Chapter 1

General introduction, objectives and outline
Historical perspective

In November 1895, Wilhelm Röntgen saw the bones of his wife’s hand on a photographic plate on the other side of an electron beam tube and described X-rays for the first time. Soon thereafter, X-rays were introduced into medicine and remarkable experimental, clinical and technological developments in imaging have continued to transform medicine\textsuperscript{1,2}. In 1971, the Computed Tomography (CT) scan was introduced. This invention was made possible through the work of most notably Godfrey Newbold Hounsfield and Allan MacLeod Cormack, who were jointly awarded the 1979 Nobel Prize for Physiology or Medicine. The advantages of CT scans are that a CT scan completely eliminates the superimposition of images outside the area of interest and that tissues with different density can be distinguished.

Between 1970 and 1980 the duration and quality of CT scans have been remarkably improved. In the 1980s, the radiology community used the digitalization of radiographic images as an integrated communication network and data management system. When this digital information is connected to a clinical information system, radiologists can readily access all information while they are reading a partial scan, which facilitates more accurate diagnoses. The transfer of imaging information has also been expedited by the advent of picture archiving and communication systems (PACS).

Radiation protection

A few years after X-rays were first used for radiologic imaging, physicians and medical radiation workers developed skin cancer, leukemia, dermatitis, and other adverse health effects\textsuperscript{3}. An early case study describes a 36 years old chemist who had worked with radium for 14 years, who suddenly developed acute leukopenia and died of bronchopneumonia within a month after the onset\textsuperscript{4}. Implementation of radiation safety procedures began in the 1930s with the advent of lead aprons and lead gloves, and continued with the introduction of thyroid shields and leaded protective eyewear for interventional radiologists. In the late 1940s, attempts were made to quantify the long-term risk from radiation exposure, including cancer. From the 1950s onwards, epidemiologic studies have linked diagnostic X-rays with increased cancer incidence, including pediatric leukemia in the offspring of mothers undergoing diagnostic X-rays during pregnancy\textsuperscript{5,6}, as well as breast cancer in women with tuberculosis who were monitored using fluoroscopy\textsuperscript{7,8} and in women with scoliosis who were evaluated with repeated X-rays\textsuperscript{9}. The International Agency for Research on Cancer concluded that there is sufficient evidence for the carcinogenicity of X- or \(gamma\)-radiation in humans, including substantial evidence suggesting a causal association between exposure to diagnostic radiation in utero and childhood cancer\textsuperscript{10}. 

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At the start of the millennium, several alarming reports and editorials appeared, raising awareness about potential population risks associated with radiation exposure from CT scans, particularly in young patients. Radiation protection was widely publicized and received high-level media attention\textsuperscript{13,15}. Since 2001, a number of educational campaigns such as Image Gently were introduced. As a result, age-specific settings were more often used which resulted in a dose reduction for the youngest children\textsuperscript{16,17}.

**Computed Tomography (CT) scans**

The basic principle of CT scanning is illustrated in Figure 1. A motorized table moves a person through the CT imaging system\textsuperscript{16}. At the same time, on the far side of the patient, a source of X-rays rotates within the circular opening and a set of X-ray detectors rotates synchronously. The X-ray source produces a fan-shaped beam. All the data will be processed by a computer to series of image slices. The computer will show a three-dimensional view of the target organ or body region\textsuperscript{16}. Besides, the images and related data are sent to the PACS, where a radiologist will be able to retrieve and interpret them. CT scanning has transformed much of medical imaging by providing three-dimensional views of the organ or body region of interest. There are currently advances in CT technology that make it extremely user-friendly.

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*Figure 1: The basic principle of CT scanning\textsuperscript{16}.*
CT scan use

Since the introduction of CT scans in medicine in the early 1970s, their use has increased rapidly in Western countries over the past two decades. In 2013, Japan had, by far, the highest number of CT scanners per capita (101.3 per 1 million people), followed by Australia (53.7 per 1 million people) and the United States (43.5 per 1 million people). In the Netherlands, the number of CT scanners in 2013 was 11.5 per 1 million people\textsuperscript{18}.

The Dutch annual number of CT scans in 2013 was 71 per 1,000 persons, almost the same as in the UK (76/1,000) and in Germany (62/1,000), whereas in the United States, Luxembourg and France, countries with the highest rates of CT scans, the rate was three times higher (USA: 240, Luxembourg: 202 and France: 193). Note, though, that large variations in the use of CT scanners not only across countries, but also within countries have been reported\textsuperscript{19}.

In the Netherlands, the use of CT scans has increased by more than 50\% since 2001 to approximately 1.4 million scans in 2014, with the steepest absolute and relative increases seen in general hospitals (Figure 2). This sharp increase is likely related to advances in CT technology that make the CT scan a user-friendly diagnostic tool.

![Figure 2: Annual number of CT examinations in the Netherlands by type of hospital\textsuperscript{20}\textsuperscript{*}](image)

\textsuperscript{*}Translation: aantal CT-onderzoeken: number of CT examinations; totaal: total; algemeen: general; academisch: academic; categoriaal: specialized; ZBC( zelfstandig behandencentrum): independent treatment centre.

CT scan use can be categorized according to the population, e.g., adults or children, and purpose of the scan, e.g., screening, diagnosis or post-treatment monitoring or follow-up of chronic conditions. Adults receive over 10 times more CT scans than children and CT scans performed for diagnosis in adults are the largest of these categories\textsuperscript{21,22}. The largest increases in CT use were seen in settings of adult screening\textsuperscript{23,24} and pediatric diagnosis\textsuperscript{25,26}. Pediatric diagnoses represent approximately 2-10\% of all medical diagnostic radiation procedures\textsuperscript{27,28}.
Empirical data on indications of pediatric CT scans are very scarce. MiGioretti et al. presented reasons for pediatric CTs of the abdomen/pelvis or the head among 149 children. The abdomen/pelvis scans were mostly done for pain, appendicitis or infection. Most head scans were done to evaluate trauma, upper respiratory issues, headache, congenital development and suspected cancer. It has been proposed that CT examination should be considered in cases of acute brain trauma, suspected pulmonary interstitial and renal calculus diseases, and some skeletal pathology. In all other cases, guidelines define strict indications for CT use and recommend non-ionizing radiation modalities (or X-rays) for many indications.

Low doses of radiation

CT scans expose patients to low doses of radiation, typically less than 100 milligray (mGy), e.g., a typical pediatric abdomen CT scan exposes the abdomen to approximately 25 mGy. Other examples of low dose radiation exposures are a single screening mammogram (approximate breast dose of 3 mGy) or working as a nuclear worker for one year (approximate whole body dose of 20 mSv). Little doubt exists that high doses of ionizing radiation above >100 mGy, such as radiotherapy, have deleterious consequences in humans, including cancer. At lower doses, however, risk quantification is challenging because a small excess risk is measured against a typically relatively high population baseline risk, for conditions with a multi-factorial etiology. Understanding the risks of low doses of radiation has societal importance since it affects screening tests for cancer, the future of nuclear power, frequent-flyer risks, and chronic occupational radiation exposures.

Although CT scans expose patients to low doses of radiation, they deliver much higher radiation doses compared with most other medical diagnostic procedures. For example, while a conventional chest X-ray delivers a dose to the lung in the range of 0.01 to 0.1 mGy, typical lung doses for a single chest CT scan are about 10 mGy, i.e., more than 100 times greater. A typical head scan of a child delivers around 30 mGy to the brain. In countries like the United States, CT-scans contribute nearly half the population’s collective radiation dose from all medical imaging. Furthermore, a patient having a CT scan will, on average, have two such scans, resulting in a further increase in dose. Compared with higher doses, cancer risks from low doses of radiation are likely to be lower, and progressively larger epidemiological studies are required to accurately quantify the risks.
Children as source population

Several recent studies of CT-related radiation risks are focused on children or adolescents. Children may be more susceptible to the DNA-damaging effects of radiation than adults, because of the high rate of cellular proliferation\textsuperscript{37,38}. With adult protocols, the radiation doses received by children are about 50% higher than those received by adults\textsuperscript{39} due to their smaller body size\textsuperscript{40}. Special pediatric machine settings of CT scans and X rays, dependent on height or weight, are available to adjust radiation exposures downwards for children, without compromising image quality. However, these adjustments are not always made\textsuperscript{34,41}, partly because CT scan digital techniques render improved images with increasing radiation exposure, in contrast to conventional X-rays which become too dark with overexposure\textsuperscript{42}. Children also can receive high cumulative radiation doses when multiple repeat or follow-up scans are done\textsuperscript{27}. In addition, it has been suggested that up to one third of CT scans performed on children are either not relevant to diagnosis or management, or could be replaced with alternative diagnostic techniques without ionizing radiation, such as magnetic resonance imaging (MRI) or ultrasound, depending on local facilities and staffing arrangements\textsuperscript{43}. Thus, because of smaller body size, sub-optimal machine settings, and repeat or unnecessary scans, CT-related radiation doses received by children may be substantially higher than required to achieve adequate diagnostic information.

Studies about low dose radiation risks have demonstrated that the developing tissues of children are particularly vulnerable so that for any given dose, radiation relative risks for acute leukemia and cancers of the brain, breast, thyroid, and skin are generally higher for children than for adults\textsuperscript{44-47}. Cancer is a very rare entity in children, affecting approximately 140-150 of every 1,000,000 children less than 20 years of age/year in Europe and the USA\textsuperscript{48,49}. Leukemia is the most common type of childhood cancer and accounts for 30% of all cancers diagnosed in children, with 140 new cases per year in the Netherlands\textsuperscript{50}. Within this population, Acute Lymphoblastic Leukemia (ALL) occurs approximately five times more frequently than Acute Myeloid Leukemia (AML) which represents 78% of all childhood leukemia diagnoses\textsuperscript{51}.

Childhood brain tumors are the second most common type of childhood cancer after acute leukemia and are associated with a high rate of morbidity and mortality. The known causes of brain tumors are limited to ionizing radiation and a few specific genetic syndromes which account for less than 5% of cases\textsuperscript{52}. It is often difficult to separate brain tumors into malignant or non-malignant behavior because many (particularly astrocytomas) may be very slow growing.
Measures of radiation dose and cancer risk

Radiation dose
Various concepts, terms, and their associated quantitative units are used to quantify radiation dose. Radiation dose is a measure of energy and the basic quantity used for scientific purposes is the absorbed dose, which is the amount of energy deposited by radiation in a unit mass of matter. The unit of absorbed dose is the gray (Gy), which equals 1 joule of energy absorbed by one kilogram of matter (J/kg). Radiation rate is the quantity of radiation absorbed per unit time. Radiation can be emitted as several kinds of particles with four primary types: alpha particles, beta particles, neutrons and photons that are either X-rays or gamma rays. The absorbed dose distribution differs significantly between these types. For pure gamma radiation, 1 Gy is roughly equal to 1 Sievert (Sv), e.g. medical exposures (CT-scan, mammogram).

The biological effects of X-rays are classified as deterministic (producing an immediate change to tissue) or stochastic (cancer development in exposed individuals or heritable disease in their cells). For radiation protection, the International Commission on Radiological Protection (ICRP) has defined two dose concepts: the equivalent dose and the effective dose. These doses are weighted absorbed doses, and are used within the system of radiological protection to broadly account for the extent of damage in different organs and tissues relevant to the stochastic health effects caused by low-level radiation exposure. The equivalent dose is a weighted average of the different types of radiation (e.g., alpha and gamma) with weights reflecting the potential to cause cancer. Unfortunately, some of the radiation type weights (not cancer related) concerning long-term damage are still unknown. The effective dose is a weighted average of organ-specified equivalent doses with the tissue-specific weights reflecting radiation sensitivity; it summarizes the exposure of an individual in one number and allows for comparisons of the cancer risk from heterogeneous exposure situations, accounting for radiation quality (X-rays, neutrons, alpha particles) and partial/full body exposure. Although effective dose is used in many surveys as a measure of cancer risk, it is not a good measure for individual risk assessment. An effective dose does not take into account age at exposure (e.g., differences in tissue-specific radiation sensitivities between adults, adolescents, children and infants) and gender (women are more sensitive than men) and it is a mix of different endpoints (e.g., cancer, hereditary factors). Absorbed dose to a given tissue or organ, the so-called organ dose, is used for estimating cancer risks. This metric is expressed in Gy.

Evaluation of radiation risks
Cancer risk in a population can be characterized by the total number of observed cases divided by the total number of person-years of observation, the incidence rate. Radiation-
related cancer risks can be evaluated by comparing incidence rates of an exposed population with those in a comparison group. The comparison group can be external or internal to the study population. External comparisons compare cancer incidence between an exposed study population and the general population. This can be done by calculating the ratio of the observed and expected number of cancer cases, the Standardized Incidence Ratio (SIR). The expected number of cancer cases is calculated by taking into account age, exam year, gender and race. However, a disadvantage of external comparisons is that the general population and the studied radiation-exposed population might differ by more than just radiation exposure which can cause confounding. Therefore, internal comparisons between the exposed and the unexposed (or low exposed) subgroups of the study population are important, e.g., by calculating the risk ratio.

Depending on the study design, different measures are estimated from epidemiological data, e.g., the odds from case-control studies and the hazard ratio (proportional hazards regression for survival times) or the risk ratio (Poisson regression for aggregated data) from cohort studies. These measures approximate the relative risk if the outcome is rare, e.g., childhood cancer. An alternative way to assess the influence of radiation exposure on cancer risk is using the risk difference rather than the risk ratio. Using the risk ratio, the radiation effect is proportional to baseline risk, which typically varies by age, sex, birth cohort and other factors, while the radiation effect does not depend on the baseline risk when the risk difference is used.

**Linear No-threshold Hypothesis**

The linear no-threshold model assumes that even the lowest doses of radiation lead to an, albeit small, increased cancer risk. The dose level at which there is considered to be direct empirical evidence of an increased risk of cancer has been gradually lowered, by extensive research, to about 50-100 mGy\(^{95}\). For radiation doses below 50-100 mGy (protracted exposure) or 10-50 mGy (acute exposure) only very large epidemiological data sets can inform the shape of the dose-response relationship. Major radiation expert committees concluded in comprehensive reviews published during 2005 to 2008 that the available biological and biophysical data support a linear no-threshold risk model for most cancers (i.e., the dose response at low levels is linear without evidence of a threshold)\(^{24-34}\). Radiation-related risks are commonly estimated from epidemiological data using a linear excess relative risk (ERR) model (\(RR=1+\beta*dose\)), where \(\beta\) is the ERR per unit dose. The linearity assumption is a conservative basis for radiation protection at low doses and dose rates. However, some recent reports, based mostly on findings from radiobiology, suggest that there is substantially greater complexity regarding low dose and low-dose rate effects because of non-targeted effects at low doses\(^{35,36}\).
Cancer risk following low-dose ionizing radiation exposure

During the past decades several long-standing, large-scale epidemiologic studies have documented the cancer risks from exposure to low levels of ionizing radiation. Some of the most important studies which had a relatively high impact in the field of radiation epidemiology and radiation protection are summarized below. For comparability all studies are categorized according to type of radiation (beta radiation, gamma radiation), absorbed dose (in Gy), dose rate (the amount of dose of radiation delivered per unit time), study population (children, adults) and exposure area (whole body, specific parts).

Atomic bomb survivors in Hiroshima and Nagasaki
In 1945, the United States dropped atomic bombs on the Japanese cities of Hiroshima and Nagasaki. According to local authorities, roughly 140,000 people died in Hiroshima and 74,000 died in Nagasaki. Survivors of the bombing suffered, among many other things, from health problems owing to both acute as well as late-onset deterministic and stochastic effects of radiation.

The Radiation Effects Research Foundation (RERF) and its predecessor, the Atomic Bomb Casualty Commission (ABCC), have conducted a systematic epidemiologic study of the Japanese atomic bomb survivors beginning in 1950 with the establishment of the Life Span Study (LSS), which has made a substantial contribution to the understanding of radiation effects on human health\textsuperscript{[57]}. The study follows 120,000 survivors of the atomic bomb blasts, including 93,000 who were in Hiroshima or Nagasaki when the explosions occurred, and 27,000 residents who were not in the cities at the time of the explosions. The average whole body dose to the exposed individuals is estimated to be 200 mSv, with the following approximate dose distributions: 0-<5 mSv, 37,000 subjects; 5-<100 mSv, 32000 subjects; and 100-<2000 mSv, 17,000 subjects.

In this cohort, all solid cancer incidence rates increased throughout lifetime for all ages and an elevated risk was still observed at the end of follow-up (for a 70 year old men exposed at age 30, the estimated solid cancer rates increase by 35% per Gy (90% CI: 28%; 43%))\textsuperscript{[58]}. For leukemia, excess cases associated with close proximity to the hypocenters began to be reported about 3 years after the bombings, and the ERR peaked 6-8 years after exposure\textsuperscript{[59]}. The leukemia results indicated that there was a clear nonlinear dose response for leukemia, with much of the evidence arising from acute myeloid leukemia\textsuperscript{[60]}. Regarding mortality rates, the LSS cohort demonstrated an increased risk of cancer mortality through lifetime and significant increases of radiation-related risks have been found for most sites of solid cancer\textsuperscript{[61]}. The relative risks for many cancer sites were higher in people exposed during childhood and the risks declined a number of years after the bombings. The mortality risk of leukemia increased in the early period after bombing and then decreased with a clear dose-response
relationship. Children of people exposed to the atomic bombs, born years after the atomic bombs, had no indications of deleterious health effects after 62 years.

The exposure in this study consists of beta, gamma and neutron radiation to the whole body of children and adults with a mean dose around 200 mSv and a very high dose rate. Nevertheless, as cited above, the cohort harbors a large population exposed to <100 mSv as well. The LSS has become fundamental to risk assessment in the radiation protection system of the ICRP and other authorities.

**Nuclear power plant accidents**

During the past decades, more than 400 major radiation accidents have occurred worldwide. The most recent ones are Chernobyl (1986, Ukraine) and Fukushima (2011, Japan). The Chernobyl nuclear power plant accident released huge quantities of radionuclides into the atmosphere. Results of epidemiological studies in heavily contaminated areas around Chernobyl showed a pronounced increase in incidence of thyroid cancer among citizens who had received high thyroid doses (>1 Gy) as children, starting a few years after the accident. Updated analyses from clean-up workers of the Chernobyl accident have yielded new insights into risks of leukemia and leukemia subtypes. In the Ukrainian cohort of clean-up workers followed until 2006, about 16% of all leukemia diagnoses were attributed to radiation exposure, resulting in a significant linear dose-response for all leukemia. Risk of leukemia was similarly, although not significantly, elevated in the cohort of workers in Belarus, Russia and the Baltic countries.

This study includes mainly gamma radiation and some beta radiation with a high dose and dose rate among children and adults with the whole body as exposure area. In terms of internal exposure to radioactive materials released into the environment, Chernobyl differs substantially from Hiroshima and Nagasaki, where the exposure was predominantly to external radiation from explosion of the bombs.

**Occupational exposure**

Risks of radiation exposure have been evaluated among radiologists, radiologic technologists, clean-up workers, intervention fluoroscopists and aircrew. In the 1990s, an international study of cancer risk among radiation workers in three countries was carried out and this study was expanded to include 15 countries. Analyses included 407,391 nuclear industry workers monitored individually for external radiation and 5.2 million person-years of follow-up. The study, with a mean cumulative effective dose of 19.4 mSv, showed a non-significant linear association between radiation exposure and mortality of leukemia excluding chronic lymphocytic leukemia (CLL). However, the excess risk for solid cancer mortality was three times higher than that observed in the LSS, and was largely driven by data from the earliest workers. Zablotska et al. concluded that the findings for the earliest workers are more
likely to be attributable to incomplete dose information than to a true effect, and that excluding these individuals from the 15-Country Study would have substantially attenuated the risk observed for mortality from all cancers excluding leukemia.75.

Cohorts of workers from France, the UK and the USA provided the vast majority of information on early nuclear workers and each of these cohorts has been updated, called The International Nuclear WORKers Study (INWORKS). The study included 308,297 nuclear power plant workers who have been monitored for external exposure to radiation with personal dosimeters and followed up for 60 years, for a total of 8.22 million person-years.75.76 This study showed evidence of a linear increase in the excess relative rate of cancer mortality with increasing exposure to ionizing radiation at the low dose rates. For leukemia, a positive association was found between cumulative bone marrow dose of ionizing radiation and death due to leukemia (excluding CLL) with an ERR of 2.96 per Gy (90% CI: 1.17-5.21, lagged 2 years) and most notably for mortality from chronic myeloid leukemia (10.45 ERR per Gy; 90%CI: 4.48-19.65). Compared with the 15-country collaborative study, this study has a longer follow-up time and included individuals exposed to internally deposited radionuclides or to neutrons which increased the number of deaths.

These studies include mainly gamma radiation with a low dose and a low dose rate among adults with exposure to the whole body. The LSS and Chernobyl studies are based on populations exposed to acute, high doses of ionizing radiation. Workers in radiation and nuclear industries are exposed to protracted and generally low dose radiation.

Medical exposure

None of the previously mentioned studies include substantial number of children exposed to low doses of gamma radiation at high dose rates. More studies were conducted on medical radiation exposure, particularly from diagnostic examinations occurring in utero and examinations during childhood/adolescence. These studies typically have vastly improved assessment of both exposure and disease by use of medical record abstraction and electronic record linkages compared to previous studies evaluating low dose radiation cancer risks. Children exposed in utero are predicted to have higher radiation-related cancer rates. Data from the United Kingdom Childhood Cancer Study was collected by interviews and searching the medical records. This study showed that any (versus no) exposure to diagnostic X-rays in utero was associated with a non-significantly increased risk of childhood cancer, driven largely by a non-significantly positive association with leukemia incidence, especially acute myeloid leukemia.77 In the US Scoliosis Cohort study, fractionated exposure to radiation from diagnostic X-rays in childhood and adolescence during 1920-1960, assessed using individual patient records, was associated with a statistically non-significantly increased risk of breast cancer incidence.78 Of seven case-control studies, of childhood radiation exposure and brain tumors incidence, two reported no evidence of associations,79.81 while five reported
at least weak evidence of positive associations\textsuperscript{37,39, 82-84}. Differences might be explained by different calendar periods during which the majority of examinations were done.

Radiation exposure from pediatric CT scans and cancer risks
In the early 1980s, natural background radiation exposure was estimated to be the predominant source of exposure to the US population, and the estimated per capita annual effective dose was 3.6 mSv. By 2006, the estimated per capita dose had nearly doubled to 6.2 mSv per year\textsuperscript{36}. This increase was due to the revolution in medical imaging, particularly CT scans. On the basis of results from various epidemiological studies, including the Life Span Study, the UN Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) concluded that children are generally more sensitive than adults to radiation for 25% of cancer types, including leukemia and cancers of the thyroid, skin, breast and brain\textsuperscript{38}. The last decade has introduced a new era of epidemiological studies of low-dose radiation facilitated by electronic record linkage and pooling of cohorts that allow for more direct and powerful assessment of cancer at doses below 100 mGy. Studies demonstrated an increased risk for cancer associated with exposure to CT scans among children.

The NCI-UK collaborative group conducted the first large record linkage study that included 178,604 young people (<21 yr) who had received one or more CT scans between 1985 and 2002 and linked these subjects with the NHS Central Registry for cancer incidence, mortality and loss to follow-up from 1985 to 2008\textsuperscript{85a}. Organ dose estimation was based on two previous national surveys. In order to avoid the inclusion of children with cancer whose first CT scan was done while the cancer was already diagnosed, follow-up for leukemia began 2 years after the first CT scan and for brain tumors 5 years after the first CT scan. The authors noted a positive association between radiation dose from CT scans and leukemia risk (ERR/ mGy 0.033 (95% CI: 0.004-0.114, p=0.02)) and brain tumors risk (ERR/mGy 0.016 (95% CI: 0.006-0.037, p<0.0001))\textsuperscript{85a}. Compared with patients who received a cumulative bone marrow dose of less than 5 mGy, the RR of leukemia for subjects who received at least 30 mGy was 2.63 (95% CI: 1.09-6.24) and the RR of brain tumors for subjects who received a cumulative brain dose of 50-74 mGy was 2.82 (95% CI: 1.33-6.03).

An Australian study\textsuperscript{86} included 11 million young people (0-19 years) from Australian Medicare records registered between 1985 and 2005. Cancers diagnosed in cohort members up to 2007 were obtained through linkage with national cancer records. The authors estimated average effective doses per scan (in mSv) scanned region, year of scan, and age. Effective doses were obtained from the published literature for specific ages and then mapped to the corresponding age band in the dataset. Cancer incidence rates were compared between subjects exposed to a CT scan more than one year before any cancer diagnosis and unexposed subjects. Overall cancer incidence was 24% greater for exposed than for unexposed patients (Incidence Rate Ratio (IRR) 1.24 (95% CI: 1.20-1.29), p<0.001). The IRR
was significantly increased for several types of cancer (e.g., digestive organs, melanoma, soft tissue, female genital, urinary tract, brain, thyroid, myeloid leukemia, Hodgkin’s lymphoma, other lymphoid cancers, and myelodysplasias) among CT scan-exposed patients compared to unexposed patients, but no excess was reported for breast cancer and lymphoid leukemia.

The authors noted a positive association between radiation dose from CT scans and leukemia (including MDS) (ERR/mGy 0.039, 95% CI: 0.014-0.070) and brain tumors (ERR/mGy 0.029, 95% CI: 0.023-0.037).

A record-linkage cohort study in Taiwan included 122,086 children (aged < 18 years) from the Taiwan National Health Insurance Research Database with at least one CT scan between 1998 and 2006, of whom 24,000 children had a head CT. Subjects were followed until a diagnosis of cancer from the national health insurance system or the end of 2008. No dosimetry was performed. The overall risk was non-significantly elevated with a hazard ratio (HR) of 1.29 (95% CI: 0.90-1.85). Children exposed to head CT scans had significantly elevated overall brain tumor risk (HR: 2.56, 95% CI: 1.44-4.54), with a significant risk for non-malignant brain tumors (HR: 2.97, 95% CI: 1.49-5.93), but not for malignant brain tumors (HR: 1.84, 95% CI: 0.64-5.29).

Smaller studies conducted in France and Germany study suggested elevated risks for leukemia and brain tumors. The study in France included 67,274 children who had a first scan before the age of 10 years between 2000 and 2010. The children were followed from the date of their first CT scan until the earliest of 2011, first cancer diagnosis, or their 15th birthday. Cumulative CT doses were estimated from radiology protocols. During a mean follow-up of 4 years, no significant excess risk was observed in relation to CT scan exposures. The study performed in Germany abstracted data for children with at least one CT scan between 1983 and 2010 from 20 hospitals. Cancer cases occurring between 1983 and 2010 were identified by linkage with the German Childhood Cancer Registry (complete until the 15th birthday). For all cases and a sample of non-cases, radiology reports were reviewed to assess the underlying medical conditions at time of the CT scan. For leukemia, the SIR was 1.72 (95% CI: 0.89-3.01) and for central nervous system tumors, the SIR was 1.35 (95% CI: 0.54-2.78). The HR was estimated per received organ dose in mGy and a HR of 1.009 (95% CI: 0.981-1.037) per mGy red bone marrow dose for leukemia and a HR of 1.008 per mGy brain dose (95% CI: 1.004-1.013) for central nervous system tumors (including tumors outside the brain) were found.
Research aims

The first studies on CT-related cancer risks have been published and reported a small excess cancer risk for children and young adults. Although these studies were able to determine risks of cancer following CT procedures among children and adolescents, there are still many gaps in knowledge about CT-related cancer risks. The reasons why the examinations were performed were not known, which might lead to overestimation of radiation-related risks in these studies due to confounding by indication, and the dose estimation was based on external estimates stratified by variables such as age, calendar period and body part or protocols. Therefore, we defined a large cohort (n= 168,394) of children who received a CT scan during childhood (0-18 years) from 1979 until 2012, the Dutch Pediatric CT Study. To obtain information on cancer incidence, the cohort dataset was linked with the Netherlands Cancer Registry (NCR) and the Dutch Childhood Oncology Group (DCOG). Moreover, patients were linked with the Central Bureau of Genealogy (CBG) for vital status and date of death. This study has almost a nationwide coverage, the exposure assessment is based on a large internal sample of CTs with dosimetric information and data about several potential confounders is available. The Dutch Pediatric CT Study on CT scan radiation exposure and related cancer risk among children aims:

- To examine the association between radiation exposure from CT scans and subsequent risk of leukemia and brain tumors
- To describe patterns of CT scan use, corresponding estimated radiation exposure, as well as collective radiation dose among children and adolescents in the past
- To examine the confounding effect of cancer susceptibility syndromes between radiation exposure from CT scans and risks of leukemia and brain tumors

For one chapter in this thesis a hospital-based cohort study among adults who received a CT scan at the Columbia University Medical Center, New York was established. This cohort study included empirical data about adults who received at least one CT scan before 2015, including personal information, date of examination, type of scan and reason for the scan, cancer incidence and vital status. The aim of this study is:

- To examine reasons for CT scans as a confounder of CT-related radiation cancer risk among adults
Structure of the thesis

Chapter 2 presents the design and methodology of the Dutch Pediatric CT Study, regarding risk of leukemia and brain tumors in children after radiation exposure from CT scans. In Chapter 3, we estimate nation-wide numbers of CT scans and describe patterns and trends of CT scan use among children in the Netherlands. In Chapter 4, the results of the Dutch Pediatric CT Study are presented on the association between radiation from CT scans and the risks of leukemia and brain tumors. Chapter 5 assesses the magnitude of the effect of bias caused by cancer susceptibility syndromes (CSS) on the CT-related radiation risks for leukemia and brain tumors. This is followed by Chapter 6, which investigates the confounding effect of reasons for CT scans on CT-related radiation risks among adults using a hospital-based cohort of adults who received a CT scan at the Columbia University Medical Center in New York City. The results of the studies described in this thesis are discussed in Chapter 7 and clinical implications and recommendations for further research are given.
References


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