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Improvements to radiation-related cancer risk assessments for radiation protection by focusing on previously disregarded sources of uncertainty

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List of Abbreviations

A-Bomb	Atomic Bomb
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
DREF	Dose Rate Effectiveness Factor
EAR	Excess Absolute Risk
ERR	Excess Relative Risk
ESA	European Space Agency
ICRP	International Commission on Radiological Protection
INWORKS	International Nuclear Workers Study
LSS	Life Span Study
M^4I	Multi-Method-Multi-Model-Inference
MMI	Multi-Model-Inference
NASA	National Aeronautics and Space Administration
PUMA	Pooled Uranium Miner Analysis
RADS	Radiation Attributed Decrease of Survival
REID	Risk of Exposure Induced Death
RBE	Relative Biological Effectiveness
RERF	Radiation Effects Research Foundation
TG	Task Group
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation

List of Publications, Presentations, Awards, and Participation in International Organisations

Publications included in this Thesis

- **Publication I: Hafner L**, Walsh L, Rühm W. (2023) Assessing the impact of different neutron RBEs on the all solid cancer radiation risks obtained from the Japanese A-bomb survivors data, International Journal of Radiation Biology, 99(4):629-643. DOI: 10.1080/09553002.2022.2117871
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- **Publication III:** Stabilini A, **Hafner L**, Walsh L. (2023) Comparison and multi-model inference of excess risks models for radiation-related solid cancer. Radiat Environ Biophys, 62:17–34. https://doi.org/10.1007/s00411-022-01013-0
  Impact factor (2023): 1.5, Impact factor best quartile (2023): Q3

- **Publication IV: Hafner L**, Walsh L. (2024) Application of multi-method-Multi-Model-Inference to radiation related solid cancer excess risks models for astronaut risk assessment. Zeitschrift für Medizinische Physik, 34(1):83-91.
  https://doi.org/10.1016/j.zemedi.2023.06.003
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- **Publication V (Appendix A): Hafner L**, Walsh L, Rühm W. (2023) Discussion of Uncertainties and the Impact of different Neutron RBEs on all Solid Cancer Radiation Incidence Risks obtained from the Japanese A-bomb Survivors Data, Annals of the ICRP, 52(1-2):17-22.
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Additional Publications

- Walsh L, **Hafner L**, Berger T, Matthiä D, Schneider U, Straube U. (2024) European Astronaut Radiation Related Cancer Risk Assessment using Dosimetric Calculations of Organ Dose Equivalents. Zeitschrift für Medizinische Physik, 34(1):92-99. https://www.sciencedirect.com/science/article/pii/S0939388923001198?via%3Dihub
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  Impact factor (2020): 6.28, Impact factor best quartile (2020): Q1

Presentations

- IRPA 16: "The Life Span Study Neutron RBE and its Impact on All Solid Cancer Radiation Risks obtained from the Japanese A-bomb Survivors Mortality Data", Orlando FL, 9. July 2024

- ICRP Symposium 2023: "A short review of published MMI studies in radiation epidemiology including methods to address related inherent problems", Tokyo, 9. November 2023

- Weiterbildungsseminar Schweizerische Gesellschaft für Kernfachleute: "Das Strahlenrisiko: Eine epidemiologische Betrachtung", Baden, 21. September 2023

- Direktoriumssitzung Fachverband für Strahlenschutz für Rupprecht Maushart Preis: "Assessing the impact of different neutron RBEs on the all solid cancer radiation risks obtained from the Japanese A-bomb survivors data", online, 17. September 2023

- ICRP Symposium 2021+1: "The Impact of different Neutron RBEs on the all Solid Cancer Radiation Incidence Risks obtained from the Japanese A-bomb Survivors Data", Vancouver, 8. November 2022

- Radiation health working group meeting of the Multilateral Medical Operations Panel: "European Radiation Risk Model". Vancouver, 6. November 2022

- ICRP TG 118 meeting: "Past and Current Work on evaluating the neutron RBE in the A-bomb Survivors and how the choice of RBE influences cancer risk". Online, 13. December 2021

Awards

Cousins Award for young scientists and professionals at the ICRP 2021+1 Symposium in Vancouver for the work and presentation of "The Impact of different Neutron RBEs on the all Solid Cancer Radiation Incidence Risks obtained from the Japanese A-bomb Survivors Data", 2022, https://www.icrp.org/page.asp?id=411

Participation and Work in International Organisations

- Since October 2022: Member of ICRP TG 122 "Update of Detriment Calculation of Cancer"

- Since January 2021: Participation in the "Medizinische Subkommission der Eidgenössischen Kommission für Strahlenschutz"

- 2020-2022: Member of the Nuclear Energy Agency "Expert Group on the Dose Limit for the Lens for the Eye (EGDLE)"

- Since October 2020: Intern of ICRP Committee 1

- Since October 2020: Intern of the ICRP Scientific Secretariat

- Since October 2020: Several contributions to the work of ICRP TG 115 "Risk and Dose Assessment for Radiological Protection of Astronauts"

- Since October 2020: Several contributions to the work of ICRP TG 118 "Relative Biological Effectiveness (RBE), Quality Factor (Q), and Radiation Weighting Factor (wR)"

- Since April 2020: Occupational Radiation Protection Specialist at the Swiss Federal Nuclear Safety Inspectorate ENSI

1. Contributions to the Publications

1.1 Contribution to Publication I

The study was designed by all authors. Luana Hafner performed the analysis, which included the statistical analysis and modelling, the data analysis, first interpretation of the results and creation of the figures and tables. Luana Hafner also wrote the manuscript and took the lead with replying to the reviewers comments. All authors critically reviewed and discussed the results as well as the manuscript. Linda Walsh and Werner Rühm supervised the project.

1.2 Contribution to Publication II

The study was designed by all authors. Luana Hafner performed the analysis, which included the statistical analysis and modelling, the data analysis, first interpretation of the results and creation of the figures and tables. Luana Hafner also wrote the manuscript and took the lead with replying to the reviewers comments. Linda Walsh helped to write the manuscript more concisely. All authors critically reviewed the results and the final manuscript. Linda Walsh and Werner Rühm supervised the project.

1.3 Contribution to Publication III

The analysis was conceived and designed by Luana Hafner and Linda Walsh, as an internship project for Alberto Stabilini. Luana Hafner gave Alberto Stabilini an introduction into the research field of radiation epidemiology and supported the project as first contact person. Linda Walsh supervised the project. Luana Hafner programmed the first version of the analysis program, with which excess risks based on the LSS data from the atomic bomb survivors of Hiroshima and Nagasaki using the Grant et al. (Grant et al., 2017) models could be calculated including Monte Carlo (MC) simulation of the fit parameters for the uncertainty assessment. Alberto Stabilini did a literature research to find all models for radiation-related all solid cancer risk calculation that were published and deemed plausible by the scientific community. Luana Hafner then fitted these models in EPICURE (Preston, 1993) to the data on the A-bomb survivors (Grant et al., 2017) in order to provide the fit parameters for the models, the covariance matrices that were needed to perform the MC simulations as well as the AIC and BIC weights used for the MMI calculation. Alberto Stabilini extended the program from Luana Hafner to include the other models found during the literature research and added the MMI-calculation to the code. Alberto Stabilini performed an analysis to identify the threshold in the number of realisations beyond which the MC estimator of the width of the 95% CI on the excess risk converges and does not further vary to any meaningful

degree. Then Alberto Stabilini conducted the calculation of the first composite MMI model based on AIC weights fitted with respect to the variable baselines. All results were critically reviewed and discussed by all authors. Alberto Stabilini wrote a first draft of the manuscript and Linda Walsh provided the abstract. The manuscript has been critically reviewed by all authors. The first version that was submitted to the journal included only results based on AIC weights using the variable baseline.

The changes requested by the reviewers were mainly elaborated by Luana Hafner, because the internship of Alberto Stabilini had ended by the time the reviewers comments became available. In the first review, one reviewer asked for a direct comparison of BIC and AIC weights and another reviewer thought it would be interesting to see only the impact of the excess risk models, by fitting all the models to the same baseline. These two analyses have been performed by Luana Hafner. This included calculations for finding the best fitting baseline to the A-bomb dataset used in this analysis, then fitting all the models again in EPICURE with the baseline found and performing the MMI analysis with the new parameters. Therefore, the program had to be expanded to include MMI based on BIC weights calculated with the variable baseline and to include the MMI calculated with the constant baseline based on AIC and BIC weights. Because of these changes, the manuscript had to be adapted accordingly. This included adding the section "Data and Software", "Weights of the models with constant baseline", "Estimation of model-averaged (or composite) excess risks" and rewriting most of the chapters "Multi Model Inference (MMI)", "Risks as Function of Dose" as well as "Weights of the models with variable baseline". Further the discussion was completed by a comparison of BIC and AIC weights, the tables 2 and 4 were extended and the tables 5 and 7 were added as well as figures 6-9. Luana Hafner was also in charge of including the minor editorial comments from the second review. Alberto Stabilini and Linda Walsh critically reviewed the changes made by Luana Hafner during both reviews.

1.4 Contribution to Publication IV

Linda Walsh designed the study. Luana Hafner performed the analysis, which included the statistical and data analysis as well as creating the figures and tables. Luana Hafner also wrote the manuscript and took the lead with replying to the reviewers comments. Both authors critically reviewed the results and the final manuscript. Linda Walsh supervised the study.

2. Introduction

The aim of radiation protection worldwide is to protect humans, animals and the environment from the harm induced by ionizing radiation. This aim is pursued where natural or man-made sources of ionizing radiation are present within different areas of application such as, for instance, in the medical section, the nuclear industry, or the aviation industry. In medicine, imaging procedures and therapies make use of ionizing radiation, not only to examine and treat diseases in humans, but also in animals. Therefore, medical staff and patients need to be protected. In the nuclear industry, radiation protection includes on one hand protecting nuclear workers, the public and the environment during normal operation, and on the other hand being prepared and ready to act during accidents involving ionizing radiation. Other professional groups such as pilots, flight assistants or astronauts require protection from cosmic radiation, and people living or working in buildings built on rocks containing uranium or built of materials from those rocks need to be protected from a potentially high radon exposure. These are just a few examples in the broad field of radiation protection, and many more scenarios could be listed here. In order to offer reliable protection in all these scenarios, ionizing radiation and its mode of action in causing or contributing to detrimental health outcomes needs to be understood. This requires activities in various research areas such as, for example, radiobiology, radiation physics, medicine, medical physics, radioecology, water chemistry and radiation epidemiology. In addition, radiation protection benefits from social sciences and humanities.

In order to bring structure and harmonization into the field of radiation protection, international organizations such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Commission on Radiological Protection (ICRP) regularly review the scientific results reported in fields relevant for radiation protection. Based on such reviews, UNSCEAR then publishes reports that summarize the current scientific knowledge and ICRP translates this into recommendations for radiation protection. These recommendations form the foundation for radiation protection legislation all over the world. In 2007, the last major comprehensive set of general recommendations was published by ICRP (ICRP Report 103 (ICRP, 2007)).

2.1 The Life Span Study of the Japanese Atomic Bomb Survivors

In radiation epidemiology, statistical analyses are performed based, for example, on data from cohorts of persons exposed to ionizing radiation and by comparing the observed detrimental health effects to those observed in a reference population (or sub-cohort) that was less exposed. In radiation protection, the study most important for radiation risk assessment is the Life Span Study (LSS) of the Japanese atomic bomb (A-bomb) survivors. A high level of statistical significance for some of the composite outcome radiation-related risks (e.g., all solid cancer), and to some extent also for individual cancer sites, have already been gained from this cohort, on account of the large number of people, the long follow up-period, and

the wide dose range of about 0 – 4 Gy. In the most recent published LSS dataset that contains all solid cancer incidence data (Grant et al., 2017), data from 120,321 cohort members over a follow-up period of 51 years is provided. To quantify the risk from ionizing radiation, models are fitted to the LSS data and the observed health effects are described in dependence on various parameters.

2.2 Recent Developments and Uncertainties in Radiation Protection

The calculations in the ICRP Report 103 (ICRP, 2007) were mostly based on the radiation related cancer risk models from the LSS data. However, since the publication of the last set of general recommendations, the research field of radiation epidemiology has advanced as new findings as well as new data have been published.

2.2.1 Recent Developments and New Findings

Some new large cohort studies have been launched in the past few years such as: the Million Person Study (Boice et al., 2022a) that analyses risk among American workers and veterans; the "Pooled Uranium Miner Analysis (PUMA) that assembles information on cohorts of uranium miners in North America and Europe" (Rage et al., 2020); the EPI-CT study (Bernier et al., 2019) that quantifies risks for pediatric computerized tomography applications; and the International Nuclear Workers Study (INWORKS) (Richardson et al., 2023; Laurier et al., 2017) that gathers "workers in the nuclear industry in France, the United Kingdom and the United States of America" (Laurier et al., 2017). Other studies provided new results on cancer risks in different dose ranges (Bosch de Basea Gomez et al., 2023; Leuraud et al., 2021), but also new analyses of non-cancer effects (Gillies et al., 2017) such as cardiovascular diseases (Boice et al., 2022b) or diseases of the central nervous system (Dauer et al., 2023). Additionally, already existing cohorts such as the LSS have been further followed and investigated (e.g., Brenner et al., 2022; Yoshida et al., 2023; Ishihara et al., 2022). All these studies contribute to a better quantification of the harm coming from ionizing radiation. Furthermore, international organizations follow these developments by initiating new working groups. UNSCEAR for instance launched a review on diseases of the nervous system and ICRP initiated an assessment on radiation-related diseases of the circulatory system (ICRP, 2024d; UNSCEAR, 2024).

However, with these new studies, also some established concepts and parameters have been questioned or improved. Focusing on the LSS studies, this concerns for example the linearity of the dose risk curve (Brenner et al., 2022), the dosimetry (Griffin et al., 2022), and the value of the neutron relative biological effectiveness (RBE) (Cordova and Cullings, 2019). The RBE is defined "as the ratio of absorbed doses of two types of radiation required to produce the same biological effect" (Castro et al., 2010). Traditionally, for neutron RBE a value of 10 has been used in LSS studies (e.g., Grant et al., 2017). However, recent findings indicate that the value for the RBE might be higher (Cordova and Cullings, 2019). Consequently, in this

thesis the LSS neutron RBE, its role in radiation epidemiology of the atomic bomb survivors as well as its impact on cancer risk assessment is investigated and discussed in detail.

2.2.2 Uncertainties

Discussions about uncertainties in radiation-related cancer risk assessment have become more prominent in the past few years, as demonstrated for example by the sensitivity analysis of Zhang et al. (Zhang et al., 2020) and that described in ICRP Publication 152 (ICRP, 2022). Furthermore, the meta-analysis of Shore et al. (Shore et al., 2017) illustrates the role of uncertainties for the dose rate-effectiveness factor (DREF), while the National Aeronautics and Space Administration (NASA) (Cucinotta et al., 2010) and Ulanowski et al. (Ulanowski et al., 2020) demonstrate the role of uncertainties for space radiation risk assessment. Generally, uncertainty assessments are important for gaining information about the reliability of the results of a study. Nevertheless, there are sources of uncertainties that have not yet or only rarely been integrated in cancer risk assessment such as the uncertainty of model choice. The importance of including the uncertainty of model choice in risk assessments is illustrated in this thesis. For this purpose, the statistical "Multi-Model-Inference (MMI)" method, which is a technique to build one composite or averaged model from several models of choice, is presented and applied to all LSS solid cancer incidence risks.

2.2.3 Stratification and Individualization in Radiation Protection

In addition, the discussions in radiation protection have been extended to not only cover radiation protection for a general population but to also assess the risks for specific groups of individuals (stratification) such as e.g., children, cancer patients or astronauts, or even individuals (individualization). As a result, further needs for research and recommendations have been identified. For instance, in medical physics the challenge of providing more individualization in radiotherapy treatment has arisen, in order to reduce the long-term risk of second primary cancer after radiotherapy for individuals or specific population groups such as children (ICRP, 2023b; ICRP, 2021). Besides, also with regard to possible future space missions, radiation protection for astronauts has become more prominent recently, and differences in radiation-related cancer risks between females and males have already been considered (Cucinotta, 2014). These trends have also been picked up by international organizations. ICRP, for example, has initiated a Task Group (TG) dealing with "Factors Governing the Individual Response of Humans to Ionising Radiation" (TG 111, (ICRP, 2024a)), another TG is reviewing "Risk and Dose Assessment for Radiological Protection of Astronauts" (TG 115, (ICRP, 2024b)) and just recently a new TG on "Individualisation and Stratification in Radiological Protection: Implications and Areas of Application" (TG 128, (ICRP, 2023b)) has been initiated.

As stated above, discussions about uncertainties have become more prominent recently and, consequently, affect risk assessment of specific groups of people. Uncertainties are especially

important when it comes to space risk assessment for astronauts, since uncertainties in detrimental health risks represent a main limiting factor in the planning of long-term space missions (Walsh et al., 2021). In the present thesis, space radiation risk calculations have been performed and the impact of uncertainties have been investigated by including the uncertainty of model choice into risk calculations.

2.3 Objectives of this Thesis

The aim of this thesis was to further develop calculation of radiation-related cancer risks based on new findings including an uncertainty assessment and, in this way, to contribute towards an enhancement of the current system of radiation protection. Specifically, the impact of the RBE for neutrons used in the analyses of the LSS and that of MMI on calculations of radiation-related cancer risks was investigated. In the following chapters 2.4-2.7 the studies performed within this thesis are briefly described and an outlook is provided. Related detailed methodologies, results and discussions can be found in the associated Publications I-IV.

2.4 Impact of the LSS Neutron RBE on Radiation Related Cancer Risk Calculation

The calculation of the radiation-related cancer risks by ICRP (ICRP, 2007) is mostly based on LSS data of the atomic bomb survivors. In order to assess the risk due to the radiation exposure of a certain dose, the accumulated dose needs to be known. The A-bomb survivors were exposed to two radiation types: gamma and neutron radiation (e.g., Ozasa et al., 2012). Therefore, the doses accumulated from both radiation types must be considered while considering differences in their biological effectiveness. To account for the different biological effectiveness of different radiation types, a quantity called "relative biological effectiveness (RBE)" was introduced by Failla and Henshaw (Failla and Henshaw, 1931; ICRP, 2003). The RBE is defined as "the ratio of absorbed doses of two types of radiation required to produce the same biologic effect" (Castro et al., 2010). With this parameter, an RBE-weighted absorbed dose can be calculated from the gamma and neutron radiation, which can then be used for risk modelling. Consequently, for risk modelling with the LSS data, the neutron RBE-weighted organ absorbed dose is used (Eq. 1):

$$D = D_\gamma + RBE * D_n \tag{1}$$

where D_γ is the gamma organ absorbed dose, D_n the neutron organ absorbed dose and RBE the neutron RBE relative to gamma radiation (Hafner et al., 2023a). Traditionally, a neutron RBE value of 10 is used by the Radiation Effects Research Foundation (RERF) in their LSS studies (e.g., Grant et al., 2017), and this value was also used in the calculations of ICRP (ICRP, 2007). However, several studies have recently been published that indicate that the neutron RBE for solid cancer in the LSS data might be higher. For example, Cordova and Cullings (Cordova and Cullings, 2019) have found the neutron RBE based on colon dose to

be 80 with a 95% confidence interval (CI) ranging from 20-190. This raises the question about the impact of any change in the LSS neutron RBE on the cancer risk estimates that are derived from these data. In Publication I "Assessing the impact of different neutron RBEs on the all solid cancer radiation risks obtained from the Japanese A-bomb survivors data" (Hafner et al., 2023a) this question is addressed.

2.4.1 Impact of Neutron Relative Biological Effectiveness on the All Solid Cancer Incidence Risk

To study the impact of neutron RBE on LSS solid cancer incidence risk, the all solid cancer incidence data that had been used by Preston et al. (Preston et al., 2007) were refitted with a range of different neutron RBEs (10-200) used for calculating the total neutron RBE weighted organ absorbed dose (Eq. 1). This allowed for analysing how the excess cancer risks change with RBE using colon, liver and organ averaged absorbed dose as organ dose types. The excess risks were found to decrease with increasing neutron RBEs (Hafner et al., 2023a). Further, a model for risk ratio variation with RBE was developed to provide a simple method to convert excess risks calculated with an RBE of 10 to excess risks pertaining to a higher RBE (Hafner et al., 2023a). Additionally, the change in the curvature of the risk to dose-response curve with increasing neutron RBE was analysed by fitting a linear-quadratic model to the LSS data (Hafner et al., 2023a). The curvature was found to become significantly negative with increasing neutron RBEs (Hafner et al., 2023a).

In the curvature analysis, Fieller's method (Fieller, 1940) was used to assess 95% CIs. The choice of this method resulted from a comparison of three different uncertainty assessment methods: Fieller's method (Fieller, 1940), Delta method (Stuart and Ord, 1994) and use of the profile likelihood bounds from Epicure (Preston, 1993). This comparison is described in detail in Publication V (Appendix A) "Discussion of Uncertainties and the Impact of Different Neutron RBEs on all Solid Cancer Radiation Incidence Risks Obtained from the Japanese A-bomb Survivors Data" (Hafner et al., 2023b).

2.4.2 Impact of Neutron Relative Biological Effectiveness on the All Solid Cancer Mortality Risk

In order to check on the consistency of these results, a follow up study "Assessing the Impact of Neutron Relative Biological Effectiveness on all Solid Cancer Mortality Risks in the Japanese Atomic Bomb Survivors" (Hafner et al., 2024) was performed (Publication II), repeating the analysis from Cordova and Cullings (Cordova and Cullings, 2019) as well as the main analysis from Hafner et al. (Hafner et al., 2023a) with mortality data instead of incidence data. For this study the dataset from Preston et al. (Preston et al., 2004) including all solid cancer mortality data was used, and an analysis similar to the one from Cordova and Cullings (Cordova and Cullings, 2019) was performed. The best fitting neutron RBE was found to be 200 (95% CI: 50-1010) for colon absorbed dose and for organ averaged absorbed dose 110

(95% CI: 30-350) (Hafner et al., 2024). In this study, the model for risk ratio variation with RBE was further developed and the change in the curvature of the risk to dose response curve was analysed. The curvature was found to become significantly negative at high neutron RBEs for males, while for females the curvature decreased but remained statistically significant up to neutron RBEs of 40 and 80 using organ averaged and colon absorbed dose, respectively (Hafner et al., 2024). Because of the uncertainties involved, for higher neutron RBEs than these values no firm conclusion could be drawn about the curvature for females (Hafner et al., 2024).

2.4.3 Comparison of the Results from Incidence and Mortality Data

Comparing the results based on the incidence and mortality data it can be observed that the best fitting neutron RBE is lower when incidence data instead of mortality data were used. This raises the question about how the results should be interpreted, because the RBE should be independent whether cancer incidence or cancer mortality data were analysed (Hafner et al., 2024). The observed differences may be caused by differences in dosimetry methodology, number of subjects, non-identical follow-up periods, and occurrence frequencies of certain cancer sites in these two datasets (Hafner et al., 2024). Further, an underestimation of the neutron colon absorbed doses in the DS02 dosimetry system (Young and Kerr, 2005; Griffin et al., 2019; Griffin et al., 2022) may partially explain the high values of the best fitting neutron RBE values found in this thesis.

In both studies, but especially in the mortality study, the obtained neutron RBE values are very high, and such high values are unsupported in the literature for the outcome of cancer. Nevertheless, a neutron RBE range (50-190 using colon dose) is covered by both studies, considering the 95% CIs (Hafner et al., 2024). Furthermore, it should be noted that the best fitting neutron RBE found by Cordova and Cullings (Cordova and Cullings, 2019) analysing incidence data, as well as the best fitting neutron RBE found by Hafner et al. (Hafner et al., 2024) analysing mortality data are higher than the neutron RBE value of 10 traditionally used in the LSS studies (Hafner et al., 2024).

In summary, these results show that the LSS neutron RBE is associated with large uncertainties and that the best fitting neutron RBE estimate is higher than the value of 10, which is traditionally used in LSS analyses. The large uncertainty and the impact the neutron RBE has on radiation-related cancer risk estimates demonstrate the importance of considering the LSS neutron RBE as a variable parameter and of including uncertainties associated with the neutron RBE in cancer risk assessments.

2.5 Uncertainties of Model Choice in Cancer Risk Calculations

In the past, updated cancer risk models have been applied to various cohorts for assessing radiation-related cancer risks. For example, existing epidemiological studies such as the LSS have gained more years of follow-up, and results of additional studies have been published

including data on the effects of ionizing radiation among other cohorts such as nuclear workers (Laurier et al., 2017). With these updated or new datasets, also new radiation-related cancer risk models have been published (e.g. Grant et al., 2017; Leuraud et al., 2021; NRC, 2006; UNSCEAR, 2006).

In order to model the effects of ionizing radiation in a dataset, risk to dose response models are chosen such that they describe the effects as mathematically simple as possible, while considering the goodness of fit. This approach is known as Occam's razor (Good, 1977). Statistical measures such as the Akaike Information Criterium (AIC) and the Bayesian Information Criterium (BIC) are used to evaluate the goodness of fit, while taking the numbers of model parameters into account. No model can perfectly describe reality, especially not with the tradeoff of being simple. Therefore, each plausible model included in an analysis of radio-epidemiological datasets should be assigned with a certain uncertainty. Even international organizations (UNSCEAR, 2006; NRC, 2006; ICRP, 2007) vary in their recommendations of which risk models to use, which fuels the question about the best model choice.

2.5.1 Methodology of Multi-Model-Inference

Even though no perfect model exists, the uncertainty of model choice can be accounted for in risk calculations by applying the statistical technique of Multi-Model-Inference (MMI). MMI is a technique to build one composite or averaged model. For this, a set of "plausible models is fitted to the same dataset and their goodness of fit is quantified via statistical" goodness of fit measures (AIC or BIC) (Hafner and Walsh, submitted 2023). "The composite model is then built as a weighted mean of all the considered models, where the value of the measure is used to calculate the weight for each model" (Hafner and Walsh, submitted 2023) taking into account the number of model parameters used in the individual models.

A first study introducing the MMI technique into the field of radiation epidemiology was done by Walsh and Kaiser (Walsh and Kaiser, 2011), who used MMI for childhood leukemia risk models that were developed with the Japanese A-bomb mortality data. Within the frame of this thesis the MMI-technique was applied to all solid cancer incidence risks from the LSS, in order to consider model uncertainty. The results were published in Publication III "Comparison and multi-model inference of excess risks models for radiation-related solid cancer" (Stabilini et al., 2023).

2.5.2 Multi-Model-Inference of Excess Risks using Radiation-Related Solid Cancer Models

In this study, seven models published in the literature for radiation-related risks of all solid cancers combined were fitted to the most recent all solid cancer incidence data publicly available from the LSS (Grant et al., 2017). Two different approaches to calculate the MMI were then applied in this study: An original baseline approach and a best fitting baseline approach.

In the original baseline approach the complete model, i.e., the published original baseline and the excess risk (excess relative risk (ERR) and excess absolute risk (EAR)) model was fitted to the LSS data. Then MMI was performed separately for the ERR and EAR using the two different statistical measures, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Finally, this procedure resulted in two MMI risk estimates for each excess risk (ERR and EAR) model: One calculated with AIC weights and one calculated with BIC weights.

In this thesis, additionally the best fitting baseline approach has been newly introduced. The risk measures that quantify the goodness of fit depend on the number of parameters of the model. The excess relative risks were either modelled with a stratified or a parametric baseline. Generally, stratified baselines have many more fit parameters (around 500) than parametric ones (around 20) since every stratum is counted as single parameter. Because of the high number of parameters, models with stratified baselines were automatically quantified as worse models and, consequently, excluded from MMI (Stabilini et al., 2023). In order to allow a more balanced consideration of the excess risk models that were originally modelled with a stratified baseline, all the excess risk models have been modelled with the same parametric baseline to the LSS data (best fitting baseline approach). For this, the best fitting parametric baseline among all the baselines had to be identified and was found to be the one from Preston et al. (Preston et al., 2007) (Stabilini et al., 2023). Then, MMI was again performed separately for the ERR and EAR using both AIC and BIC as statistical measures.

With these two MMI approaches finally eight different model-averaged excess risk estimates (four ERR and four EAR) were obtained.

Considering BIC weights and the original baseline models, the linear and linear-quadratic models from Grant et al. (Grant et al., 2017) were found to dominate, while considering AIC weights, the linear and linear-quadratic models of UNSCEAR (UNSCEAR, 2006) were found to dominate (Stabilini et al., 2023). These results confirm the theoretical properties of AIC and BIC: AIC favored the models with the most parameters in the parametric baseline, while BIC favored the model with the least number of parameters (Stabilini et al., 2023). Fitting only the excess risk models with the best fitting baseline from Preston et al. (Preston et al., 2007), the BEIR model (NRC, 2006) dominated using both AIC and BIC weightings (Stabilini et al., 2023). Further, the preferred model is the same, because in this approach the models have a similar number of parameters.

In summary, this study provided eight model-averages (four ERR and four EAR) that can be integrated in future studies which calculate radiation-related cancer incidence risks based on the Grant et al. (Grant et al., 2017) dataset, in order to account for model choice uncertainty. Further, the study illustrates a new approach on how "to overcome an inherent problem of the MMI approach, which penalizes ERR models with stratified baseline models, due

to the high number of parameters compared to risk models with parametric baselines" (Hafner and Walsh, submitted 2023).

2.6 Space Radiation Risk Assessment and the Corresponding Uncertainties

One of the fields where the uncertainty of model choice should be integrated into risk calculations, is the field of space radiation risk assessment. Ideally, radiation-related cancer risk of astronauts from space radiation would be directly modelled based on astronaut data, but because of the very small cohort of astronauts, statistical significance cannot be achieved with this approach. Consequently, for more reliable risk estimates those radiation risks must be modelled based on data from "large epidemiological cohorts that bring the advantage of cohort size and long follow-up period" (Hafner and Walsh, 2024), such as the LSS data.

In Publication IV "Application of multi-method-multi-model inference to radiation related solid cancer excess risks models for astronaut risk assessment" (Hafner and Walsh, 2024) the impact of including MMI averaged models for all solid cancer incidence in astronaut risk assessment was analyzed in order to account for model choice uncertainty. Specifically, the different ERR and EAR models identified in Stabilini et al. (Stabilini et al., 2023) were combined into four ER models:

- ER with best fitting baseline based on AIC weights
- ER with best fitting baseline based on BIC weights
- ER with original baseline based on AIC weights
- ER with original baseline based on BIC weights

These four ER models were then implemented into the time-integrated risk metric "Radiation Attributed Decrease of Survival" (RADS) (Ulanowski et al., 2019; Ulanowski et al., 2020; Ulanowski et al., 2023). With the aim to quantify the impact of the implementation of the model-averaged risk estimates, RADS was additionally assessed with only one risk model, namely the linear Grant et al. model (Grant et al., 2017).

RADS represents a cumulative risk assessment quantity that minimizes the contribution of population data in the calculations and is therefore very suitable for astronaut risk assessment (Walsh et al., 2021). This is because astronauts are not well represented by models that were calculated based on data from the general population, due to their specific age range and above average health conditions. The analysis of integrating MMI into RADS showed that the RADS estimates assessed with the model-averaged ER based on AIC weights were lower with narrower 95% CI than the other corresponding risk estimates calculated with BIC weights and with the Grant model (Hafner and Walsh, 2024). The mean estimates for a lunar mission result between 0.37% and 0.74% and for a Mars mission between 2.14% and 4.27% at age at exposure 40 years and attained age 65 years (Hafner and Walsh, 2024).

Regarding whether AIC or BIC should be used, there is no clear evidence-based reason for choosing one measure over the other. Consequently, in this study (Hafner and Walsh, 2024), a Multi-Method-Multi-Model-Inference (M^4I) approach was developed, where the RADS estimates resulting from the four methods "were combined to provide one general RADS estimate by taking the weighted mean with weights based on AIC and BIC weights" (Hafner and Walsh, 2024) for each sex. With this approach a novel method was introduced that eliminates the requirement to choose the best statistical criteria to apply.

This work shows that the uncertainties of model choice can be effectively integrated into space radiation risk assessment, in order to provide more reliable risk estimates than available to date. Further, properties of the risk metrics RADS have been explored to greater extent than in previous studies (e.g. Walsh et al., 2021), which is in line with the recommendation of the National Academies of Sciences, Engineering, and Medicine report (National Academies of Sciences and Medicine, 2021) to re-examine other metrics than "Risk of Exposure Induced Death" (REID). Finally, the M^4I-approach was introduced in this thesis that could be applied to generate one single risk estimate.

2.7 Outlook - Impact of the Findings on the System of Radiation Protection

In the previous chapters, the findings obtained within the framework of this thesis as well as their importance were described in a subject-specific context. Now the question might arise why and how the presented results might be important for the system of radiation protection.

2.7.1 The Role of the Radiation Detriment in Radiation Protection

In the ICRP Report 103 (ICRP, 2007), a metric was introduced: the radiation detriment. The radiation detriment "is defined as the excess of stochastic health effects in a group of exposed individuals to low-level radiation and their descendant compared to a non-exposed group" (ICRP, 2022). This metric is used in radiation protection to quantify the harm coming from ionizing radiation, which means that this metric does not only consider radiation related cancer risks, but also factors as heritable diseases, reduction of quality of life, years of life lost or lethality. A detailed description of the detriment calculation is given in ICRP Publication 152 (ICRP, 2022), which reviews and specifies the calculation methodology used in the ICRP Report 103 (ICRP, 2007). However, it is important to note that one of the main bases of this metric are radiation related cancer risk estimates.

In radiation protection, one major application of the radiation detriment is the derivation of tissue weighting factors by ICRP. Tissue weighting factors are derived from "the relative radiation detriments for the whole population" (ICRP, 2022), which denote the normalized radiation detriments of various organs/tissues (ICRP, 2022). However, such organ-specific relative radiation detriments were considered to be imprecise (ICRP, 2022) and,

consequently, they were grouped in four categories of tissue weighting factors that reflect approximations of the relative detriments. These tissue weighting factors find then application in the calculation of the effective dose E:

$$E = \sum_{T} w_T * H_T \tag{2}$$

where w_T is the tissue weighting factor for a certain organ T, and H_T denotes the organ absorbed dose.

Effective dose is a measure of radiation exposure that is used to assess the risk of stochastic radiation effects. Since effective dose cannot be measured, it should be predominantly seen as a risk-adjusted dosimetric quantity to be used "for the management of protection against stochastic effects" (ICRP, 2021), rather than a rigorous physical quantity. Effective dose is, therefore, used for example as a risk communication tool in radiation protection.

For exposures of workers and the public, effective dose is also used to set dose limits, constraints and reference levels, which are integrated into the radiation protection legislation of various countries. Additionally, effective dose is used as quantity to judge optimization methods in radiation protection.

Because measurable radiation quantities used in medicine often provide only little information about a potential radiation-related risk, effective dose is often used as a rough indicator of potential risk (ICRP, 2021), to justify imaging exposures or to compare different possible treatment methods including ionizing radiation. For this purpose, coefficients have been published that enable the calculation of effective dose based on measurable quantities (Martin, 2020).

In 2022, ICRP established a new Task Group (TG 122) "Update of Detriment Calculation of Cancer" that has the mandate to "evaluate the current knowledge on all aspects involved in the calculation of detriment for cancer, to assess the implications of updating components of detriment calculation where necessary and to consider potential modifications of detriment calculation" (ICRP, 2023a). For this purpose, every input parameter and all calculation steps in the detriment formulation will be reanalysed, including also the parameters used for radiation-related cancer risk modelling. Currently, most cancer-site specific risks needed for the detriment calculation are based on the LSS data, i.e., using the LSS cancer models. This practice will certainly be reconsidered and alternative models and approaches such as MMI will be reviewed. The presented work on the impact of choice of neutron RBE using all solid cancer incidence and mortality data as well as the work on all solid cancer MMI will directly leave its mark on TG 122 discussions on the role of uncertainties in detriment calculations, at the highest level of international collaboration. Further, the demonstrated methodology of analysing the impact of the LSS neutron RBE on cancer risk assessment in this thesis can be easily applied to the new dosimetry set (Griffin et al., 2022) in the future and thus help to even better understand and investigate the role of the neutron RBE. Additionally, the results

on the LSS neutron RBE are directly relevant for the work of the ICRP TG 118 "Relative Biological Effectiveness (RBE), Quality Factor (Q), and Radiation Weighting Factor (wR)" (ICRP, 2024c), that among other tasks, will review the current scientific evidence on RBE of various radiation qualities including neutrons. Depending on the decisions of these TGs, the results obtained in the frame of the present thesis may finally even be integrated in the updated new recommendations for international radiation protection currently developed by ICRP.

2.7.2 Uncertainties in the Field of Radiation Protection

In the current radiation detriment calculations, no uncertainties have been provided (ICRP, 2007). With the application of effective dose in medicine, the discussion about uncertainties and individualization has become more important (see also the ICRP Task Group 111 on "Factors Governing the Individual Response of Humans to Ionising Radiation" (ICRP, 2024a) and ICRP Task Group 128 on "Individualisation and Stratification in Radiological Protection: Implications and Areas of Application" (ICRP, 2023b)). Generally, the radiation detriment represents a mean value, which has been averaged for example over sex, age groups, and different reference populations. However, medical treatments are often individualized and, consequently, an averaged metric may not always be the best source for a risk estimate. Especially the advantages of using a stratified detriment (i.e., with respect to tissue weighting factors) for certain population groups, e.g., for children or for males and females, have been pointed out and are now under discussion (ICRP, 2023b; ICRP, 2021).

Further, growing interest in finding "the major sources of uncertainty in radiation risk assessment and quantification of their impact" (ICRP, 2022) has been identified (ICRP, 2022; UNSCEAR, 2015; UNSCEAR, 2021). To transparently communicate risks it is important to know and to address those uncertainties. For the calculation of radiation detriment, Zhang et al. (Zhang et al., 2020) have recently performed a sensitivity analysis to inform on parameters most important for detriment calculation, but direct uncertainties on the radiation detriment have not been provided so far. Since the calculation of the detriment is complicated and includes many different parameters, a discussion about the uncertainties is indispensable (ICRP, 2022) and guidance is needed. The work presented here provides examples of how uncertainties can be addressed in radiation-related cancer risk assessment and highlights some sources of uncertainties that should be considered in more detail in future.

With regard to space missions, uncertainties have also gained importance. Currently, there are no international dose limits for astronauts defined, but discussions have been going on about setting risk limits for space missions. NASA introduced a 3% limit on the upper level of the 95% CI of the cumulative REID risk assessment (Cucinotta et al., 2010), that was used in the past to assess space radiation risks for astronauts. Work promoted by the European Space Agency (ESA), in turn, has suggested a 4% limit on the upper level of the 95% CI of the cumulative risk assessment method RADS (Walsh et al., 2021). In contrast, more recently,

the NASA advocated the implementation of an effective dose career standard for all astronauts of 600 mSv, which is the NASA effective-dose equivalent for the most susceptible case, namely a "35-year-old female astronaut, whose mean REID is at 3 percent" (National Academies of Sciences and Medicine, 2021) (Shavers et al., 2023). If limits are defined on CIs, uncertainty assessment becomes essential, and guidance is needed about which uncertainties to be considered in relevant exposure scenarios. The work described in this thesis on including MMI in astronaut risk assessment helps addressing this issue by considering the uncertainty source of model choice. Further, the recommendation of the National Academies of Sciences, Engineering, and Medicine report (National Academies of Sciences and Medicine, 2021) to re-examine other metrics than REID has been followed in this thesis by investigating properties of the risk metrics RADS to greater extent. This work is directly relevant to work of ICRP TG 115 "Risk and Dose Assessment for Radiological Protection of Astronauts" (ICRP, 2024b) that aims to "develop a comprehensive framework for risk and dose assessment for radiological protection for astronauts" (Rühm et al., 2024), and that in future may also become relevant for space tourism.

To summarize, the work presented here has a direct impact on the levels of risk estimates based on the LSS data and on uncertainty assessment of radiation-related cancer risks for the general population on earth, as well as for astronauts in space. The results impact radiation detriment calculations as well as the effective dose calculation methodology and, consequently, is directly relevant for the process recently initiated by ICRP to review and revise the system of radiation protection (Clement et al., 2021; Laurier et al., 2021; Rühm et al., 2022; Rühm et al., 2023). Even though many more aspects in the radiation-related cancer risk calculation need to be considered, the results of the studies presented in this thesis may contribute to filling gaps in knowledge and to substantiating discussions on the impact of LSS neutron RBEs and the treatment of uncertainties in radiation-related cancer risk assessment.

3. Abstract

The aim of this thesis was to contribute towards an enhancement of the current system of ionising radiation protection by further developing assessments of radiation-related cancer risks based on new findings and including previously disregarded sources of uncertainties. Specifically, the impact of the following factors on calculations of radiation-related cancer risk was investigated: The relative biological effectiveness (RBE) for neutrons (relative to gamma radiation) used in the analyses of the Life Span Study (LSS) of Japanese A-bomb survivors; and Multi-Model-Inference (MMI) approaches.

The RBE is defined as the ratio of absorbed doses of two types of radiation required to produce the same biological effect. Recent studies on cancer incidence reported indications that the RBE for neutrons (relative to gamma radiation) in the LSS on atomic bomb survivors might be higher than the traditionally used value of 10 (Cordova and Cullings, 2019). Therefore, in this thesis the impact of the choice of neutron RBE on radiation-related all solid cancer risks was investigated. For this purpose, radiation risk models with variable neutron RBE were refitted to the most recently published cancer incidence dataset from the LSS for different dose ranges using colon, liver and organ-averaged radiation doses. Additionally, a model for risk ratio variation with RBE was further developed to provide a simple method for the transfer of excess risks calculated with an RBE of 10 to those calculated with higher RBE. The change in the curvature of the risk to dose-response curve with increasing neutron RBE was analysed by fitting a linear-quadratic model form to the LSS data. This analysis was then repeated with the most recent mortality data from the LSS using colon and organ-averaged doses. Finally, excess risks were fitted with different neutron RBE using mortality data, in order to find the best fitting neutron RBE.

In both incidence and mortality analyses, all solid cancer excess risks were found to decrease with increasing neutron RBE. Furthermore, using incidence data, the curvature was found to become significantly negative with high neutron RBE. Using mortality data, the curvature was also found to become significantly negative with high neutron RBE for males, while for females the curvature decreased but remained significantly positive up to neutron RBE values of 80 and 40 using colon and organ averaged dose, respectively. These results show that neutron RBE values higher than 10 would lead to a decrease of all solid cancer excess risks and to a change in curvature of the corresponding risk to dose risk curves. The best fitting neutron RBE was found to be 200 (95% confidence interval (CI): 50-1010) for colon dose and 110 (95% CI: 30-350) for organ averaged dose when using mortality data. These values are higher than the best fitting neutron RBE estimates using incidence data. However, the results need to be interpreted with caution because the RBE should be similar for cancer incidence and mortality. In any case, the best fitting neutron RBE using incidence as well as that using mortality data are higher than the neutron RBE value of 10 that is traditionally used in the majority of previously published papers on the LSS. A range of neutron RBE values of 50-190 using colon dose is covered by both the incidence and mortality results,

after accounting for the 95% CIs. Overall, the results described here confirm those reported earlier by Cordova and Cullings (Cordova and Cullings, 2019). It should be noted, however, that such high values for the neutron RBE are not backed by biological evidence. Recently published results indicate that the estimated absorbed neutron colon doses are underestimated. This could at least partially explain the high RBE values for neutrons obtained in this thesis.

In a second type of analysis, the statistical MMI technique was applied to all solid cancer incidence risks from the LSS, in order to include the uncertainty of model choice in calculations of radiation-related all solid cancer risks. Generally, MMI represents a technique that enables the building of one composite or averaged model from several suitable models. Specifically, in this study MMI was performed using seven published all solid cancer risk models with two different approaches: An original baseline approach and a best fitting baseline approach. In the original baseline approach the complete model, i.e., the published original baseline (which expresses the natural (spontaneous) cancer risk) and the excess risk (relative and absolute) model part (which describes the risk on top of the baseline due to the radiation exposure), was fitted to the data of the LSS. Then MMI was performed separately for the excess relative and excess absolute risk models using two different statistical measures that account for the goodness of fit of the model to the data: The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC).

In the best fitting baseline approach, the best fitting baseline among the seven models was identified. With this baseline, all excess risk models were then fitted and the former analysis was repeated. This approach has the advantage that all excess risk models of all studies can be directly compared, even those that would be automatically excluded in the former analysis due to their baseline forms. Finally, also here, MMI was performed separately for the excess relative and excess absolute risk using both AIC and BIC as statistical measures.

Applying these two approaches, eight estimates (two approaches with two statistical criteria for two excess risks (ERR, EAR)) for a model-averaged excess risk were obtained in total. These model-averaged excess risks can now be applied in future studies that are based on the LSS data to automatically account for the uncertainty of model choice.

The validity of these results was directly illustrated with a practical example: The identified MMI models were applied to assess space radiation cancer risks for astronauts to analyze the impact of MMI in a cumulative risk assessment metric called Radiation Attributed Decrease of Survival (RADS). It was illustrated that the uncertainties of model choice can be suitably used to provide more reliable risk estimates, particularly when the BIC-criterion was used. Additionally, in this thesis an innovative Multi-Method-Multi-Model-Inference (M^4I) approach is proposed, where the resulting risk estimates from the different methods are combined to provide one general risk estimate by calculating the weighted mean with overall weights based on AIC and BIC weights.

It is concluded that the results of this thesis indicate that the LSS incidence and mortality data can statistically be better described with higher neutron RBE values than 10. It was shown that such higher values would lead to a decrease of all solid cancer excess risks and to a change in curvature of the corresponding dose risk curves. The large uncertainty involved in the calculated neutron RBE values and the impact that the neutron RBE has on radiation-related cancer risk estimates shows the importance of considering the LSS neutron RBE as a variable parameter in cancer risk assessments. Additionally, it is also concluded that the MMI method has been illustrated to be a valid method for addressing the uncertainty of model choice in radiation-related cancer risk assessment. In future, the uncertainties in neutron RBE from the LSS as well as the uncertainties in model choice (through the MMI method) should be considered in radiation-related cancer risk analyses, in order to provide more reliable risk estimates that can be used to support the process recently initiated by the International Commission on Radiological Protection (ICRP) to review and revise the current system of radiation protection.

4. Zusammenfassung

Ziel dieser Arbeit war es, die Berechnung des strahlenbedingten Krebsrisikos aufgrund neuer Erkenntnisse und unter Berücksichtigung von Unsicherheiten, die in der Vergangenheit außer Acht gelassen worden waren, weiterzuentwickeln. Dafür wurden die Auswirkungen von verschiedenen Faktoren auf die Berechnungen des strahlenbedingten Krebsrisikos untersucht, darunter die relative biologische Wirksamkeit (RBW) von Neutronen in der sogenannten Life Span Study (LSS) über die Atombombenüberlebenden aus Japan sowie die Anwendung der Multi-Modell-Inferenz (MMI) Methode.

Die RBW ist definiert als das Verhältnis von zwei Energiedosen verschiedener Strahlenarten, die erforderlich sind, um den gleichen biologischen Effekt zu erzeugen. Neueste Krebsinzidenzstudien legen nahe, dass die RBW von Neutronen (relativ zur Gammastrahlung) in Hiroshima und Nagasaki höher gewesen sein könnte als der in Studien zum Krebsrisiko der Atombombenüberlebenden meistens verwendete Wert von 10 (Cordova and Cullings, 2019). Daher wurden in der vorliegenden Arbeit die Auswirkungen höherer RBW-Werte für Neutronen auf das Krebsrisiko der Atombombenüberlebenden untersucht. Für diese Untersuchung wurden Strahlenrisikomodelle mit höheren RBW-Werten für Neutronen an die zuletzt veröffentlichten LSS-Krebsinzidenzdaten gefittet, wobei Dickdarm-, Leber- und organgemittelte Dosen verwendet wurden. Ergänzend wurde ein weiteres Modell entwickelt, das es ermöglicht, Krebsrisiken, die mit einem RBW-Wert von 10 ermittelt wurden, in Krebsrisiken, die mit einem höheren RBW-Wert ermittelt wurden, umzurechnen. Schließlich wurde ein linear-quadratisches Dosismodell verwendet, um die Veränderung der Krümmung der Dosis-Risiko-Kurve mit zunehmenden RBW-Werten für Neutronen zu analysieren. Diese Analyse wurde dann mit den LSS-Mortalitätsdaten und unter Verwendung von Dickdarm- und organgemittelten Dosen wiederholt. Abschliessend wurden verschiedenen RBW-Werte für Neutronen verwendet, um die RBW für Neutronen zu finden, die statistisch die vorhandenen Krebsmortalitätsdaten am besten beschreibt.

Bei der Analyse der Inzidenz- und der Mortalitätsdaten wurde jeweils festgestellt, dass die Krebsrisiken von soliden Tumoren mit höheren RBW-Werten für Neutronen wie erwartet abnehmen. Unter Verwendung der Inzidenzdaten wurde die Krümmung bei hohen RBW-Werten für Neutronen signifikant negativ, wobei unter Verwendung der Mortalitätsdaten die Krümmung bei den für Männer abgeleiteten Risikokurven mit höheren RBW-Werten für Neutronen ebenfalls signifikant negativ wurde, während die entsprechende Krümmung bei Frauen mit zunehmender RBW für Neutronen zwar abnahm, aber bis zu RBW-Werten für Neutronen von 80 bzw. 40 signifikant positiv blieb, je nachdem, ob für die Analyse Dickdarmdosen oder gemittelte Organdosen verwendet wurden. Das bedeutet, dass höhere RBW-Werte für Neutronen zu einer Verringerung der Krebsrisiken und zu einer Veränderung der Form der Dosis-Risiko-Kurve führen. Der am besten passende RBW-Wert für Neutronen war bei Verwendung der Mortalitätsdaten 200 (95 % Konfidenzintervall (KI): 50-1010) für die Dickdarmdosis und 110 (95 % KI: 30-350) für die organgemittelte Dosis.

Diese RBW-Werte sind höher als die Werte, die aus den Inzidenzdaten abgeleitet wurden. Da die RBW eigentlich für Mortalität und Inzidenz ähnlich sein sollten, müssen diese Ergebnisse mit Vorsicht interpretiert werden. Die am besten passenden RBW-Werte für Neutronen sind sowohl für die Inzidenz- als auch für die Mortalitätsdaten höher als der in den meisten Veröffentlichungen der Life Span Studie verwendete Wert von 10. Abschliessend zeigte sich, dass die aus den Mortalitäts- und Inzidenzdaten gewonnenen RBW-Werte zusammengenommen einen Bereich von 50-190 abdecken, wenn man das jeweilige 95%- KI berücksichtigt und die Dickdarmdosis verwendet. Insgesamt bestätigen die hier beschriebenen Ergebnisse somit die Resultate von Cordova und Cullings (Cordova and Cullings, 2019). Dabei sollte jedoch beachtet werden, dass derart hohe RBW-Werte für Neutronen nicht durch Daten aus biologischen Studien bestätigt werden. Kürzlich veröffentliche Ergebnisse deuten darauf hin, dass die bis jetzt abgeschätzten Neutronenenergiedosen für den Dickdarm unterschätzt sind. Dies könnte die in dieser Dissertation erzielten hohen RBW-Werte für Neutronen zumindest teilweise erklären.

In einer zweiten Analyse wurde erstmals die statistische Methode der Multi-Modell-Inferenz (MMI) auf die Daten der LSS angewandt, um die Modellwahlunsicherheit bei der Berechnung von strahlenbedingten Risiken im Hinblick auf die Inzidenz solider Tumore berücksichtigen zu können. MMI ist eine Methode, die es ermöglicht, aus mehreren ähnlich geeigneten Modellen ein zusammengesetztes bzw. gemitteltes Modell zu erstellen. Die MMI-Methode wurde hier mit sieben veröffentlichten Risikomodellen für solide Tumoren mit zwei unterschiedlichen Ansätzen angewendet: entweder wurde das ursprüngliche Grundrisikomodell oder das am besten passende Grundrisikomodell verwendet. Im ersten Fall wurden aus den entsprechenden Veröffentlichungen das jeweilige Grundrisikomodell, welches das natürliche (spontane) Auftreten von Krebs beschreibt, und das entsprechende Modell des zusätzlichen Risikos (Exzess Relative Risk (ERR) bzw. und Exzess Absolute Risk (EAR)), welches das zusätzliche strahlenbedingte Risiko beschreibt, verwendet. Anschliessend wurde die MMI-Methode jeweils separat mit dem ERR- und dem EAR-Modell durchgeführt. Die MMI-Modelle wurden dabei jeweils durch die Anwendung von zwei statistischen Kriterien erstellt: Dem Akaike Informationskriterium (AIC) und dem Bayes'schen Informationskriterium (BIC). Diese statistischen Kriterien bewerten, wie gut die einzelnen Modelle die Daten beschreiben. Im zweiten Fall wurde aus den sieben Modellen das Grundrisikomodell, welches die Daten am besten beschreibt, identifiziert. Mit diesem Grundrisikomodell wurden dann unter Verwendung des ERR- und des EAR-Modells die LSS-Daten der berücksichtigten Veröffentlichungen gefittet. Dieser Ansatz hat den Vorteil, dass die Risikomodelle aller Publikationen miteinander verglichen werden können, auch diejenigen, die ansonsten aufgrund ihres Grundrisikomodells automatisch ausgeschlossen werden würden. Auch hier wurde die MMI-Methode jeweils separat mit dem ERR- und dem EAR-Modell unter Verwendung der AIC- und BIC-Kriterien durchgeführt.

Mit diesen beiden Ansätzen wurden somit insgesamt acht verschiedene modellgemittelte Schätzungen des Krebsrisikos (zwei Ansätze mit zwei statistischen Kriterien für zwei

Risikomodelle (ERR, EAR)) ermittelt. Diese Schätzungen können in zukünftige Studien, die die LSS-Daten als Grundlage verwenden, integriert werden, um so die Unsicherheit der Modellwahl zu berücksichtigen.

Dies wurde in dieser Arbeit dann am Beispiel der Berechnung des Strahlenkrebsrisikos von Astronauten im Weltraum veranschaulicht: Die identifizierten MMI-Modelle wurden verwendet, um bei Astronauten als Beispiel die strahleninduzierte Abnahme der Überlebenswahrscheinlichkeit (Radiation Attributed Decrease of Survival (RADS)) zu analysieren. Es zeigte sich, dass mit dem entwickelten Ansatz insbesondere bei Verwendung des BIC-Kriteriums zuverlässigere Risikoschätzungen als ohne diesen Ansatz ermöglicht werden. Darüber hinaus wurde der innovative Ansatz der Multi-Methoden-Multi-Modell-Inferenz (M^4I) eingeführt. Dabei werden die aus den verschiedenen Methoden und mit den AIC- und BIC-Kriterien berechneten Risikoschätzungen verwendet, um einen einzelnen allgemeinen Risikoschätzer zu berechnen.

Zusammenfassend zeigen die Ergebnisse dieser Arbeit, dass a) die Inzidenz- und Mortalitätsdaten der LSS mit höheren RBW-Werten für Neutronen statistisch besser beschrieben werden können als mit einem Wert von 10, b) höhere RBW-Werte zu einer Verringerung der Krebsrisiken führen und c) sich bei der Verwendung höherer RBW-Werte die Form der Dosis-Risiko-Kurve ändert. Diese Ergebnisse zeigen, wie wichtig es ist, die RBW für Neutronen in der LSS als variablen Parameter bei der Bewertung des Krebsrisikos zu berücksichtigen. Darüber hinaus konnte gezeigt werden, dass die MMI-Methode geeignet ist, Modellwahlunsicherheiten bei der Bewertung von strahlenbedingten Krebsrisiken zu berücksichtigen. Um im Vergleich zu früher zuverlässigere Strahlenrisiken abschätzen zu können, die dann zur Verbesserung des derzeitigen Strahlenschutzsystems beitragen können, sollten daher in der LSS sowohl die Unsicherheiten der RBW von Neutronen als auch die Unsicherheiten bei der Modellwahl wie hier beschrieben mitberücksichtigt werden. Dies wird verbesserte Abschätzungen des strahleninduzierten Krebsrisikos ermöglichen, die für den kürzlich von der Internationalen Strahlenschutzkommission (International Commission on Radiological Protection - ICRP) eingeleiteten Prozess der Überprüfung und Verbesserung des gegenwärtig gültigen internationalen Strahlenschutzsystems verwendet werden können.

5. Publication I

Hafner L, Walsh L, Rühm W. (2023) Assessing the impact of different neutron RBEs on the all solid cancer radiation risks obtained from the Japanese A-bomb survivors data, International Journal of Radiation Biology, 99(4):629-643.
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6. Publication II

Hafner L, Walsh L, Rühm W. (2024) Assessing the Impact of Neutron Relative Biological Effectiveness on all Solid Cancer Mortality Risks in the Japanese Atomic Bomb Survivors. International Journal of Radiation Biology, 100(1):61-71.
https://www.tandfonline.com/doi/full/10.1080/09553002.2023.2245463

7. Publication III

Stabilini A, **Hafner L**, Walsh L. (2023) Comparison and multi-model inference of excess risks models for radiation-related solid cancer. Radiat Environ Biophys, 62:17–34. https://doi.org/10.1007/s00411-022-01013-0

8. Publication IV

Hafner L, Walsh L. (2024) Application of multi-method-Multi-Model-Inference to radiation related solid cancer excess risks models for astronaut risk assessment. Zeitschrift für Medizinische Physik, 34(1):83-91. https://doi.org/10.1016/j.zemedi.2023.06.003

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10. Appendix A: Publication V

Hafner L, Walsh L, Rühm W. (2023) Discussion of Uncertainties and the Impact of different Neutron RBEs on all Solid Cancer Radiation Incidence Risks obtained from the Japanese A-bomb Survivors Data, Annals of the ICRP, 52(1-2):17-22.
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