been performed on children conceived after the atomic bomb explosion.[52-55]

There have been numerous studies and updates on the cohort since the first reports.[56] Dosimetry was first attempted in the T65D dosimetry[57] and was then updated, first in 1986, DS86[58, 59] and again in 2002, DS02.[60] Dosimetry has taken into account the location of each individual at the time of the atomic bomb explosions as well as possible shielding of the person in or outside of buildings, and on which direction the person was facing. Dosimetry has also taken into account that both neutron and gamma rays were produced from the atomic bombs. Other updates regarding mortality and cancer on the surviving members of the cohort has also produced new articles with the latest reports regarding the time periods 1958-2009.[48]

### 2.5.2 Medical Radiation Treatment and Diagnostics

Radiation has been used in diagnostics but also as treatment for several diseases. In both cases there have been efforts to gather these patients into cohorts for studies. Radiotherapy is used both to treat malignant as well as benign diseases. Treatment can often be substantial, 40-60 Gy to the region of interest but surrounding tissues receives lower doses and parts of the body can receive much lower doses, in the region of 100 mGy. There are some differences from the atomic bomb survivors in that patients may have been ill and the disease may not be completely unrelated to the outcome studied. Patients subjected to radiotherapy because of a malignant disease may also have a different sensitivity to radiation than healthy controls and the heterogeneous application of radiation exposure compared to uniform whole body exposure may make comparisons difficult. Some treatments used external radiation beams, but other types of radiation, such as radioactive implant have also been used.

Patients with several different malign diseases that used radiotherapy for treatment have been gathered into large cohorts. Cohorts are based on treatment for uterine cervix cancer,[61-65] uterine corpus,[64] Hodgkin's disease,[66-71] breast cancer survivors,[72] thyroid cancer,[73, 74]. There are also several studies on childhood cancer survivors.[75-77]

In addition to studies of radiotherapy there have also been several cohort studies of patients that have received radiotherapy for benign diseases. These include uterine bleeding,[78-80] ankylosing spondylitis,[81, 82] treatment for pain in joints,[83] thyrotoxicosis therapy.[84-86] There have also been cohorts gathered from children who have been treated for benign diseases with radiotherapy. Radiation was used in treatment for tinea capitis in several countries during the 1900s and follow-up studies on cohorts exists in both Israel and USA.[87-92] There are also large cohorts of patients in Sweden and France that were treated with radiation for skin hemangioma.[93, 94]

In addition to studies where patients were treated for diseases there are also some studies where the subjects' exposure was diagnostic examinations. There are several cohorts of patients with tuberculosis that had frequent fluoroscopy examinations.[95-98] There are a few case-control studies in USA and Sweden with diagnostic examination as exposure.[99-102] In Sweden there is also several cohorts that were exposed to $^{131}$I for diagnostic purposes that have been studied as well.[103-106]

There are also a few studies on children having received diagnostic examinations. One is a cohort of children with scoliosis evaluated for breast cancer.[107] The Oxfords Survey of Childhood Cancer (OSCC) is a case-control study begun in 1955 examining the radiation exposure among children with cancer and included prenatal exposure.[108-112] A cohort in USA was also investigated for prenatal exposure.[113] In Sweden a case-control study concerning brain tumors did not find any association.[114] In a Swedish study of patients after diagnostic $^{131}$I exposure also contained a small number of children.[106]

### 2.5.3 Occupational Exposure to Radiation

There is a number of studies on workers with exposure to ionizing radiation and some of the earliest studies on risks of ionizing radiation was of radiation workers.[7, 115] They all suffer from similar problems when comparing them to the type of exposure produced by medical diagnostic examinations. The type of ionizing radiation can vary greatly, with both particle and electromagnetic radiation. Usually the exposure is protracted and low-level, very different compared to exposure in diagnostic imaging. However the studies can be large, workers have been employed in nuclear industries since the 1940s and by law their doses must be measured. There are several national cohorts that have been combined into larger cohorts, including INWORKS showing slight risk increases in leukemia and solid tumors.[116-120] Another large cohort is the workers at the Mayak plutonium facility near the Techa river that caused mayor radioactive contamination.[121] The workers of the Mayak facility has been studied numerous times with radiation exposure often high, mean doses near 1 Gy.[122] Both adults as well as children exposed in utero has been studied.[123-130] Airline crews are exposed to cosmic radiation and could potentially develop adverse effects, even though the cumulative dose over 20-30 years is unlikely to be larger than 200 mGy.[131, 132] Radiologists as well as radiological technologists have been studied as well, although initial studies showed some risk increase this seems to have decreased in later studies.[7, 133-136]

### 2.5.4 Radiation exposure from environment

Radiation exposure from the environment is an additional source to the population. Many studies have considered if nuclear facilities have an effect on the nearby population but contamination from nuclear facilities and atomic bomb tests have also been examined.[137-141] The Chernobyl nuclear plant explosion in 1986 and the resulting fallout in many countries, particular in the Nordic countries led to follow-up studies in many countries.[142-144] Background radiation can vary between regions for several reasons and there are a few studies on areas with a high background radiation.[145-147] Studies on this type of exposure are generally more interesting from a perspective of radiation protection of the population rather than from a medical examination standpoint. Individual doses are rarely possible to measure and in many cases migration as well as other risk factors are often difficult to account for.

### 2.5.5 Register based studies on Computed Tomography

Since CT was first established in 1973, it is possible to study patients examined with for potential health hazards with almost 50 years of follow-up. Recently three large

retrospectively cohorts have been established. A large cohort of about 200 000 patients under age of 22 in United Kingdom was examined for health risks after CT examinations and calculated received dose to red bone marrow and brain.[44, 148, 149] The risk of leukemia was positively correlated with radiation dose to the red bone marrow and similarly was risk of brain cancer correlated with dose to the brain. In addition relative risk was calculated comparing those receiving less than 5 mGy to other dose categories. For example the relative risk of leukemia was found to be 3.18 (95% CI 1.46 to 6.94) for those receiving at least 30 mGy or less than 5 mGy and relative risk of brain tumors 3.32 (95% CI 1.84 to 6.42) when comparing the group at least 50 mGy to those with less than 5 mGy. A second study of almost 11 million people in Australia identified those exposed to a CT examination. They then compared the 680 000 exposed patients to the other 10 million unexposed patients and found an overall cancer incidence risk ratio of 1.24 (95% CI 1.20 to 1.29) for the exposed patients. There are some concerns over reverse causality, of particular concern was that the risk of most cancers increased except for breast cancer and leukemia, malignancies known to be sensitive to ionizing radiation.[45] Finally the third CT linkage study is from Taiwan examining 24 000 children who underwent CT of the head and for risk of subsequent brain tumors.[46] They found a significant increase of benign brain tumors Hazard Ratio (HR) 2.97 (95% CI 1.49 to 5.93) between the exposed cohort and a matched unexposed cohort. Oddly enough, the risk was highest shortly after a 2 year latency period after the initial CT, and the risk for benign brain tumors then decreased. This could indicate reverse causality. Two smaller cohorts have been published from France and Germany and both cohorts form part of the EPI-CT cohort.[150, 151] Both studies are fairly small and with short follow-up time. Although both studies found a slight positive correlation between CT and leukemia and CNS tumors the result were not significant with broad confidence intervals.

## 2.6 ADVERSE HEALTH EFFECTS FROM RADIATION

### 2.6.1 Cancer and Mortality

The latest report from the LSS-cohort is the third report of cancer incidence in the cohort, and it considers both overall cancer risk from ionizing radiation as well as site specific cancer risk.[48] The total follow-up period for the cohort is 52 years (although 64 years after the atomic bomb explosions). As the cohort is growing older, only 36% of the initial cohort is still alive. For the latest report, even though it is only 11 more years of follow-up after the previous report, the new cancers diagnosed in this time period account for 26% of the total amount of cancers diagnosed in the group (22 538 solid cancers).[35] The most common cancer was stomach cancer and other common sites were cancers of liver, breast, lung and colon.
Overall, for all cancers and for both sexes the excess relative risk (ERR) per Gy of absorbed ionizing radiation was 0.50 (95% CI 0.42 to 0.59). Taking into account age at exposure shows decreasing risk with 19% for each decade older the subjects were at the time of exposure. For CNS tumors non-significant increases were found for both meningioma at 0.64 ERR/Sv (95% CI: -0.01 to 1.8) and glioma 0.56 ERR/Sv (95% CI -0.2 to 2.0).[35]

Irradiation for tinea capitis was common in the early 1900s, these patients have been followed for later adverse effects. A large cohort in Israel of 20 000 patients has been followed over a long period of time showing significant increases for both meningioma ERR/Gy of 4.63

(95% CI 2.43-9.12) and malign brain tumors ERR/Gy 1.98 (95% CI 0.73-4.69).[87, 89] The patients received high doses, in the range of 1 to 6 Gy. A Swedish study of two cohorts treated with radiation for skin hemangioma, received lower doses, with mean dose of 700 mGy also found increases in brain tumors with ERR/Gy of 2.7 (95% CI 1.0 to 5.6) for the whole population.[152]

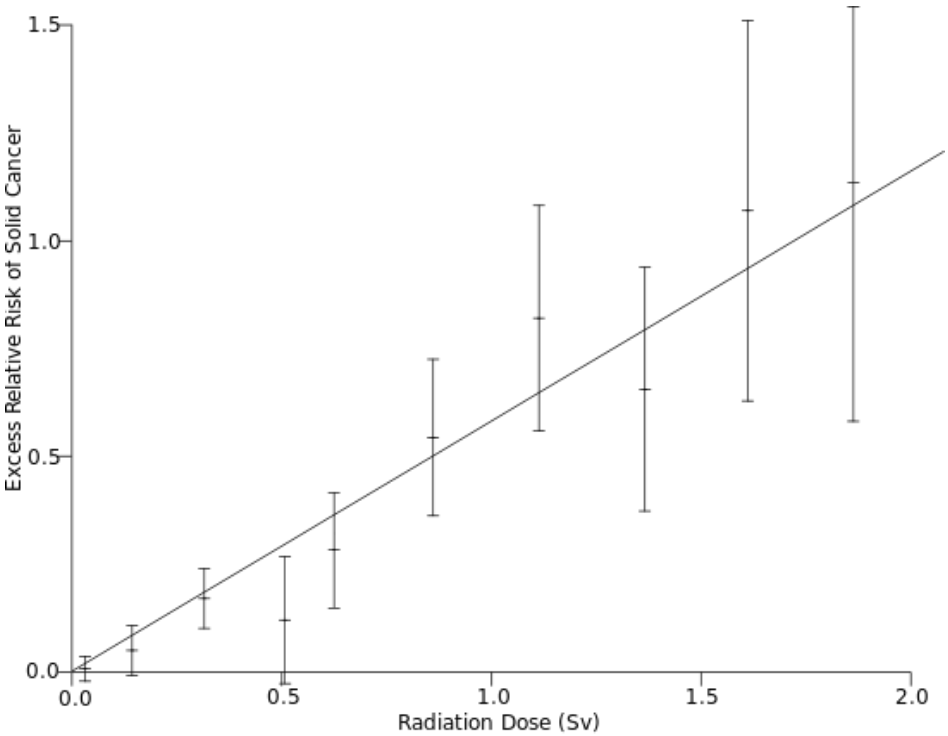


*Image 6- Excess relative risk of solid cancer from radiation dose for Atomic bomb survivors[153]*

### 2.6.2 Leukemia

An increased risk of leukemia amongst radiologist was reported as early as 1944.[7] Studies on the survivors of atomic bomb explosions of Hiroshima and Nagasaki further strengthened this finding as the studies progressed.[42, 154, 155] The LSS studies on leukemia have shown that younger individuals are more sensitive and that most of the leukemia cases appear early after the exposure, peaking after 6 to 8 years, and then taper off to a slight persistent risk increase even after 50 years of follow-up.[154] The overall risk for all leukemia other than chronic lymphatic leukemia (CLL) and Acute T-cell leukemia (ATL) (neither seems strongly correlated with radiation[154]) is about 4.66 (95% CI 4.07 to 6.88) at 1 Sv and depending on age at and time since exposure. One effect of this is that the risk is three times higher at 1 Sv than 0.1 Sv.[44, 156] Furthermore the effect of radiation seems to be most pronounced in certain types of leukemia notably acute lymphatic leukemia (ALL) and chronic myeloid leukemia (CML). Other types of leukemia show slightly less increase of. Studies of a population near the heavily polluted Techa River in Russia also show increased risk of leukemia with 4.9 relative risk increase per Gy (95% CI 1.6 to 14.3).[123, 124] Other exposures includes population living near nuclear facilities[157] as well at workers at nuclear facilities without

finding any increased risk.[116] Studies of children exposed to medical examinations in utero show slight increase in relative risk but they lack statistical significance.[158, 159] There are a few other studies with radiation exposure and leukemia as outcome. A study on cervix cancer survivors with a mean dose of 7 Gy showed a slight increase in leukemia with ERR/Gy 0.88.[61] The Israeli tinea capitis cohort has also been examined for leukemia mortality showing a slight increase at 2.3 (95% CI 1.0 to 5.6).[88] The Swedish patients treated for skin hemangioma did not show any increase in leukemia.[160]

### 2.6.3 Cognition

The risk of adverse effects of ionizing radiation exposure to the fetus was investigated as early as during the 1920s with studies finding the possibility of severe cognitive damage caused by ionizing radiation.[161] The children that were in utero at the time of the atomic bomb explosion were followed and during the 1950s were examined for possible cognitive effects. Initially this was defined as severe mental retardation,[162] being unable to perform simple arithmetic or form coherent sentences and manage personal affairs and or requiring institutionalization. Other outcomes include head size[163], IQ[164], school grades[165] as well as history of seizures.[166] Later, some children were examined with Magnetic Resonance Imaging (MRI).[167]
Some general conclusions of these studies can be drawn:[168] there is a period where the fetus is more sensitive to ionizing radiation during week 8-15 of the pregnancy. Most of the cases of mental retardation were found to have been irradiated during this period. To a lesser extent children, exposed in utero in gestational age 16-25 weeks also showed a sensitivity to radiation. The risks from ionizing radiation increased with increasing dose and they were statistically significant for all studies at radiation doses above 500 mGy. A negative effect on both school performance and IQ was shown for lower doses, however, for doses below 100 mGy the bounds of the confidence intervals were broader and not statistically significant. Furthermore, there was a suggestion of a threshold at 0.55 Gy (95% CI 0.31 to 9.61) for the most sensitive group exposed between 8-15 weeks.[169] For school performance and IQ, no such threshold was found although both these studies contain fewer subjects.[164, 165] Cell death is a possible mechanism for these effects but MRI examinations indicate that another possible mechanism for the lower cognitive function is that the migration of neuronal cells mostly occur between the 12th and 24$^{th}$ week of gestation which is similar to the time period where the fetuses brain seems most vulnerable to radiation.[170]

There have been a few other studies on prenatally irradiated children. One study on 544 children irradiated in utero from the Chernobyl accident showed decrease of IQ compared to a control group.[171] A study on children living in Sweden exposed in utero to fallout radiation from the Chernobyl nuclear plant accident found a significant decrease in school performance compared to children born in areas with less radiation from nuclear fallout.[172] This finding suggests that neurological effects of radiation may be more subtle than what was shown in the In Utero cohort from Hiroshima and Nagasaki. Similarly, a study on Norwegian children exposed in utero to the fallout from Chernobyl also found a negative effect on IQ for those exposed during the sensitive week 8-15.[173]

There are also some cohorts where the radiation exposure occurred postnatally. In one study from Israel there were 20 000 children treated with X-rays for tinea capitis.[174] Although

individual doses were not available, the estimated average dose was 1.3 Gy, the study found differences between the irradiated children and their controls in both school performance and IQ tests. The exposed cohort were less likely to complete elementary school and also had slightly lower score at the army IQ test-score compared to the unexposed group. In a small study of cognitive abilities of patients treated with radiation for leukemia showed a majority of patients with learning disabilities, the dose in the cohort tended to be high, 18-24 Gy.[175] A study on 3 094 children irradiated as infants before 18 months of age for skin hemangioma studied school graduation as well as psychological tests at 18 years of age.[176] Doses were low with an average dose of 52 mGy and found that children receiving higher doses (>100 mGy) to the brain were about half as likely to graduate from secondary school compared to children whose brains did not receive any radiation. A follow-up study on other patients in the Swedish skin hemangioma cohorts did not find any significant cognitive negative effect of radiation to the head.[177]

# 3 METHODS

Sweden uses a personal identification number (PIN) as the Swedish national identification number for every resident in Sweden. This PIN is used in contact with hospitals and other health services as well as with other governmental services. The government also uses the PIN when collecting health data in health registries which can be used for both statistics as well as made available for health research.[178]

## 3.1 DATA SOURCES

### 3.1.1 The National Patient Register

The National patient registry is maintained by the Swedish National Board of Health and welfare and provides data on patient treatment. It started in 1964 with gradual coverage of parts of Sweden and since 1987 it covers all regions of Sweden for in-hospital care. Outpatient treatment were added in 2001. It contains data on treatment as well as hospital discharge codes according to the ICD-classification, and for most diseases the data have a high validity.[179]

### 3.1.2 Swedish Cancer Register

Swedish National Board of Health and welfare is responsible for gathering data on cancer incidence and survival and maintains the Swedish Cancer register since 1958 that contains data on diagnosed cancers for research purpose and statistics. It covers the whole of the population in Sweden and has a high completeness of data.[180]

### 3.1.3 Total Population Register

The total population registry was started in 1968 and today it's maintained by Statistics Sweden (SCB). It contains data on residents in Sweden.[181] The register contains data on life events such as birth, death, emigration, immigration, marital status, as well as family relationships. It also registers address and migration within Sweden.

### 3.1.4 Multi-Generation Register

The Swedish Multi-generation register is maintained by Statistics Sweden and contains information on all individuals born in Sweden since 1932 as well as all people alive in Sweden 1961. The register contains data on individual's parents as well as their children.[182].

### 3.1.5 Radiological Information System

The Radiological Information System (RIS) is a type of medical journal for radiological departments adjusted to their practices. It's used for receiving requests for examinations, planning and scheduling examinations as well as reporting findings. In Sweden they are usually based on PIN, and it is therefore easy to collect data from RIS and link this information to other registers. Apart from PIN, important data in RIS includes type of examination and date of examination. The use of computerized RIS in Sweden started in the 1980-ies with the region of Östergötland one of the first in Sweden. Gradually the rest of the regions were also converted to using digital RIS with the latest converting in the late 2000s.

### 3.1.6 PACS

Picture archiving and communications system (PACS) is used in radiological departments for storing and viewing the images of radiological examinations.[183] The images are sent from radiological equipment after the examinations is performed and the RIS system is then able to retrieve the images for the radiologist for evaluation. PACS contains not only the images but also information about the examination in DICOM (Digital Imaging and Communications in Medicine) headers attached to each image that may include data on the radiation exposure used in the examination. For a CT examination information about radiation is stored in each slice of the original examination. Thus it is possible to retrieve data on radiation from PACS to reconstruct dose to the patient. [184]

## 3.2 STUDY I

Study I was a cohort study of children born in the 1980s in the region of Östergötland in Sweden. The cohort consisted of one group that was exposed to a pelvimetric examination in utero and one unexposed group. We gathered data from a RIS in Östergötland that encompassed all major radiological departments. The RIS was digitalized in the 1980s and we gathered data on radiological examinations of the abdomen on all women, but included only pelvimetry. All women who had a pelvimetry were then linked to the Multi-Generation register in order to find any children born within 9 months of that examination, as well as any siblings. Primary school grades were gathered for all children in Östergötland from the Nationella Betygsdatabasen (BEDA). Additional data on emigration, parental income and education levels were gathered from Total population register. Lacking individual dosimetry in RIS data, doses were instead estimated to be 1 to 3 mSv based on standard practices during the time period.[185]

## 3.3 STUDY II AND III

At the Neuroradiologic Department in the Karolinska Hospital in Stockholm they had a radiological archive with stored carbon copies of original referral notes for CT examinations. These carbon copies contained PIN as well as type and date of examination and the report from the radiologist, clinical history was usually available as well. Data from the archive was abstracted into a database where additional data on Gamma Knife treatment was added. The database was then prepared for linkage and Statistics Sweden selected four unexposed controls matched on age, sex and residency at time of first examination. Both groups were then linked to the Cancer Register and National Patient Register for outcome data. Outcome data was based on ICD-codes as well as histopathology codes in the Cancer register. ICD revision 7 were used with codes to identify brain tumors (193.0, 193.1 193.2, 193.8, 193.9). In addition histopathological codes C24 were used to identify the type of tumor. In study 2 histopathological codes 461, 463 and 466 for meningioma was used. In study 3 histopathological codes 475, 476, 481 and 485 was used for glial tumors. The National patient register was examined for possible confounding diseases: neurofibromatosis type 1 and 2 (NF1 and NF2) and tuberous sclerosis since these diagnoses were possible confounders.[186] The radiological archive contained additional clinical data that was not abstracted into the database. For all cases in the exposed cohort the data on both referral notes and radiological report was also examined for history of tumor, cancer or previous radiation

therapy. Individual dosimetry was not possible but it was possible to identify the type of scanner used for the examination as well as the number of series performed. The Neuroradiologic department initially installed the EMI Mark I scanner and later the GE 8800 scanner. Dosimetry was based on historical exposure data in the literature while taking the number of series into account.[187]

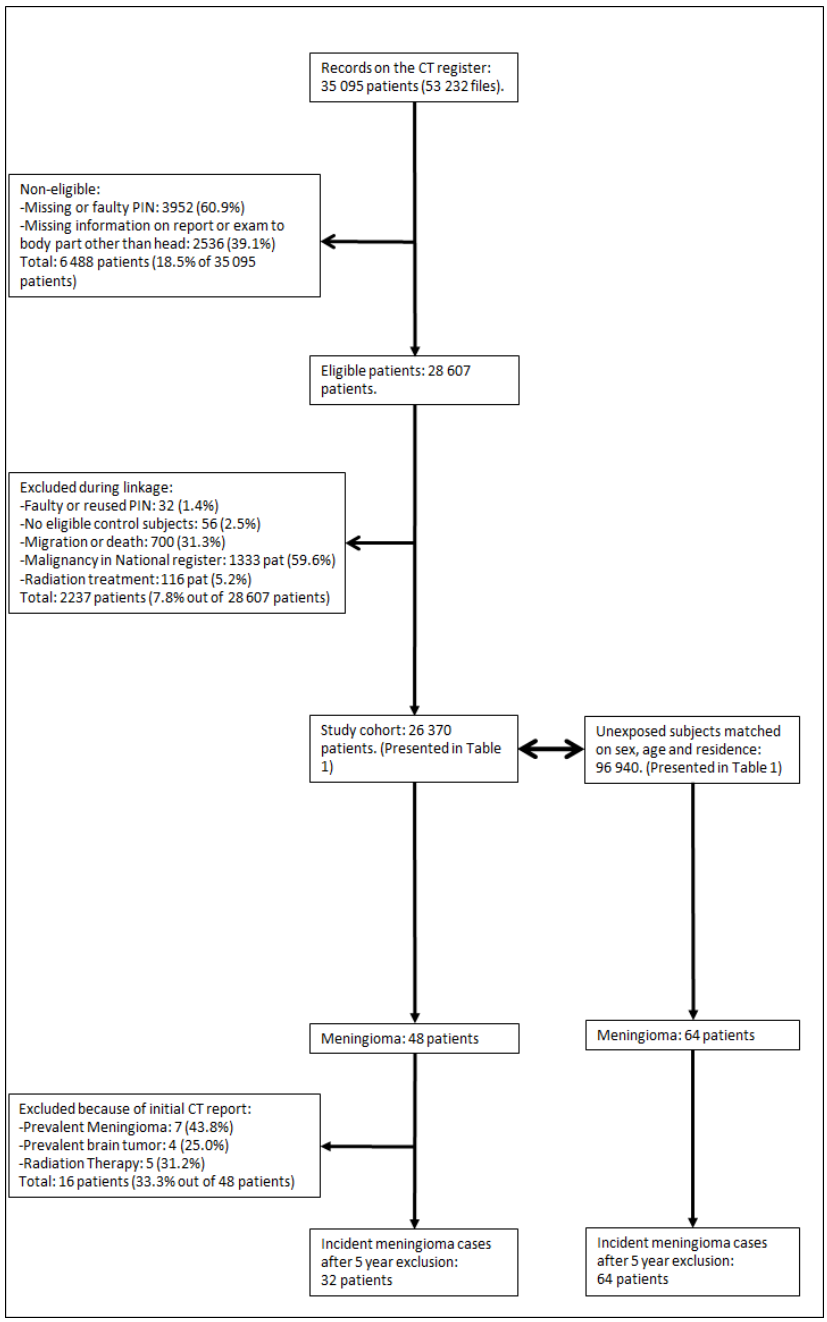


*Image 7- Selection of cohort in Study II*

## 3.4 STUDY IV

Study IV is an article describing the method of how the data was collected and the assembly of the cohorts was made, analyzes of outcome data has yet to be performed.

EPI-CT is an international study aimed at gathering a sufficient large cohort to examine if the ionizing radiation used in radiological examinations causes cancer. In order to collect one million exposed children several countries are contributing study subjects. The majority of data comes from United Kingdom with a previously described cohort[44] of 320 000 patients and Sweden contributing more than of 100 000 patients. In addition to Sweden and the United Kingdom a further seven countries will provide data: Belgium, Denmark, France, Germany, Netherlands, Norway and Spain. The Swedish data is principally RIS-data collected from four major regions in Sweden; Stockholm, Göteborg, Skåne, Östergötland. The regions all had RIS-data collected from several hospitals and any individual examined with a CT examination before 18 years of age was selected and information on all examinations for those individuals both as children and adults was collected. Additionally PACS-data were collected in Stockholm for dosimetry. Outcome data was collected from the Cancer Register as well as the National Patient Register and some socioeconomic data was collected from the Total Population Register. The initial primary outcome diagnosis will be mortality with leukemia also studied, since previous epidemiological studies indicate this malignancy having the lowest incubation period. The article describes the general method used in order to construct the study population.

## 3.5 STATISTICAL ANALYSIS

For statistical analysis of data Study 1 used linear regression. Linear regression is used where there is one outcome and one or more independent variables. Simple linear regression is used where there is only one independent variable and multiple linear regression where there are multiple independent variables. The analysis were performed on STATA (v10, StataCorp, College Station, TX).

The data was analyzed with final grades of primary school expressed in centiles as outcome variable, and pelvimetric examination during pregnancy as exposure. The statistical analysis was performed with linear regression with school grades as outcome variable and sex, pelvimetry, birth position, birth order, maternal income, and maternal education as independent variables. In both the simple and multiple linear regression analysis, data were stratified on birth year. A separate analysis restricted to the exposed children and their siblings was also performed. In this analysis, sex, pelvimetry, birth order, and birth position were used as independent variables. As in the other analyses, data was stratified on birth year in both the simple and multiple analysis. In cases where individuals had missing data in one category, they were omitted from analysis.

In Study II and III Cox proportional hazard regression was used for the statistical analysis.[188] Cox proportional hazard regression is a type of survival model. Survival models follow subjects over time until an event of interest occurs. Cox proportional hazard regression (HR) models the ratio between two different hazard rates.

The relative risk of a CT examination were calculated with a proportional hazard model with meningioma or brain tumors as dependent outcome variable and CT-exposure or radiation dose as independent variables. In addition HR was calculated in two year intervals after the first CT examination. Analyses were stratified on the basis of sex, age and year of inclusion in the study in 5 year intervals. The analysis was performed on SAS (v9.4, SAS Institute, Cary, NC).

Study IV describes the EPI-CT cohort as well as the Swedish part of the cohort in regards to how the data was collected and assembled. No statistical analysis on outcomes has yet been performed in Study IV. Analysis will be focused on dose-response between radiation exposure from CT examinations and mortality in both cancer and overall mortality. Outcomes in the study population will then be compared to Standardized Mortality Ratios (SMR), calculated as ratio of observed and expected number of deaths based on national reference levels.

## 3.6 ETHICAL CONSIDERATIONS

Although the risks of radiation in doses above 100 mGy are well established there is still uncertainty of the risks below this level. Since many radiological examinations have doses below 100 mGy there is still a need for research in this area.

In all of the four studies performed, informed consent was waived after approval from the local ethics board. There are several reasons why the studies was performed without informed consent. All studies consists of patients and controls where the data was gathered from archives. In study II and III the long follow-up time combined with the fact that many examined patients were older as well as likely to have a serious disease. It is thus probable that a significant proportion of patients would be deceased, making it impossible to secure informed consent in the same way between alive and deceased, therefore introducing significant bias in those studies. In study I and IV, although most patients would likely be alive, since their examinations were performed in a later time period than study II and III it would still be difficult to collect consent without introducing bias.

The studies use clinical data received from hospitals with personal information. The data has been stored and handled by a small number of people during research within closed facilities. The data analysis after linkage to national registries was performed on anonymized data where name and PIN were removed.

# 4 RESULTS

## 4.1 STUDY I

The study cohort consisted of a total of 46 066 children, with 1 536 children exposed to a pelvimetric examination in utero with their 1 095 siblings. In addition there were 43 435 unexposed children. In the initial crude analysis we found that being exposed to a pelvimetry increased the grades by 3 points (95 % CI, 1.5 to 4.6). However with a multiple regression analysis including potential risk factors such as sex, birth order, the mother's highest graduation level and birth position the estimate decreased. Instead we found a non-significant increase in grades at 1.4 (95 % CI, -0.1 to 2.8). A separate analysis was performed comparing only the exposed children with their siblings. Neither simple nor multiple regression analysis showed any significant negative effect on grades after radiation exposure.

| | | Simple analysis[1] point estimate (95 % CI) | Multiple analysis[2] point estimate (95 % CI) |
|---|---|---|---|
| Pelvimetry | | | |
| | Yes | 3.0 (1.5 to 4.6) | 1.4 (-0.1 to 2.8) |
| | No | 0 (ref) | 0 (ref) |

| | | Sibling Analysis Simple analysis[1] point estimate (95 % CI) | Multiple analysis[3] point estimate (95 % CI) |
|---|---|---|---|
| Pelvimetry | | | |
| | Yes | 1.7 (-0.5 to 3.9) | 1.5 (-0.9 to 3.9) |
| | No | 0 (ref) | 0 (ref) |

[1] All models controlled for birthyear

[2] Model controlled for birth year, sex, pelvimetry, birth order, birth position, mother's education level and mother's income

[3] Model controlled for birth year, sex, pelvimetry, birth order

*Table 1-Analysis of covariates and effect on percentile rank in primary school grades between children exposed to pelvimetric examination during pregnancy and unexposed children as well as between exposed children and unexposed siblings*

## 4.2 STUDY II AND III

The radiological archive that forms the basis of study II and III initially contained records on 35 095 patients. A significant portion of the patients was removed due to missing information of either PIN (3 952 patients, often foreign patients) or missing information on the examination (2 536 patients) and 28 607 patients remained before linkage to national registries. After linkage additional preparation of the cohorts was performed and the final study cohort consisted of 26 370 patients in study II and 26 315 patients in study III. In study III a further 55 patients were removed due to a diagnosis of tuberous sclerosis. We performed analyses with a 5 and a 10 year exclusion period after the initial CT examination.

In initial analysis in study II we found a total of 48 meningiomas cases among the exposed group and 64 meningiomas in the unexposed group. After analysis an increased risk for meningioma of 2.28 (95 % CI 1.56 to 3.33) with a 5 year exclusion period was found and 2.33 (95 % CI 1.49 to 3.64) with a 10 year exclusion period. Analysis on dose was performed after dividing patients into groups of total dose of 50 mGy and after both exclusion periods significant risk increase of meningioma were found in groups having received more than 50 mGy. In addition trend analysis for the groups were significant. However having access to the original referral notes these were examined for any additional risk factors. The referral notes contained information on 16 patients that had reasons for exclusions but with data not found earlier in national registries or in gamma knife treatment registry. Of these 16 patients 7 had a meningioma at first CT examination, 4 had a non-meningeal brain tumor and 5 had received radiotherapy to the head. Taking these data into account and excluding these additional 16 patients decreased the risk of meningioma after CT examination. The HR after the 5 year exclusion was 1.49 (95 % CI 0.97 to 2.30) and after 10 year exclusion was 1.49 (95 % CI 0.87 to 2.48). The previously seen increased risk for different dose categories as well as trend analysis for dose groups also decreased and were no longer statistically significant.

| Outcomes | 5 year exclusion period | | 10 year exclusion period | |
|---|---|---|---|---|
| | Without referral check | With referral check | Without referral check | With referral check |
| | point estimate (95 % CI) | point estimate (95 % CI) | point estimate (95 % CI) | point estimate (95 % CI) |
| Meningioma | | | | |
| Exposed[1] | 2.28 (1.56 to 3.33) | 1.49 (0.97 to 2.30) | 2.33 (1.49 to 3.64) | 1.49 (0.89 to 2.48) |
| Non exposed | 1 | 1 | 1 | 1 |
| Glial Tumors | | | | |
| Exposed[1] | 1.38 (0.94 to 2.03) | 0.81 (0.51 to 1.30) | 0.92 (0.53 to 1.60) | 0.69 (0.37 to 1.29) |
| Non exposed | 1 | 1 | 1 | 1 |

[1]Stratified by age, sex, time-period for inclusion

*Table 1-HR for meningioma and glial tumors for exposed and unexposed group using either a 5 or 10 year exclusion period as well as with or without check of referral notes*

In study III we restricted our analysis to tumors originating from glial structures and found 37 tumors in the exposed group compared to 88 in the unexposed group. After analyzing the clinical information on referral notes 15 of the 37 tumors in the exposed group were removed from final analysis, 14 due to presence of brain tumor at first CT and 1 due to radiotherapy. Initial analysis without clinical information did not find any significant increase in tumors after a CT examination, a significant increase in trend when considering doses was found. After taking clinical information into account the HR for a CT examination was 0.81 (95 % CI 0.51 to 1.30) after a 5 year exclusion period and HR after 10 year exclusion was 0.69 (95 % CI 0.37 to 1.29).

### 4.3 STUDY IV

Study IV describes the collection of data and assembly of EPI-CT cohort. Final results on the EPI-CT in regards to outcome data on mortality or incidence of leukemia and solid cancers have yet to be performed. The projected size for the Swedish part of the EPI-CT cohort is 95 000 patients (9.2%) out of total cohort of 1 032 000 patients. The Swedish patients were examined between from 1984 to 2013 and the age of patients are between 0 and 18 years.

# 5 DISCUSSION

In our studies of the risk of adverse events after exposure to diagnostic X-rays, we found no effects on school grades after in utero exposure to pelvimetry, nor did we find any increase in risks of brain tumor or meningioma after CT exposure to the head. In addition, we found that in studies of risk of brain tumor and meningioma after CT exposure, information from radiology reports are essential in order not to overestimate the risks.

The knowledge of the adverse effects on cognition after low dose radiation to the head is in large part based on cohort studies of the survivors of the atomic bombs over Hiroshima and Nagasaki, in particular of the in utero cohort of children exposed before birth and born after the explosion.[189] The cognitive abilities of the children in this cohort have been measured in several ways. IQ and school performance were measured when the children were 10 or 11 years old, and the results suggest that the most sensitive time for the fetus was during weeks 8-15, and, to a lesser extent, during weeks 16-25. Study I included a total of 1 536 exposed patients compared to the 1 613 children included in the in utero cohort, and cognition was measured as primary school grades at approximately age 15. The radiation exposure in our study was a pelvimetric examination which was mostly performed later in pregnancy, after week 25, and doses were both lower and within a more narrow range than was the case for the atomic bomb survivors. Although the radiation exposure in our study occurred late in pregnancy and therefore should, on the basis of what is known from the in utero cohort, have little effect on cognition, the larger cohort size and the more uniform dose interval still add important information. Pelvimetry may no longer be as common an examination as it was when our cohort was exposed in the 1980s, but there are other types of radiological examinations during pregnancy that exposes the fetus to radiation, and it is therefore reassuring that doses in the range as conveyed to the fetus from a pelvimetry can be considered safe with regard to school performance.

Counterintuitively to an expected decrease in school grades after radiation exposure to the head, Study I found a slight increase in grades in the simple regression analysis. In the multiple regression analysis, however, this increase was no longer statistically significant, even though the point estimate was positive, and similarly, a slight increase in grades was found when the analysis was restricted to families with exposed children and unexposed siblings. It is likely that this is due to a residual bias from socio-economic factors and birth order. Finally, although for other fields than radiation research, it is noteworthy that some of the factors we controlled for strongly influenced the children's school grades, in particular the mother's education level and sex of the child.

Study II and III examined if there were any increases in risk of brain tumor or meningioma after CT examinations to the head, and we found no statistically significant increases in risk. Risk of solid tumors increase in most organs after radiation exposure although there was only a slight indication of increased risk in the latest report of the LSS studies of relatively low doses of radiation.[34] Previous studies have indicated that meningioma is the most radiosensitive tumor of the head,[87] and there have been some indications of an increased risk of meningioma after medical examinations.[101, 190] More recent studies on risk after CT examinations of the head, however, have shown much larger increases in risk than in studies based on other exposures.[44-46] There are, however, some results in these

studies that differ to what is known from other radiation studies:[191] The risk of cancer appeared much earlier than expected, the risk of brain tumors were increased even though CT examinations were not of the head,[45, 46] and the risk increase was larger for older children than for younger.[44] There are also some indications that the risk increase may partly be explained by predisposing factors.[151] In both study II and III we found that without the information in radiology reports from the time of the first CT examination, patients with a history of radiation treatment to the head and prevalent tumors at time of examination would have been erroneously included in the study and the estimates of risks would have been falsely high.[192] This finding have been further studied in the CT cohort from United Kingdom and found that clinical information from 40% of patients did not affect results meaningfully.[193] The studies that found unexpectedly high risks of brain tumors and meningiomas after CT exposure were performed without access to the radiology reports, and it is likely that this may have influenced the results. Furthermore, an additional complication when studying the risk of meningioma as an outcome lies in the fact that the diagnosis of meningioma is likely to be delayed compared to most other brain tumors. Delayed diagnosis should be suspected since pathological diagnosis, and thus registration in cancer registries, of meningioma often is delayed until operation. Since meningiomas does not metastasize, this operation may be delayed for a long time. In Study II, one patient had a delay of more than 15 years from diagnosis of meningioma in the radiology report to registration in the cancer register. This delay in registration may, evidently, also skew the results.

Although we found no overall increase in risk of meningioma after CT exposure to the head, there was a slight suggestion that the risk increased near the end of follow-up. This would be consistent with what is expected from cancer biology, and it is possible that a new assessment of risk of meningioma in the cohort with additional follow-up time may shed light of this finding. Likewise, a study with longer follow-up may reveal whether the nonsignificant suggestion of a stepwise increase in risk of meningioma with increasing radiation dose - larger than what was expected from the studies of the LSS cohorts – was a true finding or due to chance. Additional studies of the cohort at a later time should also be considered to see if, similarly to LSS studies, any increases in risk persist as subjects grow older.

In study III glial tumors were examined. Since glial tumors exist in both slow growing and faster growing forms, it is not surprising that the results of study III were similar to study II. In addition, glial tumors in general have not been shown to be particularly radiosensitive. The decreased risk that we found should be considered in contrast to the increased risk in glial tumors found in the English cohort of CT exposed patient.[44] In study III we had knowledge of clinical status at first CT examination and could therefore exclude patients that were not eligible. There may still be residual reversed causation in study III if there were a glioma giving symptoms leading to a CT scan, and thus present at time of first CT, but not found in the radiology rapport. Even today, with much improved scanners compared to the scanners used in our study, low-grade astrocytoma may show only subtle signs on CT, and with older equipment they may have been even harder to identify.

One serious limitation with both Study II and III is that exposed and unexposed cohorts were treated differently since the information from the radiology reports on the exposed

cohort was not available for the unexposed cohort. If there were other hospitals in the Stockholm area giving gamma knife therapy to patients that could be included in the control cohort of our study, or if exposure to CT of the head at other radiology departments was a common exposure during the study period, this would bias the results. Since this is not the case, however, we do not consider this being a threat to the validity of our results.

The EPI-CT study is an attempt to further investigate the risk of radiation exposure from CT examinations. The study includes children, who are more radiosensitive than adults. CT examinations are likely the diagnostic examination with the largest amount of radiation dose that children are likely to be exposed to. EPI-CT will study leukemia since this is a disease that in the LSS cohorts has been shown to increase shortly after exposure but with a long-term persistent risk increase.[154] The potential bias emanating from long time periods between disease occurrence and diagnosis that we have found in Study II and III will therefore not be a problem in EPI-CT. In order to have sufficient statistical power to find an increase in risk of leukemia after CT exposure, a cohort of 1 million children was found to be necessary. Hopefully, in the EPI-CT study it will also be possible to model dose-response curves, although obtaining accurate radiation doses for the exposed children may be challenging since it is possible to identify the body part that was examined, but it may be more difficult to identify which protocol was used. The protocol for a CT examination may indicate one or several series as well as different settings for the X-ray tube, leading to large variations in dose between different protocols. In spite of all challenges, the EPI-CT study will provide excellent opportunities to address the potential risks associated with diagnostic x-ray exposure.

# 6 CONCLUSIONS

In conclusion, we have found that:

- There was no indication of adverse effects on cognition measured as school grades after in utero exposure to pelvimetry.
- Without information from the radiology reports, studies of the association between CT exposure and risk of brain tumor and meningioma may give erroneus results since these may be biased by patients with prevalent tumors at time of exposure or a history of radiation treatment to the head being included in the study.
- In a cohort of more than 26 000 patients examined with CT and followed for up to 21 years, there was no increase in risk of meningioma or glial tumors .

There is still need for further research in regards to low doses of radiation, similar to what patients may receive after a medical examination. The EPI-CT study will hopefully be a useful addition to these types of studies since the study population is drawn directly from health care systems and bias, as experienced in study II and III, can be addressed.

# 7 KORTFATTAD VERSION PÅ SVENSKA

Röntgenstrålningen upptäcktes 1895 och blev snabbt anammat av sjukvården. Dock upptäcktes snart att det fanns risker med röntgenstrålning både för patienter och för personal om försiktighetsåtgärder inte vidtogs. 1973 blev datortomografin (DT) tillgänglig för medicinen. Patienter som undersöks med DT ligger på en brits i maskinen och sedan roterar röntgenröret runt patienten och tar många exponeringar från flera vinklar. Dessa exponeringar kan sedan sättas samman till ett tvärsnitt av patienten. DT var en stor framgång och antalet undersökningar ökade kraftigt, dock så innebär en undersökning med datortomografi högre stråldoser än vid konventionell röntgen. Dessutom har den tekniska utvecklingen sedan upptäckten lett till att datortomografier har blivit snabbare och vanligare undersökningar, och starkare röntgenrör har lett till att DT kan göra mer komplexa undersökningar vilket också ökar stråldosen för undersökningen. De ökade stråldoserna från DT har lett till att den genomsnittliga strålningen till populationen har ökat. Det finns nu en ökande oro för att ökningen av strålning från DT kan leda till negativa effekter på hälsan hos befolkningen.

Röntgenstrålning kan skada cellernas DNA, båda bryta sönder DNA-kedjan men även orsaka mutationer. Upprepade mutationer i cellernas DNA kan över en lång tid ge upphov till cancer.

Tidigare studier på riskerna med röntgenstrålning har visat en ökad risk för både leukemi och solida cancrar, men röntgenstrålning på barn har även visats kunna ge skador på hjärnan som lett till nedsatt intelligens. En stor del av kunskapen om riskerna med strålning i de doser som förekommer vid datortomografi kommer från studier på atombombsöverlevarna från Hiroshima och Nagasaki. Andra studier som har genomförts har bland annat undersökt patienter som fått strålning från diagnostiska undersökningar och strålterapi. Det finns också studier som undersökt individer som exponerats för strålning i samband med yrkesutövning eller som utsatts för strålning från föroreningar eller från levt i områden med ökad strålning. Kunskapen från studier om röntgenstrålning har tydligt visat att höga doser, över 100 mGy kan ge cancer. De flesta röntgenundersökningar har dock mycket lägre stråldoser och även om det finns flera studier som visar på en ökad risk för cancer i dessa nivåer finns det en större osäkerhet. Idag anses varje röntgenundersökning kunna utgöra en risk för att orsaka cancer men det finns en osäkerhet i hur stor den risken är vilket gör det svårt att ställa den mot nyttan med en undersökning.

I vår första studie har vi undersökt 1 500 barn som på 80-talet var exponerade för röntgenstrålning in utero när deras mamma gjorde en bäckenmätning under graviditeten. Dessa barn har sedan jämförts med icke-exponerade barn, inklusive deras syskon avseende barnens skolbetyg i högstadiet. Vi kunde inte se några negativa effekter på skolbetyg av strålning från en bäckenmätning.

I studie II och III hade vi samlat patientdata från ett arkiv med röntgenremisser i pappersform. I arkivet fanns data om 26 000 patienter med namn, personnummer och vilken undersökning som gjorts. Efter att ha matchat patienterna med 4 ggr så många oexponerade individer länkades alla till nationella register som Cancerregistret för att undersöka om det fanns ett samband mellan DT undersökningen och meningiom eller gliala tumörer. Vi fann ingen ökad risk för varken meningiom eller gliala tumörer efter att ha gjort DT-undersökningar. Vi fann dock att det var nödvändigt att ha tillgång till röntgenremisserna för att korrekt kunna exkludera patienter som hade en tumör redan vid första undersökningen. Utan informationen från remisserna hade vi hittat ett falsk förhöjt samband.

Studie IV är pågående och beskriver metoden för hur den internationella studien EPI-CT ämnar genomföras. EPI-CT har som mål att samla in 1 miljon barn som är undersökta med DT och beräkna stråldoser för att kunna undersöka sambandet mellan DT och cancer och leukemi hos barn. Leukemi är en sjukdom som tidigare har visats komma snart efter strålning och man kan därför ha en kortare uppföljningstid.

För att undersöka sambandet mellan röntgenstrålning och negativa hälsoeffekter som cancer behövs lång uppföljningstid vilket dom retrospektiva studierna I-III möjliggör. Ingen av studierna I-III kunde påvisa negativa effekt på dom utfallen vi studerade. En möjlig orsak till detta kan vara att studierna har för få patienter. EPI-CT som ämnar undersöka 1 miljon patienter har förhoppningsvis tillräckligt många patienter för att med större säkerhet klarlägga om det finns risker med datortomografiundersökningar.

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