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Malignancies in Sweden after the Chernobyl accident in 1986

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In memory of Olav

ABSTRACT

On 26 April 1986 an accident occurred in the Chernobyl nuclear power plant resulting in the release of large amount of radionuclides. Almost five percent of the total released caesium-137 was deposited in Sweden. The incidence of malignancies in the most affected counties in Sweden was investigated in three epidemiological studies.

In the first study the incidence of malignancies in children and adolescents was studied for the period 1978-1992. The parishes and their inhabitants were classified according to the ground deposition of caesium-137 on an analogue map provided be the Swedish Radiological Protection Authority. A continuous increase of brain tumour incidence observed during the time of the study had no clear relationship to the Chernobyl fallout. A somewhat decreased relative risk of ALL was observed in areas with increased deposition. Other malignancies showed no changes in incidence over time or with regard to the exposure of caesium-137. In study II and III we enlarged the study base by including adults. We improved the methodology by defining a cohort of subjects who lived in the same parish from 31 December 1985 to 31 December 1987. The inhabitants from seven counties were included. Parishes were classified the same way as in study I. Due to the large number of individuals six exposure categories could be created; <3, 3–29, 30–39, 40–59, 60–79, and 80–120 kBq caesium-137/m^2. The inhabitants of the 117 non-affected parishes (<3 kBq/m^2) served as reference. During the 1988-1996 follow-up, 22,409 malignancies were recorded. The MH-IRR in the fully adjusted model was 1.00 (reference), 1.05, 1.03, 1.08, 1.10 and 1.21, respectively. ERR was 0.11 per 100 kBq/m^2 (95% CL 0.03;0.20). A more advanced method was used in Study III by ignoring the exposure classification for parishes, and instead matching the dwelling coordinate to a digital map of deposition of casesium-137. In spite of a more valid exposure classification the risk estimates were similar in study II and III. Also, the ERR during the longer follow-up of 1988-1999 was almost identical, 0.10 per 100 kBq/m^2 (95% CL 0.00;0.23). The strongest dose-response relationship was seen in the first four years (1988-1991). No obvious excess for leukaemia or thyroid cancer was recognised in either study II or III. The estimated number of exposure related cases was calculated to 849 in study II and 1,278 in study III. Our interpretation is that we have shown an increased incidence of total malignancies with dose-response relationship for caesium-137, only a few years after the Chernobyl accident. In study IV we compared the two different ways of classifying the exposure in study II and III. Out of the 450 parishes 111 got a different classification. The similar risk estimates in study II and III could probably be explained by relatively homogenous exposure in the parishes making the intra-parish difference less influential, especially when included in categories. In study V we examined the uri-

nary excretion of 8-OHdG in Belarussian children from areas with high and low fallout of caesium-137, respectively. We found significantly lower urinary 8-OHdG levels in children from rural contaminated areas compared to urban uncontaminated areas, suggesting an urban, rather than a radiation related, risk factor.

Using the Hill criteria for causality there is support for a causal inference between the fallout of caesium-137 from the Chernobyl accident and the increased incidence in total malignancies in Northern Sweden.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by Roman numerals:

I. Tondel M, Carlsson G, Hardell L, Eriksson M, Jakobsson S, Flodin U, Skoldestig A, Axelson O. Incidence of neoplasms in ages 0-19 y in parts of Sweden with high 137Cs fallout after the Chernobyl accident. *Health Phys* 1996; 71: 947-950.

II. Tondel M, Hjalmarsson P, Hardell L, Carlsson G, Axelson O. Increase of regional total cancer incidence in North Sweden due to the Chernobyl accident? *J Epidemiol Community Health* 2004; **58**: 1011-1016.

III. Tondel M, Lindgren P, Hjalmarsson P, Hardell L, Persson B. Increased incidence of malignancies in Sweden after the Chernobyl accident – a promoting effect? *Am J Ind Med* 2006; **49**: 159–168.

IV. Tondel M, Lindgren P, Garvin P, Persson B. Parish classification or dwelling coordinate for exposure assessment in environmental epidemiology – a comparative study using Geographical Information System. *Submitted.*

V. Tondel M, Arynchyn P, Jonsson P, Persson B, Tagesson C. Urinary 8-hydroxydeoxyguanosine in Belarussian children relates to urban living rather than radiation dose after the Chernobyl accident: A pilot study. *Arch Environ Contam Toxicol* 2005; **48**, 515–519.

CONTENTS

ABBREVIATIONS

8-OHdG: 8-hydroxydeoxyguanosine

ALL: Acute Lymphatic Leukaemia

Bq: Becquerel

CL: Confidence Limits

CML: Chronic Myelogenous Leukaemia

EAR: Excess Absolute Risk

DNA: DeoxyriboNucleic Acid

ERR: Excess Relative Risk

GIS: Geographical Information System

Gy: Gray

H-regions: Homogeneity-regions

IARC: International Agency for Research on Cancer

ICD: International Classification of Diseases

ICRP: International Commission on Radiological Protection

mGy/y: milliGray per year

MH-IRR: Mantel Haenszel Incidence Rate Ratio

mSv/y: milliSievert per year

nGy/h: nanoGray per hour

PBq: PetaBecquerel (10^{15} Bq)

SIRD: Standardized Incidence Rate Difference per 100 000 person-years

SMR: Standardised Mortality Ratio

SRR: Standardised Rate Ratio

TGR: Terrestrial Gamma-Radiation

UNSCEAR: United Nations Scientific Committee on the Effects of Atomic Radiation

USSR: Union of Soviet Socialist Republics

WHO: World Health Organization

INTRODUCTION

On 26 April, 1986 an accident occurred at the Chernobyl nuclear power plant and a large amount of radioactive material was released with the highest ground deposition of caesium-137 in Belarus, Russia and Ukraine[32]. Almost five percent of the total released caesium-137 from the reactor was deposited in Sweden and unequally distributed in the eastern coastal regions from Stockholm in the south to Umeå in the north[78]. There was a public concern, especially in the regions with the highest fallout, and also awareness among authorities, that the accident might have a health impact.

The first public worldwide report of the accident was in a Swedish local radio station (Radio Uppland) at 12.05 on Monday, April, 28 after increased radioactivity had been measured in the Forsmark nuclear power plant at 7.00 o'clock that morning. After analyzing radiological measurements at the other nuclear power plants in Sweden together with weather information it was absolutely clear to the Swedish Radiological Protection Authority at 13.30 o'clock that the origin of the measured radioactivity was from a reactor accident in the Ukraine, rather than an accident in the reactor of Forsmark, or due to a nuclear weapons test. However, the first admission by the Russian authorities, of an accident in Chernobyl, was made the same evening on television during the news program Vremja at 21.00 Moscow time[117].

During the afternoon and evening of April, 28 it rained heavily in Västernorrland and Gävleborg counties. Two medical doctors in these counties Göran Carlsson, Department of Health Policy, Härnösand and Sören Jakobsson, Department of Public Health Medicine, Gävle were concerned about the potential health consequences, on the very day that the news about the accident was broadcasted. The weeks following the accident were intense as their counties were the most affected in Sweden by the fallout. Meetings with local authorities and information to the public stressed the importance to follow-up the health consequences. Therefore, contacts were taken with professor Olav Axelson, Division of Occupational and Environmental Medicine at Linköping University and with oncologist Lennart Hardell, Department of Oncology, University Hospital in Umeå. On 8 April, 1987 a planning meeting took place in Linköping with these four physicians to discuss the possibilities and design of an epidemiological study. Martin Eriksson from Gävle and Ulf Flodin from Linköping had also joined the team of scientists in the inaugural meeting in Linköping. The radioactive fallout was extremely unequally distributed in Sweden and therefore suitable for such a study. After discussions on latency period, it was agreed to study leukaemia in children, supposed to have a very

short latency. Martin Tondel joined the group late January, 1993. The members of this group together with the statistician Åsa Sköldestig were the authors of study I. It was obvious from the very beginning that it would be a challenge to study the low dose exposure to the Swedish population, and therefore the emphasis was on selecting the appropriate study methods (p. 19). The purpose of the study on the impact of the fallout on malignancies was twofold: to be able to respond to the exposed persons whether there was an effect or not, and also take a scientific contribution to epidemiological studies on low dose ionising radiation.

The follow-up of malignancies among Japanese survivors after the atomic bomb attack over Japan in 1945 has been fundamental for our understanding of the carcinogenic potential of ionising radiation, and in fact, has become a template for later studies. Historically, the impact has been paramount on radiological protection worldwide. For more than a half a century a lot of effort was spent on quantifying the risks of ionising radiation with numerous dose-response models. However, there are some important differences with the exposure from the Chernobyl accident, outlined in table 1, which is yet another justification for our studies. Due to the much larger exposed population after the Chernobyl accident, the follow-up studies may have as large impact on future radiological protection than the Hiroshima-Nagasaki catastrophe.

The literature on ionising radiation is so immense it has become necessary to restrict the literature review to environmental exposure to ionising radiation in relation to cancer epidemiology with focus on the Chernobyl accident.

Table 1. The two largest man-made exposures from ionising radiation to humans.

	Hiroshima-Nagasaki, Japan	Chernobyl accident, USSR
Source	Atomic bombs	Nuclear reactor explosion
Exposure	Instant high in 1945	Protracted low since 1986
Radiation	Neutron, gamma	Gamma
Route of exposure	External	External and internal
Dose assessment	Final dosimetry 2002?	Ongoing
Follow-up	1950-	1986-
Population	Two cities, 560,000 in 1945	Europe, 572,000,000 in 1986
Malignancies	Mortality	Incidence, mortality
Strength	Already long time follow-up	Long time follow-up in future
	High doses	Low doses
	Individual dose assessment	Dose assessment from 1986
Weakness	No data 1945-1950	Short follow-up period
	Few persons with low dose	Few persons with high dose
	Extrapolation to low dose	No individual dose assessment

AIMS OF THE INVESTIGATION

The overall aim of our studies is to answer if there is an impact of the radioactive fallout from the Chernobyl accident on human health. The primary objectives for this thesis are:

Is there a detectable increased incidence of malignancies in northern Sweden related to caesium-137?

Can increased incidence of leukaemia or thyroid cancer be identified i.e. malignancies with *a priori* short latency period, especially in childhood?

If there is an increased incidence of malignancies, can also a dose-response relationship be described?

Is there a temporal pattern in the incidence of malignancies?

Is it possible to identify confounding factors in an epidemiological environmental study of this type?

How exact can exposure assessment be made in a large cohort, given the prerequisites?

Can increased excretion of urinary 8-OHdG in children be detected as an effect of radioactive contamination in Belarus?

BACKGROUND

Chernobyl accident versus Hiroshima

The accident at the Chernobyl nuclear power plant in Ukraine, USSR occurred on 26 April, 1986 and was the most serious accident in the history of nuclear power industry. In short, due to basic engineering deficiency of the reactor model as such, and due to faulty actions by the operators, including switching off the emergency safety system, the steam pressure in reactor 4 built up, until a steam explosion occurred at 01.23:49. The reactor lid went off and the reactor core was exposed together with the graphite moderator. In the resulting fire the release of 5,300 PBq of radioactive material (excluding noble gases) continued until it could be stopped after 10 days. Within a few days to weeks 30 power plant employees and firemen died including 28 persons with acute radiation syndrome who had received a whole body dose of 2-16 Gy[137], which equals a dose at 1,000 metres from the hypocentre in Hiroshima[149]. During 1986 approximately 116,000 people were evacuated from areas surrounding the Chernobyl nuclear power plant i.e. areas with a ground contamination of >1,480 kBq caesium-137/m^2. Approximately, 600,000 persons took part in the recovery work (liquidators) until 1990[137]. The total amount of released radioactive substances has been calculated to be 200 times more than the combined release from the atomic bombs dropped on Hiroshima and Nagasaki[145].

Ionising radiation

Physics

Ionising radiation can either be particles (electrons, protons, alpha-particles or heavy particles) or electromagnetic radiation (X-rays or gamma-rays, also called photons). When radioactive substances spontaneously disintegrate they give rise to particles and/or photons. The number of disintegrations per second is called Becquerel (Bq). After the Chernobyl accident caesium-137 and other nuclides were deposited in Sweden. The Swedish Radiation Protection Authority produced maps with deposition of caesium-137, as this nuclide was supposed to be the largest contributor to the long-term effective dose in Sweden, and the deposition was given in kBq/m^2.

The absorbed dose is the energy absorbed per kilogram of tissue (Joule per kilogram or Gray) and can be used to estimate the effective dose taken into account the quality of radiation (particles or electromagnetic radiation, with different relative biological effectiveness) and the sensitivity of developing malignancies in different organs. The effective dose is given in

Sievert (or more often in mSv). In the case of gamma-radiation the absorbed dose and the effective dose will have the same numerical value because the relative biological effectiveness is one. Dose rate is the absorbed dose by hour and usually expressed as nGy/h. Assuming a constant absorbed dose rate, the annual absorbed dose can be calculated by multiplying the dose rate with the number of hours per year.

Biological effect

Photons travel relatively large distances in tissue unimpeded and transfer part or all of the energy to electrons. The resulting energetic electrons interact with the DNA molecule and create damage in form of strand breaks or damaged bases i.e. direct effect. Indirect effects can occur after a photon interacts with a water molecule creating highly reactive free radicals that subsequently can damage DNA[26]. The cell can often repair these damages, however more unlikely double strand breaks. The result in terms of carcinogenic potential depends on where the DNA molecule was damaged, and also on how successful the repair was. At low doses the DNA lesions are few and therefore the repair mechanism is more often successful with fewer defect cells compared to repair after high dose exposure. High energetic neutron radiation, an important contribution to the dose in Hiroshima-Nagasaki, but not after the Chernobyl accident, is more likely to cause double strand breaks in DNA compared to gamma-radiation, hence a higher relative biological effectiveness. Different types of radiation therefore have different biological effect. The environmental exposure to ionising radiation consists of gamma-radiation from uranium, thorium and caesium; alpha-radiation from radon; muons and neutrons from cosmic radiation. The relative biological effectiveness is one for gamma-radiation and muons, 20 for alpha-radiation, and 5 for neutrons[58]. Not only the biological effect of radiation differ (radiation weighting factors), but also the sensitivity of different organs to develop malignancies varies (tissue weighting factors) which is taken into account when calculating the effective dose[58].

Ionising radiation generates free radicals *in vivo* which can cause oxidative damage to DNA and contributes to carcinogenesis[63, 71]. The modified base 8-OHdG is an oxidative adduct-form of deoxyguanosine and considered to be a useful marker of oxidative stress[23, 40, 47, 48, 148]. The oxidative hydroxylation of guanine in 8-position is a frequent and highly mutagenic lesion in the nuclear DNA. It leads to lack of base pairing specificity and misreading of the modified base and adjacent residues[148]. If not removed from DNA, replication of the damaged sequence will lead to transversion of guanine to thymine. Another mechanism for 8-OHdG mutagenesis is the incorporation of free 8-OHdGGTP from the nucleotide pool into DNA opposite of adenine during either replication or repair. Such mis-incorporation will lead to

transversion from adenine to guanine through activation of the mismatch repair pathway which will remove adenine opposite 8-OHdG and replace it with cytosine. This base pair will be repaired in turn by base excision repair which will remove 8-OHdG opposite cytosine and replace it with guanine[48]. 8-OHdG was first identified in DNA that had been irradiated by X-ray in an aqueous solution *in vitro*; the formation of 8-OHdG was found to increase linearly with radiation dose and was almost completely inhibited by an $OH^{\bullet}$ radical scavenger[64]. Later studies demonstrated increased urinary excretion of 8-OHdG after radiation treatment of cancer patients[15, 125], but also due to environmental radiation exposure, at much lower dose rates than in cancer patients[119]. However, the interpretation of an increased urinary 8-OHdG excretion can be difficult, either a result of oxidative stress on the DNA, with potential carcinogenic effect, or an indication on effective repair of DNA.

Environmental exposure to ionising radiation

The Swedish average of the so-called background radiation is 3.22 mSv per year[151]. The background radiation includes TGR (0.08 mSv), indoor gamma-radiation (0.54 mSv), food and water (0.20 mSv), radon (2.10 mSv) and cosmic radiation (0.30 mSv). Additional, the body content of the naturally occurring potassium-40 gives an annual dose of 0.17 mSv, medical diagnostics 0.70 mSv and other sources 0.11 mSv including dose contribution from the atmospheric nuclear weapons tests, releases from nuclear facilities etc. The total average exposure in Sweden is therefore 4.20 mSv per year. It is important to know that these doses are averages with large individual variability.

Terrestrial and indoor gamma-radiation

TGR originates principally from the radioactive decay of potassium, uranium and thorium which can be found naturally in the upper soils and/or rocks[4]. In Sweden uranium can be found in granites, but also in alum shale, the latter used for lightweight alum shale concrete, for house construction, and was produced between 1929 to 1975[81]. In masonry buildings most of the gamma-radiation emanate from the building materials extracted from the earth, whereas in wooden buildings a larger part of the dose comes from the ground. The indoor exposure to gamma-radiation varies from about 20 nGy/h in wooden buildings on ground with low radioactivity to about 1,100 nGy/h in houses constructed out of lightweight concrete made of alum shale. The average indoor gamma dose rate in all Swedish buildings is 111 nGy/h[150].

From aerial measurements performed by the Swedish Geological Survey the mean outdoor gamma-radiation in Sweden is 90 nGy/h[150]. Comparison of the Swedish average to the highest

terrestrial gamma-radiation in the world i.e. Kerala, India with up to 70 mGy per year[86] and in Yangjiang, China with 6.4 mSv per year[127], shows that these places are a factor 90 and 8 higher than in Sweden, respectively.

Food and water

All food we eat contains different natural radionuclides. The highest dose contributed by food intake, comes from grain and leaf vegetables, although radionuclides are present in fish products at higher concentration. If, however, the household depends on drinking water from a well drilled in uranium containing bedrock, the highest dose is contributed by radon in the water. The annual average dose from food and water in Sweden is 0.2 mSv. High fish consumption may reach 0.7 mSv per year. Consumers of water from a highly radioactive well may intake a dose of 10 mSv[3].

Radon

Uranium-238, as well as thorium-232, decay into radon. There are three radon isotopes, but radon-222 presents the main health concern for man. Because radon is a gas and can enter the human body through inhalation, the main target organ is the lung. Radon dilutes quickly in open air. Therefore the environmental exposure take place indoors[4]. Normal concentrations of radon is 2-15 Bq/m^3 in outdoor air[108]. The exposure can either be from radon entering the buildings from the ground, from groundwater used for drinking, or from radon present in building materials. Lightweight alum shale concrete is used in about 10 percent of the Swedish houses. An annual average exceeding 200 Bq/m^3 has been estimated for 400,000 out of about 4 million dwellings in Sweden[108].

Cosmic radiation

At ground level muons are the dominant component of cosmic radiation, although a significant dose is contributed by neutron radiation with a relative biological effect of 5, compared to muons with one[58]. In Sweden at sea level the annual effective dose from cosmic radiation is 0.27 mSv including a neutron contribution of 0.03 mSv. Although both latitude and altitude play a roll with about 10 percent less cosmic radiation at the equator in comparison to Sweden, no important difference exists between south and north Sweden. The altitude factor is much more important with an annual effective dose of ionising radiation of 1.12 mSv, including a neutron contribution of 0.90 mSv, in La Paz (3,900 metres above sea level), the capital of Bolivia[135]. In Sweden 80 percent of the population are settled between sea level and an elevation of 100 metres. Hence, all have practical the same dose contribution from cosmic radiation[150].

Hiroshima-Nagasaki

After the explosion of the atomic bombs in Japan neutron-radiation dominated, but also gamma-radiation contributed to the dose, with the neutron component decreasing with increasing distance from the hypocentre. Out of an estimated population of 560,000 in Hiroshima and Nagasaki, approximately 284,000 persons survived to the census 1950. The cohort of survivors was established in 1950 and included 120,000 persons; 94,000 exposed and 26,000 unexposed. Individual dose assessment has repeatedly been re-calculated up to the latest dosimetry in 2002[149]. In the most recent follow-up of 86,611 atomic bomb survivors, the dose for solid cancer ranged from <0.005 to >2 Sv[102].

Nuclear weapons test

A total of 543 atmospheric nuclear weapons tests were conducted between 1945 and 1980 with a wide range of nuclides transported into the stratosphere with the result of a global fallout until the mid of 1980's. The two main test sites have been the Nevada test site in the US where 86 atmospheric tests were conducted 1951-1962 and the Semipalatinsk test site in the USSR with 116 atmospheric tests 1949-1962. The United States has also conducted 41 atmospheric nuclear weapons tests in Bikini and Enewetak atolls 1946-1958 and USSR 91 tests in Novaya Zemlya 1955-1962. France performed 41 atmospheric nuclear weapons tests in French Polynesia 1966-1974[136]. A total of 948 PBq caesium-137 was released into the air during 30 years of atmospheric nuclear weapons testing and 1.25 PBq was deposited in Sweden[78, 136]. This amount can be compared with the 4.25 PBq caesium-137 deposited in Sweden after the Chernobyl accident[78]. In contrast to the fallout in Sweden from the Chernobyl accident the deposition of radionuclides from the atmospheric nuclear weapons tests was almost uniform in Sweden with a remaining caesium-137 activity of 0-3 kBq/m^2 in 1985[105, 107]. However, there was a long-term transfer of nuclides into the food chain and caused considerable internal dose levels not only for some specific groups, but also for the general public, because no food restrictions were applied in Sweden in the 1960's. From whole body measurements the peak of internal dose was estimated in 1965 both for reindeer herders (1 mSv), and for city residents (0.03 mSv)[106].

Chernobyl

Five percent out of the total 85 PBq released caesium-137 from the Chernobyl reactor was deposited in Sweden during the ensuing days, especially during the heavy rainfall on April 28-29, with an unequal distribution in the eastern coastal regions from Stockholm in the south to Umeå in the north[78]. The main contributors to the dose rate in the first weeks were short-lived nuclides replaced by the long-lived caesium-134 and caesium-137[37]. The maximum ef-

fective dose to the population the first two years (1986-1987), including all nuclides, has been calculated to about 7-10 mSv[37]. This dose received during the first two years after the accident, represents some 20 percent of the dose received during a 50-year period[37]. When the extent of exposure in Sweden was revealed, the authorities issued recommendations on food intake to the population including a food regulation program with a maximum allowed activity in food sold to the public of 300 kBq caesium-137 per kilogram[96]. This threshold limit was set to keep the dose from food intake below 1 mSv per year. In 1987 a new limit of 1,500 kBq/kg was introduced for game and reindeer meat, wild berries, mushrooms, sweet water fish and nuts sold to the public. The argument was that the Swedes have such low consumption of this food that the annual dose to the general public would not exceed 1 mSv with this new regulation. However, specific information was given to higher exposed groups such as hunters, anglers and reindeer herders. Despite these rather far-reaching actions the body content of caesium-137 after the Chernobyl accident peaked in 1987 with reindeer herders even exceeding the levels in 1965. Also the urban populations had a corresponding increase in the body content of caesium-137, reaching the same internal dose as in the mid 1960's. In between these extremes were doses measured in farmers and hunters of Gävleborg and Uppsala counties[106]. After these experiences it has become possible to develop an algorithm for effective dose over a 70 years period depending on the ground deposition of caesium-137 i.e. the transfer values has been calculated to 700 μSv/kBq m^{-2} for reindeer herders, 100 μSv/kBq m^{-2} for hunters, 40-150 μSv/kBq m^{-2} for rural populations, 50 μSv/kBq m^{-2} for farmers and 20-30 μSv/kBq m^{-2} for urban populations, respectively[107].

At the time of the Chernobyl accident 2.2 million inhabitants in Belarus lived in areas with a caesium-137 deposition over 37 kBq/m^2, which by definition was considered as being exposed by the authorities[68]. This is comparable to 41,477 individuals classified over 37 kBq/m^2 in study III. Initially, a considerable part of exposure to the population in Belarus came from external irradiation and inhalation, followed by ingestion of foodstuff containing caesium-137 for those people living in regions with high fallout.

Malignancies

Carcinogenesis

Gamma-radiation is both mutagenic and carcinogenic and therefore classified as a complete carcinogen (group 1) according to the International Agency for Research on Cancer[56]. Radiation is unique, because it has been able to stimulate cancer growth in almost all organs. The carcinogenic process can be described as a multi-step process emanating from a single cell and involving tumour initiation, tumour promotion and tumour progression. The initiation is a

mutation in a single cell with altered DNA function as the first step to a malignancy. The result of the promotion is an early tumour development including mechanisms of cell-to-cell communication, growth stimulation, cellular differentiation, mutational as well as non-mutational (epigenetic) processes in the initiated cell. The malignant progression is a late tumourogenic phase in which the cells become increasingly autonomous and acquire capacity for invasion. This capability for malignant growth includes self-sufficiency in growth signals, insensitivity to anti-growth signals, evading programmed cell death, limitless replicative potential, sustained growth of new vessels, tissue invasion and metastasis[49]. After initiation of a cell these steps are necessary before a malignancy can be large enough to be diagnosed.

Even if ionising radiation is recognised as a tumour initiator agent it is also known to play a role throughout the multi-step process. A single acute dose of gamma-radiation produces a dose-dependent increase in risk of malignancies in humans, more pronounced than for chronic or fractionated doses, with children and adolescents being more sensitive. Certain organs seem to be more prone to develop malignancies, hence the tissue weighting factor for calculating the effective dose, although a statistically significant effect of radiation for all malignancies as a group has been demonstrated[137]. In the first follow-up of the atomic bomb survivors, the mortality from leukaemia was increased and believed to be the only malignancy related to ionising radiation. More and more sites have been included on this list. In the report to the general assembly in the United Nations[137] risk estimates on total malignancies were included, while later BEIR VII regarded all solid cancer and leukaemia to be related to radiation[26]. Total malignancies were increased in the latest follow-up of the atomic bomb survivors[102]. For decades it has been widely accepted that chronic lymphatic leukaemia is not associated to ionising radiation, however questioned in a recent review[109].

Classification

The cases of malignancies in our studies were retrieved from the National Cancer Registry using the coding in ICD-7[144]. The National Cancer Registry defines malignancies as all malignant neoplasms (carcinoma, sarcoma, malignant lymphoma, leukaemia and malignant teratoma), but also histological benign tumours of the central nervous system and some specified endocrine tumours[128].

Cancer epidemiology

In general

Epidemiology seeks to describe the populations at risk and to discover causes of disease. Most diseases are multifactorial i.e. a combination of factors are necessary to develop disease, not identical factors for all individuals with the disease[111]. In epidemiology it is usually not possible to identify all these factors, but increased risks indicate that such factors have been revealed. Epidemiological studies have been of particular importance in assessing the potential human health risks associated with radiation exposure.

Environmental malignancies

In Kerala, India there is still no evidence that the incidence of total malignancies is consistently higher because of the high terrestrial radiation[86]. The mortality of malignancies in Yangjiang, China has not increased, including leukemia mortality[127]. However, other epidemiological studies on adult populations have shown statistically significant increased incidence or mortality of different malignancies due to the terrestrial gamma-radiation[129, 134]. Other studies have failed to show such a relation[2, 52, 91, 133, 138]. For leukaemia the results have been similar with studies both showing a relation to TGR[36, 50, 129, 134] and studies without any relationship[28, 38, 52, 60, 91, 115].

Results from epidemiological studies have been very consistent regarding lung cancer and interaction between radon and tobacco smoking, but no clear association has been seen between radon and other forms of malignancies[30]. In comparison, radon released from tap water is probably a weak risk factor for lung cancer, in the United States accounting for only about 0.8 percent of the total number of radon-associated lung cancer deaths[20]. However, radon in drinking water has also been suggested to be a risk factor for stomach cancer by direct exposure from the water or indirectly through swallowed pulmonary secretion[66]. In Finland leukaemia, stomach cancer and cancer of the urinary organs, respectively, have been studied in relation to drinking water contaminated with uranium, radium and radon without any indication of increased risks from either of these nuclides[7, 8, 69] .

Only a few epidemiological studies on cosmic radiation have been performed, due to lack of national cancer registries in countries with high altitude, but also difficulties related to finding a proper comparison group. However, four such studies have been performed in the United States with no excess mortality from leukaemia or other malignancies in relation to high altitude[29, 35, 76, 140].

In the first follow-up of the survivors of the atomic bombs over Hiroshima and Nagasaki a significantly increased incidence in leukaemia was found[41]. In further follow-up studies an additional number of cancer sites has been associated with ionising radiation from the atomic bombs. In the latest follow-up of the Hiroshima-Nagasaki cohort there were 10,127 deaths in solid cancer, compared to 9,647 expected, and an additional 296 leukaemia deaths (203 expected). For the first time a statistically upward curvature in dose-response was seen for solid cancer in the dose range 0-2 Sv[102]. This upward curvature was even more pronounced in the dose range 0 to 0.5 Sv[99].

Results of reviews of the epidemiological studies on the general population around the nuclear weapons test sites (Nevada, Semipalatinsk) have been inconclusive because of shortcomings in design[26, 56]. On the contrary, a recent review concludes that a clearly excess of thyroid cancer has been demonstrated among the highly exposed Marshall Islanders close to the nuclear weapons test site at Bikini and Enewetak atolls. In addition, a likely increased risk of thyroid cancer and leukaemia was demonstrated around the Nevada test site[43]. A significant 2-3 times increase in thyroid cancer incidence has also been seen, in the period 1985-1995, among Maohis in the French Polynesia compared to Maoris in New Zealand and Hawaiians in Hawaii, with supposedly the same ethnic origin[33]. A non-significant ($p=0.1$) increase in thyroid cancer incidence was observed with decreasing distance between place of birth and the Mururoa test site in females born between 1950-1975. In the follow-up of 19,545 persons around the Semipalatinsk test site a significant trend of solid cancers with dose was seen ($p<0.0001$) 1960-1999[11]. Incidence in childhood leukaemia in the Nordic countries has indicated a small increase in relation to fallout from atmospheric nuclear weapons testing[31]. A study on incidence of thyroid cancer by birth cohorts in Norway and Sweden showed the highest risk in children born during 1951-1962, i.e. the highest exposed group from radioactive iodine from the atmospheric nuclear weapons tests in Novaya Zemlya, compared to unexposed children born 1963-1970[72].

In Belarus, Ukraine and the western part of Russia there has been a dramatic increase in thyroid cancer incidence in children in relation to the Chernobyl accident. So far, 1,800 cases of thyroid cancer among children can be attributed the exposure from the accident[137]. An overall evaluation by an expert group assigned by the WHO has found, that apart from the large increase in thyroid cancer incidence, there is no clearly demonstrated radiation-related increased cancer risk in the former USSR[21]. However, there exist a study from the former USSR indicating an increased risk for acute leukaemia in the general population related to the Chernobyl accident[93]. In all regions of Belarus there has been a significant increase in incidence of total

malignancies in the period 1990-2000 compared to 1976-1985, which was most pronounced in the Gomel region with the highest contamination after the Chernobyl accident[94]. However, there has been no recognizable increase in childhood leukaemia in the most contaminated part of Belarus up to 1998[42].

In Western Europe concerns about the consequences of the Chernobyl accident have focused on childhood malignancies, especially leukaemia, since the shortest latency period after irradiation seems to be for leukaemia in children. Several studies on childhood leukaemia, have been performed outside the former USSR[6, 54, 74, 95, 97, 132], but none has shown any clear relationship to the fallout from the Chernobyl accident. However, exposure to radiation *in utero* from the Chernobyl accident has shown a significantly increased risk of childhood leukaemia in Greece, Germany and Ukraine[80, 92, 98, 122], but not in Belarus [59]. In an additional study a peak in the incidence of infant neuroblastoma in West Germany in 1988 could not be explained by the Chernobyl fallout because parents of cases tended to eat less locally grown food than the parents of controls[79].

Recent studies outside the former USSR have also shown an increase in the thyroid cancer incidence suggested to be related to the accident[27, 44, 85, 90], but other studies have failed to link an increase to the Chernobyl accident[19, 24, 83, 100, 113, 124].

Geographical Information System

The Geographical Information System (GIS) is a computer based analytical tool for spatial analyses. Its capability to quickly and easily link large geospatial databases with health databases represents an important technological breakthrough in environmental epidemiology[18]. Overlays can be done using various maps with different geochemical data, geographical data, population characteristics and information on disease. Data can then be analyzed on different levels e.g. county, parish, postal code area or address. Important for the result is the resolution on exposure and disease, because the analyses need to be on the same level to which the variables have been assigned. The geographical distribution of diseases in relation to various exposures with a spatial distribution can therefore be used to generate hypotheses, but also in analytical epidemiology. Relatively new applications for GIS are control of communicable diseases, environmental health protection and health care planning and policy[73, 112].

METHODOLOGY

Epidemiological methodology in general

It is important in epidemiology to use appropriate epidemiological methods in relation to the hypothesis, but the method also depends on the prerequisites for obtaining data. In radiation epidemiology there has been lot of effort to find such methods to determine the risk of malignancies. It is widely accepted for ionising radiation that the dose-response curve is linear for all sites of malignancies, with no threshold, except for leukaemia where a linear-quadratic dose-response is a better fit[26, 137]. In other words a well-designed epidemiological study with high power could detect even a small increased risk of malignancies in a population, as no radiation dose is too low for such (stochastic) effect. Power is the probability that the study will yield a statistically significant departure from the null association. In a cohort study the power depends on the disease rate in the non-exposed group, the relative risk under the alternative hypothesis, the sizes of exposed and non-exposed groups, and the total number of the study participants[22]. It is therefore inevitable to rely on registers when studying large cohorts. Leukaemia is so rare that the cohort must be extra large to show a significantly increased incidence related to any risk factor. Hence, with limited economical resources there is a contradiction between detailed exposure assessment in environmental epidemiological studies and the magnitude of risk.

Register based epidemiology

Epidemiological studies with only register information are preferable descriptive studies, often referred to as ecological, although they could also be analytical studies. Ecological studies have certain characteristics such as the analysis is not individual, have no information on potential confounding factors, the outcome is not confirmed on the individual level, do not account for population migration i.e. sensitive to random fluctuations in the spatial or temporal distributions. Analytical studies are more sophisticated usually including information on exposure or disease at the individual level, providing the opportunity to adjust for potential confounding factors. Either incidence or mortality statistics on malignancies (or other diseases) can be used in these two epidemiological study designs. The former is to prefer because not all malignancies are mortal, hence not recorded on the death certificates.

Ethical considerations

An important issue in all register-based epidemiology is informed consent. According to the Helsinki declaration everyone included in a scientific study has the right to give consent to participate[147]. On the other hand the information obtained from registries is seldom controver-

sial, with the most important exception a diagnosis of malignancy or other sensitive outcomes. There is of course practical and financial problem to obtain a signed paper from all individuals in a large cohort, but the Data Inspection Board agreed that advertising in the newspapers, about our Chernobyl study, fulfilled the requirement for informed consent. Interestingly, none contacted us to withdraw from the study or wanted information in the files about themselves[130]. After matching the personal characteristics with the parish codes and dwelling coordinate, respectively, our file could be analysed unidentified.

Risk estimates

When analysing small increased risks it is of particular importance with adjustment for potential confounding factors in order to minimize a wrong interpretation. However, there can be a risk of an over-adjustment if the confounding factors are too closely inter-linked, with perhaps the consequence of a significant result being not significant. To describe the statistical uncertainty the CL (or confidence interval) is often used. A 95 percent CL should be interpreted so that if the study is repeated a 100 times, the point estimate will be within the boundaries of the uncertainty 95 times. However, adjustment for confounding can either result in an increased risk (negative confounding) or to a decreased risk estimate (positive confounding). In environmental studies risks are often small which in turn makes interpretation a challenge, but also emphasises the need for exposure assessment and adjustment of potential confounding factors. The increased risk can be seen as a relative or an absolute risk. However, if the background incidence of a disease is high an increased risk can be more evident in absolute terms.

In traditional radiation epidemiology ERR (ERR=SRR-1) and EAR (definition below) are used to compare results. The ERR implies a linear dose-response relationship and has been justified as a risk estimate because the consistent linear dose-response in several evaluations on radiation risks[26, 137]. The ERR is expressed per unit dose in order to compare the risk estimate between studies. The advantage to use ERR is that a single risk estimate quantifies the risk, which however can be misleading if a linear dose-response does not exist. In study II ERR was calculated using Poisson regression taking the midpoint in each exposure interval as the exposure level, while in study III caesium-137 could be treated as a continuous variable.

EAR per 10^5 person-years is based on the SIRD per 10^5 person-years, between two time periods using the following formulas:

$SIRD_{ij} = (SIR_{ij} - SIR_{jk})$

$EAR_{ij} = (SIRD_{ij} – SIRD_{0i})$

where

i = time period or follow-up, 1988-1996 in study II and 1988-1999 in study III,

j = exposure category,

k = 1986-1987,

0 = reference category, <3 kBq/m^2 in study II and 0-8 nGy/h in study III.

By definition $SIRD_{0i}$ is not influenced by the exposure i.e. is an underlying time trend or secular trend. The EAR has the advantage that it can be compared between studies provided that the incidences have been directly standardised for age using the same standard, e.g. in our case the European population as defined by the WHO[146].

Confounding

Confounding can be regarded as a mixing of the effects of the exposure being studied with effects of other factor(s) on risk of the health outcome of interest[22]. In register-based epidemiology the possibilities of adjusting risk estimates by potential confounding factors is limited because information on the individual level is usually limited. However, to assert confounding, such factor needs to be a risk factor at the same level as the exposure under study e.g. in order for tobacco smoking to be a confounding factor, it needs to be a risk factor on the parish level if the studied exposure also is classified at parish level. Confounding can be controlled either by stratification e.g. MH-IRR, or using regression models e.g. Poisson regression.

Attributable fraction

The attributable fraction is the proportion of cases that would not have occurred in the absence of exposure either among the exposed population or among the total population[121]. To calculate the absolute number of preventable cases of a disease the attributable fraction is multiplied by the total number of cases. The attributable fraction is calculated as the (RR-1)/RR, where RR stands for Rate Ratio. If there are several exposure categories the total number is the sum of preventable cases in each exposure category[121].

Statistical methods

In study I the statistical package SAS (SAS Institute Inc., SAS Campus Drive, Cary, NC 27513) was used. The epidemiological analyses in study II and III were performed in STATA Statistical Software, release 6.0, College Station, TX: Stata Corporation. In study V the statistical package SPSS, version 11.5.1 was used for non-parametric tests including Mann-Whitney test and Spearman when calculating correlation coefficients.

Exposure assessment – GIS and aerial measurements

The Geological Survey of Sweden conducts regularly aerial gamma spectrometry measurements on uranium-238, thorium-232 and potassium-40 since the end of the 1960's and annually after 1986 on caesium-137. The three former nuclides are natural, but caesium-137 is not. Because all these nuclides have their own unique gamma-spectra they can be measured separately in the aerial measurements. The flight distance from the ground is 60 metres with 200 metres between each line resulting in high accuracy. The Geological Survey compensates for factors that can influence the accuracy of the measurements such as absorption in air, humidity of the ground and close proximity to radon. A calibration programme reassures accurate measurements[1]. Thereafter digital maps are produced based on the content. Because of absorption of gamma-radiation in the soil, 80 percent of the measured radiation emanates from the upper 0.2 metres, i.e. upper surface of soil and/or the underlying rock. Uranium and thorium are expressed in parts per million and potassium in percent. Caesium-137 is expressed on the map as deposition in kBq/m^2.

The geophysical measurements from the Geological Survey of Sweden are collected in a database with coordinates from the Swedish national system (RT90). With conversion factors from the Geological Survey the total TGR from uranium, thorium and potassium can be calculated in nGy/h. One percent potassium gives a dose rate of 13.296 nGy/h, one ppm U-238 6.625 nGy/h and one ppm Th-232 2.309 nGy/h, respectively. By adding the dose rates for the different nuclides a total TGR can be obtained. With yet another conversion factor the caesium-137 can be calculated in nGy/h (1 kBq/m^2 equals 2.513 nGy/h)[39]. Hence, with all nuclides expressed in the same unit it enables comparison of risks for malignancies between caesium-137 and TGR.

The digital map on caesium-137 has over time successively become more and more detailed and is always backdated to May 1986. The data on the TGR are stored in coordinates and caesium-137 is given in a 200x200 metre grid. The coordinates on the TGR was transformed by us into a grid-format with GIS-technique in ArcView 3.2, in the same 200x200 metre grid for caesium-137.

Methodology by studies

Paper I

Study I was an open cohort of children and adolescents 0-19 years of age in six counties (Norrbotten, Västerbotten, Jämtland, Västernorrland, Gävleborg and Uppsala county) which

had a corresponding population of 346,000 on 31 December 1986. The annual incidence of malignancies was analysed in relation to the fallout of caesium-137. We used an analogue map on the ground deposition of caesium-137 produced by the Swedish Radiation Protection Authority, on the assignment of the Geological Survey of Sweden, to classify all 374 parishes in these 6 counties. The map had been produced after aerial gamma-measurements over the entire Sweden from May to October 1986 and given into 12 exposure categories. Due to the small size of the study, these categories had to be merged into three categories (<3, 3-39, >40 kBq/m^2). Information on individuals with malignancies was obtained from the regional cancer registries in Umeå and Uppsala for the period 1978-1992 i.e. name, age, address, diagnosis and year of malignancy. The total number of cases was 746 with the most frequent diagnosis being brain tumours (ICD-7 193.0, n=203) and ALL (ICD-7 204.0, n=151). The annual population statistics were provided from Statistics Sweden. The annual incidence of total malignancies was calculated in each exposure category, as well as the incidence of brain tumours and ALL. The advantage in the study design was that the incidence was compared before (1978-1986) and after the Chernobyl accident (1987-1992) in the same categories, hence eliminating many confounding factors with a geographical distribution.

Paper II

After study I we realized that the study base needed to be enlarged and therefore we decided to include adults in order to have enough power to detect an increased risk of malignancies, if it could be detectable with epidemiological methods. Secondly, we wanted to include as many counties as possible with significant fallout, in order to create more exposure categories, but also to include areas and populations within these counties having low fallout to serve as the reference. Thirdly, as the incidence in malignancies is higher in the cities, we did not want to include the population of Stockholm. Fourthly, if people had moved after the Chernobyl accident, for whatever reason, it could obfuscate an increased risk and therefore we decided to apply a two-years inclusion criterion i.e. living in the same parish from 31 December, 1985 to 31 December, 1987. Fifthly, to be able to detect an increased relative risk for malignant disease we wanted to have a low background incidence, hence we defined the cohort to individuals being 0-60 years in 1986. Sixthly, it was necessary to use as detailed information as possible on exposure and disease.

Because of these reasons, the resulting cohort included 7 out of Sweden's 21 counties (Norrbotten, Västerbotten, Jämtland, Västernorrland, Gävleborg, Västmanland and Uppsala county). All 450 parishes, with its inhabitants, were coded into six exposure categories after the fallout of caesium-137: <3, 3–29, 30–39, 40–59, 60–79, and 80–120 kBq/m^2. The inhabi-

tants in the 117 non-affected parishes (<3 kBq/m2) served as reference. Malignancies for the cohort members diagnosed during the follow-up period were retrieved from the National Cancer Registry.

We chose the most sensitive statistical method possible for accurate risk estimates by a) using the highest possible contrast without loosing power in the highest exposure category or in the reference category, b) using 5-year age bands for maximum adjustment of confounding from age, c) identifying and controlling for other confounding factors by first evaluating the confounding properties and then create strata for maximum adjustment.

Each individual was followed over time and the number of person-years was calculated from 1 January 1988 until 31 December 1996, or until the occurrence of the first malignancy or death, whichever came first. MH-IRR estimates were calculated and a log-linear Poisson regression model with maximum likelihood estimates was applied for the trend analyses i.e. the ERR. The EAR was calculated according to the formula at page 16.

Apart from age, four potential confounding factors were controlled for: population density in two models, lung cancer incidence and malignancies 1986-1987.

Population density has in previous studies been and determinant for total malignancies[114], probably due to air pollution, different life styles and occupational exposures in the cities. Smoking habits may to some extent be related to city life style as earlier studies have shown increasing lung cancer incidence with increasing population density[51, 88, 138]. As the fallout from the Chernobyl accident was higher in areas with higher population density we controlled for this potential confounding effect by two models. The first model was based on the number of individuals per km^2 in each parish. The other model involved the official classification by Statistics Sweden in so called homogeneity-regions that classifies municipalities into six categories depending on the population density and the number of inhabitants in the nearest vicinity of the main city in that municipality[120].

To account for smoking habits, industrial and environmental exposures and ill defined other risk factors, usually subsumed as socioeconomic risk factors, the age standardised lung cancer (ICD 7, 162.1) incidence by the municipality for the period 1988–1996 was taken as a proxy indicator for this aggregate of risk factors.

Similarly, the total number of malignancies in 1986–1987 (before any expected effect of the fallout) was considered a proxy determinant in the follow-up period, because a large part of our reference parishes had a low pre-Chernobyl incidence of malignancies.

Finally, we used the classification suggested by Dreyer *et al*[34] for studying the distribution of malignancies related to tobacco smoking in the different fallout categories, calculating age adjusted MH-IRR. In these calculations we ignored, for simplicity's sake, the other adjustment variables, as they were found to have had only a weak influence.

Paper III

In study III we improved the design through a) enlargement of the cohort by including the individuals in another county (Södermanland), b) extension of the follow-up period and c) performing additional analysis for the three time periods i.e. 1988-1991, 1992-1995 and 1996-1999, respectively. More importantly, d) we refined the study design by using the individual dwelling coordinates. Each dwelling in Sweden has been appointed a coordinate by the National Land Survey of Sweden, made available from the Statistics Sweden. The accuracy of the coordinate has been calculated to 100 metres. Therefore, it was the Statistics Sweden that appointed each cohort member with their unique dwelling coordinates.

With a geometric join the digital map on caesium-137 and TGR, respectively, could be matched with the dwelling coordinates using the GIS-technique in ArcView 3.2. By this method each individual got a unique value on TGR and caesium-137 in dose-rate (nGy/h). In all 1,137,106 individuals could be appointed both a value of TGR and caesium-137 (87.1 percent of the original cohort of 1,305,939 individuals), and hence could be included in the statistical analyses. The missing exposure values were almost entirely due to lack of information on TGR (11.7 percent out of the total cohort, or equal to 152,601 persons), which explains why the number of coordinate points was less in study III compared to study IV, in spite of one additional county in study III.

We followed each individual over time and calculated the number of person-years from 1 January 1988 until 31 December 1999, or until the occurrence of the first malignancy or death, whichever came first. Throughout all the analyses, five-year age groups were applied. MH-IRR estimates were calculated and a log-linear Poisson regression model with maximum likelihood estimates was applied for the trend analyses with caesium-137 as a continuous variable i.e. ERR.

We controlled for the same confounding factors as in study II and maintained the same categories for comparison, but also included TGR as an additional confounding factor. Because we studied caesium-137 as a risk factor, not the total radiation, we explored and found the TGR to exert some negative confounding. Hence, we included this variable in the analyses. To show the confounding effect in study III we conducted a stepwise Poisson regression after assessing the strength of each confounding factor.

Table 2. Comparison of study I-III.

	Study I	Study II	Study III
Counties	6	7	8
Individuals (n)	346,000	1,143,182	1,137,106‡
Age in 1986 (years)	0-19	0-60	0-60
Follow-up period	1987-1992 (6 years)	1988-1996 (9 years)	1988-1999 (12 years)
Time periods	1	1	3
Malignancies (n)	331	22,409	33,851
Person-years	NA	10,115,849	13,391,362
Exposure unit	374 parishes	450 parishes	122,220 coordinates
Mean individuals (n)	925 per parish	2,540 per parish	9 per coordinate
Caesium-137	kBq/m^2	kBq/m^2	nGy/h
Exposure categories	3	6	6
Adjusted by confounding factors	No	Age, population density x 2, lung cancer, cancer 1986-1987	As in study II + TGR
Risk estimates	RR	MH-IRR, Poisson regression-RR, EAR, ERR	MH-IRR, EAR, ERR

‡ In spite of one additional county the number of individuals was slightly lower compared to in study II, because of missing values on TGR.

Paper IV

Similar risk estimates were obtained in study II and III, although quite different methods in classifying the exposure, which justified study IV as a methodological study comparing the two ways of classifying exposure. Out of the cohort in study II a total of 1,126,960 individu-

als (98.6 percent) could be included in the study IV, with the remaining persons lacking either coordinates or caesium value. A population weighted parish average was calculated as the total sum of all individual caesium values divided by the number of persons in that parish.

The resolution in exposure assessment could therefore be compared i.e. 132,770 coordinate points with an average of 8 individuals per point and an individual min-max of 0-107 kBq/m^2 compared to 450 parishes with an average of 2,504 individuals per parish with a min-max of 1-6 exposure categories.

Paper V

In this pilot-study morning urine samples were collected from children in Belarus, living in contaminated and uncontaminated areas after the Chernobyl accident. The samples were collected in two numbered, 10 ml plastic tubes, and immediately frozen and stored at –20 degrees Celsius until analysis of 8-OHdG. Concentrations of 8-OHdG were determined by coupled-column high-performance liquid chromatography with electrochemical detection[125], blind for exposure status of the sample. All concentrations were adjusted for urine density as described by Bergman *et al*[14]. The detection limit was 1.6 nmol/l.

Seventy-seven healthy children, 2 to 17 years of age, were randomly selected from the population of Belarus. The exposed group consisted of 31 rural children permanently living in three villages in southeast Belarus that got a ground contamination of caesium-137 of 185-555 kBq/m^2 after the Chernobyl accident. The unexposed group consisted of 46 children permanently living in uncontaminated territories (1-4 kBq/m^2); 5 rural children in the northwest of Belarus and 41 children from the city of Minsk. The exposed children were examined in October 1999 and the unexposed in February to May 2000.

The annual effective dose of radiation was calculated for each child as the sum of the internal dose assessed from body content of caesium-137 and the external dose from gamma-rate measurements on the ground where the children lived[10]. The body content of caesium-137 was measured in a whole body counter by registration of gamma quantum in a scintillation detector with a sodium iodine crystal activated with thallium. The whole body counters are permanently located at the regional centres in Belarus and calibrated on a regular basis as part of a national program for calculating annual internal dose to the population. The calculation of the external dose was based on the annual gamma-rate measurements in the villages of Belarus and performed by the Belarus State Committee for the Control of the Radiological Situation.

RESULTS AND COMMENTS

Paper I

A continuous increase of brain tumour incidence during the period 1978-1992 without clear relationship to the Chernobyl fallout was discovered. A somewhat decreased relative risk of ALL appeared in areas with increased exposure. Other malignancies showed no changes in incidence over time or with regard to exposure.

An obvious shortcoming was that we could only use three exposure categories, due to the limited study size, hence difficult to study a dose-response relationship, if existing. We did not control for confounding in this study. Compared to the design of study II, and especially study III, this first study can be regarded as a pilot study.

Paper II

The age-adjusted relative risk for total malignancies showed a slight increase in all exposure categories, except in the category 60-79 kBq/m^2, using <3 kBq caesium-137/m^2 as the internal reference. This pattern remained in the successive adjustments for the confounding factors. To show the confounding effect we included the factors one by one in MH-IRR, and all of them asserted weak confounding (table 3 in paper II). The most pronounced confounding effect was seen in category 60-79 kBq/m^2 with an increase in age-adjusted MH-IRR of 0.98 to a MH-IRR of 1.10 in the fully adjusted model. Women had an age-adjusted relative risk of 1.34 compared to men, and as expected there was no confounding effect by sex as the distribution of men and women was the same in all exposure categories.

In the fully adjusted model the MH-IRR for the deposition categories (p. 19) were 1.00 (reference), 1.05, 1.03, 1.08, 1.10 and 1.21. The ERR was 0.11 per 100 kBq/m^2 (95% CL 0.03;0.20). To allow comparison with other studies the ERR could be converted into 11 per Sv (95% CL 3;20), using the maximum dose of 10 mSv at 100 kBq/m^2.

The EAR per 100,000 person-years for total malignancies between 1988-1996 and 1986-1987, were 0 (secular trend eliminated), 6.5, 11.7, 15.5, 19.8 and 26.1 in the exposure categories (p. 19). No clear excess occurred for leukaemia or thyroid cancer.

With small increased risks it is essential to adjust for confounding factors to obtain valid risk estimates. We did our best, with available data, but did not succeed annihilating the increased risks in MH-IRR by adjusting for age, population density, lung cancer incidence and cancer 1986-1987 as potential confounding factors. We saw the same tendency of increased risks in separate analysis of malignancies clearly related to tobacco smoking and unrelated to smoking, respectively. Therefore, it confirmed that the dose-response relationship for total malignancies could not be explained by different smoking habits in the exposure categories of caesium-137.

Paper III

The extended follow-up period allowed an analysis in three time periods each showing an increased risk, but with the most evident dose-response in the first time period 1988-1991. To allow comparison with study II the ERR was also expressed as 0.10 per 100 kBq/m^2 (95% CL 0.00;0.23), in spite of different follow-up periods (table 3). As in study II we did our best to annihilate the increased risks in MH-IRR, EAR and ERR, respectively by controlling for the same confounding factors, but also treating the TGR as a confounding factor. The TGR asserted weak negative confounding confirming an *a priori* suspected negative association with caesium, because the fallout of caesium-137, due to rainfall, tended to be higher in areas with lower ground radiation (table 4, paper III). Interestingly, in the fully adjusted model we saw an obvious negative confounding in MH-IRR compared to only the age adjusted MH-IRR estimates.

Table 3. Comparison of results from study II and study III.

	Study II (1988-1996)	Study III (1988-1999)
ERR per 100 kBq/m^2 (95% CL)	0.11 (0.03;0.20)	0.10 (0.00;0.23)
Attributable cases‡ of total malignancies (%)	849 of 22,409 (3.79%)	1,278 of 33,851 (3.78%)

‡ calculated according to Steenland[121].

The attributable cases of total malignancies in our studies can be compared to the theoretical value based on the risk estimates of the ICRP i.e. 300 deaths of malignancies in Sweden, during 50 years time after the accident[82]. Our estimate of about 1,000 incident malignancies after

a decade represent 3.8 percent of the total number of malignancies in the 8 most contaminated counties of Sweden (table 3).

An increased risk for thyroid cancer or leukaemia, in study II and III was in statistical terms less likely in relation to the fallout, but could not be excluded taking the CL into account, hence can be called a non-positive studies[9].

Table 4. Characteristics of study II and III in design and interpretation of results.

Strengths	Weaknesses
Maximum number of exposed counties	--
Exposure by parish or dwelling	No individual exposure information
Exposure categories independently given by the Geological Survey in study II	Fixed exposure categories constrained by the Geological Survey in study II
Exposure categories by population distribution in study III	--
Maximum exposure contrast	Small numbers in highest category
Same external exposure 1986-1987	No exposure assessment 1988-1996 (study II) and 1988-1999 (study III)
Low incidence of malignancies 0-60 years of age	No separate analysis on children
Valid and precise population/cancer registries	--
Similar results in MH-IRR, ERR and EAR	Difficult to interpret small risks
Weak confounding	Uncontrolled confounding?
Power to detect both an early and a small increase in total malignancies at low exposure	No latency, no increased risk for leukaemia or thyroid cancer, exposure too low to explain the increased risk

Paper IV

To evaluate the exposure classification we took the population in study II and included all individuals with dwelling coordinates from study III. Therefore, the individuals with dwelling coordinates classified on the digital map could be compared with the individuals classified by parish using the analogue map. The population-weighted parish average of caesium-137 based on the digital map reached a maximum of 56 kBq/m^2 i.e. no parish in the two highest expo-

sure categories when the analogue map was used (60-79 or 80-120 kBq/m^2). However, a total number of 11,902 persons had an exposure exceeding 60 kBq/m^2, with a maximum value of 107 kBq/m^2. The two lowest categories were very stable with more than 90 percent of the parishes remaining in their original classification. Analyzing all parishes with the different classification (111 out of the 450 parishes), two explanations for the difference were identified, firstly the unequally distributed population in the parish (skewed population) and secondly, a higher resolution both for caesium-137 exposure, through the digital map, and also for the population through the dwelling coordinate (scattered population). With the former definition 25 parishes could be explained and with the latter definition 86 out of the 111 parishes with different classification could be explained.

There was a systematic down classification using the digital map to classify the parishes compared to use of the analogue map. Our similar risk estimates can probably be explained by the relatively homogenous exposure in the parishes, especially when included in categories, making the intra-parish difference less influential. The conclusion in study IV is therefore that use of aggregate data can be justified in environmental epidemiological studies.

Paper V

The annual summary effective dose, calculated as the sum of the internal and the external dose, was seven times higher for the children in the contaminated areas than for the unexposed children (median 1.77 versus 0.25 mSv). However, the median urinary 8-OHdG concentrations were significantly higher in the unexposed children (18.75 nmol/l) than the exposed (8.49 nmol/l), $p<0.001$. Unexposed children living in urban areas had significantly higher urinary 8-OHdG concentrations than unexposed children living in rural areas confirming an urban effects, table 5. Instead, testing the two rural groups on 8-OHdG excretion was a way to eliminate the urban factor, but unfortunately the two groups were too small to allow any conclusion on the effect of the radiation exposure ($p=0.30$). These results indicate that the 8-OHdG excretion is lower in children living in caesium-contaminated rural areas of Belarus than in children unexposed to caesium-137, but living in an urban environment.

Although the number of children was small, the difference in 8-OHdG excretions was significant. Because the individual dose was calculated accurately, it suggests that radiation 13 years after the Chernobyl accident is a less important contributor to oxidative stress in Belarussian children than is urban living. One plausible explanation for the apparent lack of effect from radiation in our study is that the radiation dose received by the children could be too low to

affect the excretion of 8-OHdG. The effective dose for the radiation-exposed children in our study was thus only about 1/1000 of the therapeutic doses after which increased excretion of 8-OHdG has been seen. Another more speculative explanation could be that there is no long-standing effect, in increased excretion of 8-OHdG, after an initial and higher radiation exposure. However, this is not possible to confirm in our study as our samples were collected several years after the Chernobyl accident. There is also no support in the literature for lack of a longstanding effect, however no such follow-up of 8-OHdG excretions, after acute medical radiation, has been performed. The somewhat unexpected results in study V illustrate the importance of conducting a pilot-study before finally design of a study, especially if it includes a large-scale field sampling.

Table 5. Simplified table from paper V. Urinary excretion of 8-OHdG in Belarussian children exposed and unexposed to ionising radiation from the Chernobyl accident divided into urban and rural living.

	Exposed (n=31)	Unexposed (n=46)		
Urinary excretion	Rural (n=31)	Urban (n=41)	Rural (n=5)	p-value
8-OHdG (nmol/L)	8.49	19.40	11.77	<0.05
		18.75		<0.001

GENERAL DISCUSSION

Causality

Interpretation of small risks is always a challenge. However, small risks in a large population can contribute to a considerable absolute number of cases. The so-called Bradford-Hill criteria are often seen as the standard criteria and used in medical science to assess if there is a causal relationship between exposure and disease[53]. However, critique has over time modified these criteria e.g. Checkoway points out that temporality is essential, other criteria are supportive, and that each study should be evaluated on its own merits[22]. Rothman defines a cause of a disease as an event, condition, or characteristic that preceded the disease which not would have occurred at all, or been postponed[111]. Etiology of diseases is multifactorial. According to IARC ionising radiation is a carcinogen with both sufficient evidence for carcinogenicity in humans and in experimental animals[56], but can our results in study II-III be interpreted as a causal relationship? To discuss our findings in relation to the Hill criteria is one way to determine whether the fallout from the Chernobyl accident in Sweden, and the increased incidence in malignancies in our studies, can be interpreted as a causal relationship.

Hill's first criterion is *strength,* i.e. the higher the risk, the higher the likelihood for a causal relationship. In study II we had a maximum MH-IRR of 1.21 in the highest exposure category in the fully adjusted model and in study III a corresponding maximum of 1.302. These risk estimates are traditionally considered as low in epidemiology[139], but nevertheless rather high for studies in environmental epidemiology. However, it is necessary to be cautious in the interpretation of small risks, because the possibility of confounding explaining or contributing to the results. Given the definition of strength, Hill's first criterion may not be fulfilled. However, Hill also emphasised not to dismiss a cause-effect hypothesis merely on the grounds that the observed association appearing to be slight.

The second criterion is *consistency* which refers to the repeated observation of an association in different populations under different circumstances. Lack of consistency, however, does not rule out a causal association because some effects are produced by their causes only under unusual circumstances[111]. Ionising radiation including gamma-radiation easily fulfils the criterion of consistency. If there is a consistency between ionising radiation and total malignancies, the answer is more complicated (p. 38) With regard to later reviews on low dose exposure and total malignancies our findings seems to fulfil the second criterion[26, 89]. There is also scientific support for short latency after low dose exposure (p. 39). However, there is no con-

sistency regarding an effect after the Chernobyl accident and malignancies outside the former USSR (p. 14). In summary, the results in our studies could possibly fulfil the criteria of consistency.

The third criterion is *specificity*, a well-defined association rather than a general one. Rothman recognizes this criterion as totally invalid because causes of a given effect cannot be expected to lack other effects for any logical grounds[111]. And it is known that ionising radiation has several effects. The diagnosis of malignancies, as a disease entity by itself, is also well defined and confirmed by pathologists and unequivocally classified and recorded by the National Cancer Registry. On the contrary, if malignancies can be regarded as different diseases, radiation can be an event according to the definition by Rothman. Granted that all types of malignancies can be linked to ionising radiation, which seems to be the trend in international evaluations (p. 38), the caesium exposure in our studies will have a specific association (although total malignancies at first sight seem to be a diverse outcome). Interestingly, Hill mentions that the importance of this characteristic should not be over-emphasized i.e. a specific exposure can lead to several diseases and often the causes of a specific disease is multifactorial. The criterion on specificity is fulfilled for our studies.

Temporality is the fourth criterion and obvious: exposure before disease. However it is more complicated as there might be an incubation time in case of infectious diseases and the so-called latency period for malignancies. Hill mentions only slow developing diseases and does not address latency. The fourth criterion can therefore be fulfilled.

The fifth criterion is *biological gradient* i.e. dose-response. However, a causal dose-response relationship is not necessarily monotonous and linear, and one can not take for granted that all dose-response relationship are causal[111]. The advantage of studying ionising radiation is that it can be measured on a continuous scale and therefore in statistical calculations be treated as such, but also analysed in categories to explore dose-response relationships. Our results favour true dose-response and therefore, the fifth criterion of biological gradient seems fulfilled.

The sixth criterion is *plausibility* i.e. the observed relationship is biologically plausible. However, the interpretation of plausibility depends on the present knowledge. Few carcinogens are so well studied as ionising radiation with several international organizations making regular evaluations. The biological plausibility emanates from in vitro and in vivo experiments (p. 10). This is actually the background for launching our epidemiological studies in Sweden after the Chernobyl accident. Hence, the sixth criterion is obviously fulfilled.

Coherence is the seventh criterion mentioned by Hill i.e. new data should not seriously conflict with the generally known facts of the natural history and biology of the disease. However, caution should be taken when interpreting conflicting information, it may indeed refute a hypothesis, but can also be misinterpreted[111]. Although our results are coherent with the present knowledge that ionising radiation can cause malignancies, they are not unanimously coherent with the views on low dose radiation. Hence, fulfilment of the seventh criteria can be discussed.

The eight criterion is *experiment* which is defined as experimental or semi-experimental evidence i.e. reduce or stop exposure and then expect to see a decrease in disease occurrence. This is not applicable for our studies and therefore the eight criterion cannot be evaluated.

The ninth and last criterion mentioned by Hill is *analogy* which can be seen as a rather weak criterion and can be used when the plausibility criterion can not be applied. This criterion is irrelevant for our studies.

An overall evaluation on our results using the Hill criteria for causality is therefore that our major findings point to a causal inference between exposure to caesium-137 after the Chernobyl accident: increase in total malignancies at low exposure in study II and III, although a short latency period was observed. Interestingly, Hill does not mention statistical significance in his criteria, probably because the strength of the observed relationship is more important than the size of the study. The results for leukaemia and thyroid cancer in our studies can therefore be seen as non-positive findings, rather than negative, since both are too rare to show significant increase in incidence[9].

Epidemiological considerations

The accuracy of an epidemiological study encompasses precision and validity. Precision or random error is outlined below. Random error can be reduced (improved precision) by increasing the total study size or the size of the reference population, hence our methodological considerations in the design of study II (p. 19). Validity or systematic error includes information bias (p. 32), confounding (p. 33) and selection bias (p. 34). Systematic error can not be reduced by increasing the study size, but can be reduced by improving the study design[22].

Precision or random error

The random error in our studies depends probably on the exposure assessment, both on the maps themselves, but also the manual classification of the parishes. Such bias, regardless of influence, could hardly explain the dose-response seen for total malignancies in the study II and even more unlikely in study III where the individuals in different exposure categories were scattered more or less over all the study area. Random error can theoretical occur in the diagnostic procedure, but less likely on reporting to the National Cancer Registry as reminder is sending out to the pathologist or clinician depending on a missing report from either of them[128].

Validity or systematic error

Information bias

Information bias is the result of misclassification of study participants with respect to disease or exposure status. Misclassification is either non-differential or differential[22]. In our studies we ignore radiation exposure from other sources than the outdoor radiation i.e. the residential exposure from gamma- and radon-emitting building material, occupational and medical examination. Therefore, the total radiation exposure from all the mentioned sources, apart from the contribution of the internal dose, can probably be regarded as a non-differential misclassification, random in nature and working towards the null value i.e. tends to make the relation between exposure and effect weaker[61, 111]. In general, a weak risk factor with a great deal of exposure misclassification is bound to produce weak results, which may not be reproduced, even if the exposure is common and therefore has a comparatively high population attributable risk[67]. In cohort studies exposure misclassification is typically non-differential because exposure assessment is independent from diagnosis of disease[16]. Concerning our studies, it is also interesting that Rothman concludes that non-differential exposure and disease misclassification is a greater concern in interpreting studies with absence of an effect, rather than studies with positive findings[111]. On the contrary, non-differential misclassification of a confounding factor is a more serious problem as it will result in remaining uncontrolled confounding[111].

Differential misclassification occurs when the probability of misclassification of exposure is different in diseased and non-diseased persons, or when the probability of misclassification of disease is different in exposed and non-exposed persons[22]. It is highly unlikely that there has been any relation between exposure categories and reported cases of malignancies since the National Cancer Registry seems to be complete to about 96 percent[77] and screening is only

possible for a limited number of malignancies. Likewise, the procedure of diagnosis malignancies was not affected by the exposure.

Confounding

A confounder is a factor that is predictive of disease in the absence of the exposure under study and associated with that exposure[22]. A confounding factor has to be a rather strong risk factor or closely associated to the exposure; a weak risk factor can still assert confounding if closely associated to the exposure. The strongest confounding factor in our studies, on theoretical grounds, was the population density because the incidence of malignancies is higher in cities compared to countryside and the fallout was highest in the coastal cities of Gävleborg and Västernorrland counties. The maximum strength of the included risk factors in calculating the MH-IRR for total malignancies was 1.11 (malignancies 1986-1987) and 1.083 (population density) in study II and study III, respectively.

Tobacco smoking is often regarded as an important concern in epidemiological studies and therefore we have tried to control for it by stratifying for lung cancer incidence. If it is not possible to obtain information on an individual level a surrogate variable like lung cancer incidence can be used. Such a surrogate variable has the advantage, in our case, that it not only adjusts for confounding from tobacco smoking. It also adjusts for other potential confounding factors like socio-economic factors because smoking is not evenly distributed over socio-economic class. Our concern for confounding from smoking might have been exaggerated as it is rare to find substantial confounding in epidemiology, even by risk factors that are strongly related to the outcome of interest[16]. Both definitions of population density in study II-III were associated not only with the incidence of total malignancies, but also with exposure categories of caesium-137, thus confirming an *a priori* suspected confounding effect. Adjustment of the incidence of malignancies 1986-1987 was a way to control for the reference areas pre-Chernobyl low incidence in total malignancies. In the study III a new potential confounding factor was included i.e. TGR. This factor is unique in such a large cohort because of its high precision and as detailed as the studied exposure of caesium-137.

Overall there were weak confounding effects seen in the risk estimates, after adjustment with the available confounding factors (paper II-III). To some extent our confounding factors were inter-correlated, especially the two population density risk factors. However, we could show that using also the official H-region density classification we could adjust for some residual confounding on population density. The explanation could be that H-region takes into account

that people may live in a sparsely populated parish and commute to work in the nearest large city.

Selection bias

Selection bias evolves from the procedures by which the study participants are chosen from the source population[22]. In study II-III there can have been selection bias if concerned people moved out from the highly exposed areas 1986-1987, hence not included in the cohort definition. It is highly unlikely that this exposure related moving would have been large and selective enough to affect the risk estimates. In study III there can have been a selection bias because the measurements of the TGR was not complete in the interior of Northern Sweden i.e. a geographical bias reducing the number of low caesium-exposed individuals. Missing value of TGR accounts for 11.7 percent of the cohort (or 152,601 individuals out of 1,305,939) and can practically explain all of the incomplete data, leaving 87.1 of the individuals to be included in study III. As the missing information on TGR reduced the number of individuals in the reference category it can have affected the CL, but probably not the risk estimates to any greater extent.

Other epidemiological considerations

To be included in our cohort we had a two years exposure criteria i.e. living in the same parish 1986-1987, instead of using cumulative exposure. It probably had the advantage of minimising the high correlation between cumulative exposure and age which in turn tends to eliminate an exposure effect, after adjustment for age[62].

The way we classified both radiation from caesium-137 and TGR in study III is rather unique in register-based epidemiology because of the detailed exposure assessment. The analogue map that we used in study II can be seen to be rather crude, compared to the digital one, but in an international perspective fairly detailed. Most of the parishes are small by area, especially in the cities with relatively large populations, hence city parishes are more likely to have a homogenous exposure.

Reliability or reproducibility

In 1991, two of the authors in the first paper (Martin Eriksson, Sören Jakobsson) classified the parishes independently of each other and then compared the result with a good agreement. In study II the same map was used in 1997 to classify the parishes in one additional county (Västmanland). At the same time the parishes in part of the most contaminated areas of Gäv-

leborg county, but also all of Uppsala county, were re-classified. The result was that only 5 out of 122 reclassified parishes got a different category, hence a high reproducibility, and therefore the original classification was kept. In 2006 during study IV two of the authors (Peter Lindgren, Martin Tondel) once again used the analogue map. All 111 examined parishes, got identical classification as the original parish classification when re-examined, hence again a high reproducibility.

Dose assessment

Internal exposure from caesium-containing foodstuffs is probably the most important shortcoming of our exposure assessment, probably a differential misclassification. To avoid introducing even more misclassification we chose to express our risk estimates using the primary exposure information on the analogue and digital map i.e. kBq/m^2 (study II) and nGy/h (study III), instead of estimating individual doses from the external exposure. Example on external exposure that we do not account for is given under "Environmental exposure to ionising radiation" (p. 7).

Restricted distribution of foodstuff and recommendations issued by the authorities has probably resulted in lower doses in general to the Swedish population especially to those living in higher exposed areas. Such precautionary actions can only result in decreased risks in the highly exposed areas, if effective. Studies on reindeer herders have shown a significant lower transfer to body burden of deposited caesium-137 after the Chernobyl accident compared to the fallout from the nuclear weapons tests in the 1960's when there was no food restrictions (p. 10). Further support for the effectiveness of preventive measures is the lower transfer values to the herders in Västerbotten county with an average deposition of 14 kBq/m^2 compared the reindeer herders in Norrbotten with 2 kBq/m^2 as the average deposition[107]. Rural populations have higher intake of wild berries, mushrooms and game meat compared to urban populations resulting in a higher radiation dose. This is also confirmed in the algorithm from deposition to effective dose with a higher coefficient for rural compared to urban populations (p. 10). Effective food restrictions can therefore give people in rural areas with high ground deposition a lower than presumed intake of caesium-137, with the consequence of less difference in effective dose compared to the urban population. If this has been the case it would have lowered the radiation-induced cancer risk in rural areas with high fallout in comparison to what would otherwise have prevailed.

The individual dose assessment in study V is optimal as it takes both the external dose and the internal dose into account by calculating the dose from food intake by measuring the body

content of caesium-137, at the time of examination. It is, of course, superior and the most valid method of exposure assessment on an individual level, which is desirable but not possible for calculating individual doses in large cohorts.

Ecological studies

Ecological bias refers to the failure of ecological level associations to properly reflect individual-level associations by insufficient adjustment for confounding factors[46]. A potential strategy to reduce ecological bias is to use smaller units, in order to make the groups more homogenous with respect to the exposure[111]. All individuals in study I-II were appointed the same exposure as the classified parish, hence an ecological study in that sense. But, as the cancer diagnosis was on an individual level, rather than parish, at least the second study can be seen as a semi-ecological study because individual data existed on outcome. In ecological studies there is a risk of the so-called ecological fallacy i.e. the associations found on a group level do not reflect the individual level association[46, 73, 101]. Using several exposure categories, and with increased risks as in study II, might have reduced the risk of ecological fallacy. Study III, can on the other hand be regarded as an analytical environmental epidemiological study because each individual was appointed unique exposure information based on the fallout on the dwelling coordinate i.e. disregarding parish as the exposure unit. And, as the information on malignancies also was on an individual level it can on theoretical grounds be seen to have the most valid results.

Dose-response after Chernobyl accident

The carcinogenic potential of ionising radiation in human populations has been studied extensively and evidence for a causal association comes from studies on survivors of the atomic bombings in Japan, occupational groups and patients exposed to radiation for medical reasons. Evaluations of the carcinogenic potential at low doses are more complicated and therefore the follow-up of the Hiroshima-Nagasaki cohort is of particular importance, where excess in malignancies have been seen down to around 100 mSv. However, it should be discussed how appropriate it is to extrapolate the dose-response curve from this relatively high dose down to the low dose range. However, the linear non-threshold model is now widely accepted[26, 58, 137] and also by IARC at low dose rates[56]. In a review on dose-response curves it was concluded that it is possible to find support in the literature for a downwardly curve, as well as an upwardly curve, both with or without threshold in the dose-response[17]. The first model underestimates the risk for malignancies, the second model overestimates the risk compared to the linear non-threshold dose-response model, respectively. In a linear model

without threshold the Hiroshima-Nagasaki ERR for total malignancies is 0.42 per Sv[102] which can be compared to a steeper slope in study II of ERR 11.0 per Sv, table 6. Our results are therefore compatible with an upwardly bending dose-response curve compared to the extrapolation of the Hiroshima-Nagasaki risk down to the low dose range. Interestingly, such curve for solid cancer has been demonstrated in the "the low dose" range in Hiroshima-Nagasaki of less than 300 mSv, challenging the linear dose-response curve at lower doses even in that cohort[99].

The threshold model, whatever curve, will give a dose under which no malignancies can be attributed to the exposure and radiation can on the contrary be preventive within the low dose range (hormesis).

Table 6. Comparison between different epidemiological studies

Cohorts	Follow-up period	Malignancies (n)	Person-years	Dose (mSv)	ERR per Sv (95% CL)
Chernobyl[131]	1988-1996	22,409‡	10,115,849	0-10	11 (3;20)
Atom bombs[102]	1950-2000	10,127†	3,184,354	5-3,000	0.42 (0.33;0.51)
Semipalatinsk[11]	1960-1999	889†	582,750	20-4,000	1.77 (1.35;2.27)

‡ incident cases of total malignancies

† deaths in all solid cancer

Possible mechanisms for low dose effect

Recent research has provided new possible mechanisms for the effect of low dose ionising radiation. Radiation induced genomic instability has been defined as the manifestation of genetic damage in a certain fraction of irradiated cells over many cell cycles. Bystander effect induced by radiation in non-exposed cells actually drives the process of genomic instability which in turn precedes and facilitates the evolution of clonal (potentially carcinogenic) mutations[84]. Genomic instability probably plays a more important role in progression than in initiation of a malignancy. However, the relationship between radiation-induced genomic instability and radiation-induced malignancies is still uncertain and questioned whether it can be applied under 100 mGy.

In vitro it has been demonstrated that cells not directly hit by alpha-particles, but in close contact with such cells, have capability for cell killing, induction of mutations and malignant transformation[26]. The molecular mechanism how an irradiated cell can signal to a neighbouring un-irradiated cell is not clear in detail and if it can be applied for gamma-radiation as alpha-radiation. This so called bystander effect may involve cytokines or long-lived reactive oxygen species and activation of the p53-mediated DNA damage[26]. Remarkably, the bystander effect has been demonstrated down to dose of 10 mSv. If the bystander effect also could be demonstrated in vivo, at even lower doses, it could be a potential mechanism for radiation risk in the low exposure range that we have in our studies[89]. An indirect evidence of an effect in vivo is that plasma from radiotherapy patients was able to induce chromosomal damage in normal un-irradiated lymphocytes[103]. Bone marrow irradiated in vivo with gamma-rays and grown in vivo for up to 2 years continues to exhibit chromosomal instability and exhibit bystander effect when transplanted into marrow ablated mice, hence supporting an in vivo effect[12]. The genetic instability together with the bystander effect constitutes processes in addition to the established effects of ionising radiation e.g. mutation and clonogenic survival[12]. Most observations also support that the bystander effect tends to have a saturating response above a threshold dose of about 200 mGy, hence a potential explanation to an upwardly bending dose-response curve[103].

Total malignancies after Chernobyl accident

After the atomic bombs the first observation of increased malignancies was increased mortality in leukaemia, but since then more and more malignancies have been associated with radiation. UNSCEAR now gives risk estimates also for total malignancies[137]. BEIR gives in the latest evaluation of low dose radiation risk estimates for solid cancer (all malignancies except lymphatic and haematopoietic tissue)[26] and also given by Preston *et al* in the follow-up of the atomic bomb survivors[102].

Our findings with a dose-response relationship for total malignancies was somewhat unexpected, and we could not detect any single site being responsible for this increase, such as leukaemia or thyroid cancer both regarded to have a short latency period. Therefore, the increased incidence in total malignancies suggests that the ionising radiation might have acted as a general promoter. Ionising radiation is undisputable an initiator, but there is still uncertainty about the strength and mechanism of the promotive effect[26, 137]. The study size in study II-III was just large enough to show an effect on total malignancies, but might not have had

enough power to detect an increase in leukaemia or thyroid cancer. Other possibilities for the absence of effect on the incidence on thyroid cancer could either be a too low exposure to radioactive iodine in Sweden, or a good iodine status, through iodised salt, making the Swedish population less sensitive to develop thyroid cancer.

Latency after Chernobyl accident

Latency is defined by the time from induced disease until manifestation and is preceded by induction period from first exposure to induced disease[22, 111]. However, regarding malignancies it is impossible to identify when the disease is induced, so for practical purposes latency period can be seen as the time period between the first exposure and the disease manifestation (in our case the time elapsed between April 28, 1986 until the date of registration of a malignancy in the National Cancer Registry). In the literature much emphasis has made to estimate the medical effects after the atomic bombs over Hiroshima and Nagasaki. However, there are limitations when interpreting these data into the low dose range of ionising radiation, but also because the cohort was created five years after the explosions i.e. ignoring early cases[123].

The first reports on an increase in childhood thyroid cancer in Ukraine[104] and in Belarus[65] were published in 1991-1992 and met with scepticism and were criticized to be a result of screening, random variation, over- and/or wrong diagnosis of cases, or previous underreporting. Conclusion on causality was claimed not possible due to lack of individual thyroid doses or simply because the latency period was too short to make a relation biologically plausible[13, 110, 116].

Evaluations of radon progeny exposure and lung cancer is of interest in this context as it indicates that relatively recent exposure might hold a stronger effect according to the analytical models applied in a comprehensive report on this issue[25]. A short latency period has also been seen in a mortality study on 14,111 patients with ankylosing spondylitis where a significant increase in total cancer mortality was noted already 0-2 years after the X-ray treatment[118]. In a cohort of radon exposed uranium miners, different latency periods to lung cancer were tested. A latency period of six years for cumulative exposures fitted the data best[55], which is short compared to smoking with a minimum of 10 years latency[57]. In yet another study on uranium miners there was a continuously increased relative risk for lung cancer 2.0-8.5 years since first exposure followed by a subsequent decline in risk[70]. In a follow-up of the Three Mile Island accident in 1979 for the period 1979-1998, deaths in total malignancies were non-

significantly increased for both men and women in 1979-1984 and followed by a decline. Then, there was an increased SMR again for men in 1990-1998[126].

In a recent review it was concluded that the minimum latency period in children, after exposure from X-rays, nuclear weapons test fallout and the Chernobyl accident, can be as short as 5-10 years for various types of malignancies including leukaemia, thyroid cancer and other malignancies[75]. The number of thyroid cancers in children of Belarus increased in 1990, four years after the Chernobyl accident. Now, this increase can be linked to specific genetic rearrangements caused by radiation and resulting in increased growth rate and a subsequent shorter latency period. This rapid form of thyroid cancer was followed by slow growing form with yet another chromosomal re-arrangement, hence it took longer time until diagnosis[141-143].

Similar findings on leukaemia have also been observed. Radiation-related ALL, and probably also CML, can probably be attributed to a small number of predisposed individuals with relatively large numbers of translocation-carrying pre-leukaemic cells[87]. These predisposed individuals are then already on their way to malignancy where radiation could induce additional mutations in the target pre-leukaemic cell on the pathway to manifest malignancy. Hence, a both individual susceptibility to low dose of radiation and a short latency. Estimation by Nakamura indicates that individuals with clonally expanded populations of pre-leukaemic cells during fetal live have a 25 times higher relative risk to develop ALL than the general population[87]. These observations can probably explain the sudden initial increase in EAR, in the atomic bomb survivors, for ALL and CML and their following decrease in risk.

In study II there was an increase in total malignancies in Sweden nine years after the Chernobyl accident, but it was not analysed in time periods because of a relatively short follow-up. In study III we applied three time windows with the strongest increase in total malignancies in the first four years after the Chernobyl accident (1988-1991), and also seen in the total follow-up period of 1988-1999. Our suggestion of a dose related increase in total malignancies in Northern Sweden has been criticised as not being related to the fallout from the Chernobyl accident[5]. The critical point was a too short latency period to explain the increase. The latency period is short, but there is still a possibility of a second peak in future, with a latency period more coherent with the existing view.

Our findings of an increase in total cancer incidence in Sweden soon after the Chernobyl accident are not unique. An interpretation of our results in study II-III could therefore be that the

ionising radiation might have acted as a late stage general promoter for all form of malignancies, or subtypes with shorter latency, resulting in early detection.

The lead time has been defined as the time interval by which the time of diagnosis is advanced by screening and early detection through extra vigilance[45]. However, it is unlikely that our short latency could be explained by different reporting of malignancies to the National Cancer Registry as the exposure categories were scattered over the studied region i.e. not a systematic bias through geographic registration. Registration of new cancer cases is also compulsory for both clinicians and pathologists in Sweden and therefore only a few cases could have escaped from being reported to the National Cancer Registry, which seems to be complete to about 96 percent[77]. Moreover, screening is only possible for a limited number of malignancies and as there was no screening program in the most affected areas in Sweden it cannot explain the increase in total malignancies. However, we cannot exclude the possibility that people in the higher exposed regions cared sought doctor's care, but it is impossible to distinguish such an effect from promotion i.e. an early increase in incidence of malignancies due to radiation. A prerequisite for such an effect needs to be that early stages of several sites of malignancies can be detected before they otherwise would be diagnosed, resulting in a temporary increase. However, the increase in total malignancies in study III was still increased 1996-1999.

Challenge of present paradigms

The present paradigm is that ionising radiation is an undisputable carcinogen. The risk of developing malignancies is proportional to the dose (linear non-threshold hypothesis), several tissues are sensitive to develop malignancies after exposure, leukaemia and thyroid cancer have a few years latency period, but other malignancies can have latencies up to decades.

Our studies have shown a positive dose-response relationship for total malignancies at low exposure for caesium-137 in Northern Sweden after the Chernobyl accident and with a short latency.

In this thesis the results and interpretations have been put into context of the present paradigms to discuss the possibility of a causal inference between the fallout of caesium-137 and the increased incidence in malignancies seen in our studies. It seems more likely that our findings support a causal link, rather than being a result of chance or bias.

CONCLUSION

The Chernobyl accident itself was a very unlikely and rare event i.e. hence beyond everyone's imagination both in technical terms, extent of radioactive release to the atmosphere, but also the transport of a wide range of radionuclides to large part of Europe. The first reports of an increase in incidence of childhood thyroid cancer came 1991-1992 and were recognised as unlikely to be related to the accident. Our results were unexpected i.e. increase in total malignancies in Sweden so soon after the Chernobyl accident. However, the relative precision and validity for a cohort of our size might explain why it was possible to detect a small increased risk in relation to the exposure to caesium-137. Therefore, our findings on increased incidence of malignancies in Sweden after the Chernobyl accident contributes to the epidemiological literature on low-dose radiation. Our findings are a challenge to the existing paradigm on ionising radiation and should be interpreted with caution, also when translating the risk estimates to other populations and other dose ranges.

FUTURE PERSPECTIVES

To get a better knowledge on the effects of ionising radiation it is important to study the exposed groups after the Chernobyl accident. This is a challenge, because of the low dose, hence requires a large study base. Sweden has the advantage of holding valid registries on both the population and health outcomes and together with the unique data on radiation exposure makes Sweden suitable for these studies. Next step needs to be a more thorough individual dose assessment taking internal dose into account, before calculating the risks. Our studies point to the importance of focusing on latency periods, time trends and specific sites of malignancies. Also other outcomes, e.g. cardiovascular diseases and malformations, should be studied in relation to the radioactive fallout in Sweden after the Chernobyl accident. The influence of age on the sensitivity to develop different diseases should be addressed in future studies. Finally, of great importance for future radiation protection is to evaluate the effectiveness of food restrictions, and other recommendations by the authorities, in relation to health in the affected regions.

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