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# Clinical and epidemiological observations on individual radiation sensitivity and susceptibility

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## ABSTRACT

**Purpose:** To summarize existing knowledge and to understand individual response to radiation exposure, the MELODI Association together with CONCERT European Joint Programme has organized a workshop in March 2018 on radiation sensitivity and susceptibility.

**Methods:** The workshop reviewed the current evidence on this matter, to inform the MELODI Strategic Research Agenda (SRA), to determine social and scientific needs and to come up with recommendations for suitable and feasible future research initiatives to be taken for the benefit of an improved medical diagnosis and treatment as well as for radiation protection.

**Results:** The present paper gives an overview of the current evidence in this field, including potential effect modifiers such as age, gender, genetic profile, and health status of the exposed population, based on clinical and epidemiological observations.

**Conclusion:** The authors conclude with the following recommendations for the way forward in radiation research: (a) there is need for large (prospective) cohort studies; (b) build upon existing radiation research cohorts; (c) use data from well-defined cohorts with good exposure assessment and biological material already collected; (d) focus on study quality with standardized data collection and reporting; (e) improve statistical analysis; (f) cooperation between radiobiology and epidemiology; and (g) take consequences of radiosensitivity and radiosusceptibility into account.

**Abbreviations:** CLL: chronic lymphatic leukemia; CT: computed tomography; CTCAE: common terminology criteria for adverse events; DICOM: digital imaging and communications in medicine; DVH: dose-volume-histogram; EORTC: European Organization for Research and Treatment of Cancer; EPIC: expanded prostate cancer index composite; EUD: equivalent uniform dose; EURAMED: European Alliance for Medical Radiation Protection Research; FACIT: Functional Assessment of Chronic Illness Therapy; FACT: Functional Assessment of Cancer Therapy; HLEG: High Level Expert Group; ICRP: The International Commission on Radiological Protection (ICRP); IMRT: intensity modulated radiotherapy; IR: ionizing radiation; LENT-SOMA: Late Effects in Normal Tissue – Subjective, Objective, Management, Analytic criteria; MELODI: Multidisciplinary European Low Dose Initiative; MRI: magnetic resonance imaging; NTCP: normal tissue complication probability; RgC: Radiogenomics Consortium; RR: relative risk; RTOG/EORTC: Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer criteria; SRA: Strategic Research Agenda; STAT: Standardized Total Average Toxicity score

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## 1. Introduction

In 2007, the European Commission set up a High Level Expert Group (HLEG) to help improve the knowledge on low dose ionising radiation health effects and radiation protection. Low dose is defined as up to 100 mGy of low-LET

radiation (Wakeford and Tawn 2010; UNSCEAR 2012a, 2012b) and, for the purposes of this review, doses between 0.1 and 1 Gy are referred as ‘moderate doses’, and those above 1 Gy as ‘high doses’. HLEG came up with the following recommendations: In addition to the necessity to deal

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with existing uncertainties in radiation protection, the areas of individual radiation sensitivity and radiation-induced (non-)cancer effects need to be explored (HLEG 2009). The Multidisciplinary European Low Dose Initiative (MELODI) Association was founded in order to promote scientific work on all these issues, and as a first step a European research network (see the DoReMi project 2010–2015, Averbeck et al. 2018) was launched to advance knowledge and understanding of the health effects of radiation and provide a basis for improved radiation protection.

In early 2018, MELODI carried out an analysis of knowledge gaps in low dose health risk evaluation, by reflecting the topics and outcome of the FP6 and FP7 Euratom projects. While all projects have made progress in building the evidence base, there remain areas where additional work could be beneficial. To understand the potential impact of individual susceptibility on radiation-induced health effects, MELODI concluded that there is need for (a) studies that lead to the identification and validation of biomarkers of disease risk and/or susceptibility; (b) studies that identify and validate cohorts suitable for molecular/biomarker epidemiological studies; (c) studies of tissue level effects and the role of individual differences in tissue architecture that impact on the susceptibility to radiogenic diseases; and (d) for studies that potentially lead to the identification of biomarkers of resistance to radiation health effects.

Although there is a large number of biological and epidemiological studies investigating the health effects after exposure to low dose ionizing radiation, results are not always consistent and a clear understanding of the observations from experimental and epidemiological results is still missing.

One possible explanation (or hypothesis) among others (e.g. differing length of follow-up and statistical power or different data quality between studies) is the existence of individual sensitivity to radiation which may explain heterogeneous results between epidemiological studies. Thus, further scientifically based information about the extent of variability in individual reaction to radiation exposure should be obtained. To summarize existing knowledge and to stimulate further research in this matter, the MELODI Association together with CONCERT European Joint Program has organized a specific workshop in March 2018 on individual radiation sensitivity/susceptibility. The workshop reviewed the current evidence on this matter, to inform the MELODI Strategic Research Agenda (SRA), to determine social and scientific needs and to come up with recommendations for suitable and feasible future research initiatives to be taken for the benefit of an improved medical diagnosis and treatment as well as for radiation protection.

The present paper gives an overview of the current evidence in this domain, based on clinical and epidemiological observations. The overview includes the frequency of adverse effects, the dependency on certain radiation parameters and potential effect modifiers such as life-style, age, gender, genetic profile, and health status of the exposed population. The main focus in this workshop was on health effects after exposure to low dose radiation such as occupational exposure, exposure from diagnostic procedure and

environmental exposure. Additionally, individual response to radiation in patient cohorts exposed to high radiotherapy doses were also discussed as those results contribute to the understanding of low dose effects in several regards. Organs outside the radiotherapy target tissue may be exposed to low or medium doses through scatter from the RT beam, imaging or other radiation exposure. Further, observations in populations exposed to high dose (radiotherapy) can help to evaluate the dose-response relationship.

### 1.1. Terminology

In general, two types of radiation effects can be distinguished: so-called deterministic effects and stochastic effects. The mechanisms underlying these two phenomena are thought to be quite different, deterministic effects arising from cell killing or malfunction of cells, and stochastic effects arising from clonal expansion of mutated cells (Hall and Giaccia 2006; ICRP 2007). Deterministic effects generally have a threshold dose below which the effects do not manifest and, above this threshold, the effect becomes more severe as the dose increases. It is generally thought that there is no threshold dose for the stochastic effects and their probability but not severity increases with dose. Traditionally, stochastic effects include cancer and hereditary effects. We acknowledge that the division of radiation effects into deterministic and stochastic categories is not so clear cut (Hamada et al. 2018), especially as the threshold doses for some effects previously considered as deterministic such as lens opacities and vascular diseases are much lower than previously thought and there may even be no threshold (e.g. Averbeck et al. 2018; Thome et al. 2018). For cataracts, there might be a high dose non-stochastic type and a low dose type of cataracts with long latency effect that causes cataracts to occur earlier in life than if not exposed to radiation. The International Commission on Radiological Protection (ICRP) has recently adopted a new term ‘tissue reactions’ for the non-cancer effects of deterministic nature (ICRP 2007; 2012).

Variation in radiation sensitivity refers here to differences in the threshold for developing tissue reactions induced by ionizing radiation. It has been described in the first decade of the 20th century (as summarized by Foray et al. 2012). Radiation susceptibility defined as the proneness to radiation-induced cancers was first reported during the same period (Friebe 1902). Radiosensitivity and radiosusceptibility are regarded here as two different types of individual responses to ionizing radiation. At least up to date, there are no studies clearly showing that radiation sensitive individuals are also at higher risk for stochastic effects, that is radiation susceptible. Accordingly, throughout the paper, we propose to use the term radiation sensitivity/radiosensitivity for individuals who are at higher risk for early or late reactions in normal tissue after radiation and the term radiation susceptibility/radiosusceptibility for individuals who exhibit higher cancer risk after radiation than the general population (Foray et al. 2016). Radiosensitivity is particularly relevant in the clinical setting (e.g. after radiotherapy), whereas

radiosusceptibility is an important issue for both low dose and high dose radiation exposure. We acknowledge though that the distinction into the two terms ‘radiation sensitivity’ and ‘radiation susceptibility’ is under discussion (e.g. Wojcik et al. 2018).

Radiation-induced risk of health outcomes is not necessarily similar for all individuals. Risk is defined as the probability of an event in a given population and time span (Porta 2014). The concept in itself implies a probability of an event, and risks that are not one or zero are not necessarily homogeneous within the population, that is some subjects are affected and others are not. For an individual, the outcome is either experienced or not. It is a dichotomy, that is the condition is absent or present, and not a degree of probability.

Effect modification is defined as variation in the magnitude of effect across the levels of another factor that means that the effect of the exposure is not similar in the entire study population, but another factor alters the dose effect. In statistics, this phenomenon is called interaction. For radiation-induced health risks, this means heterogeneity or non-uniformity of the dose effect. Effect modification is analyzed by dividing the study population into subgroups, and then examining if the effect of the exposure is comparable between the various strata (Rothman et al. 2012). The overall difference between the sub-groups is evaluated using an interaction term, testing the hypothesis of uniformity of the effect.

There is one study that demonstrated in mice that relative risk can be applied to different backgrounds (Storer and Fry 1995), but this is still debatable for example, in terms of generalizability (NRC 2006).

## 1.2. Why is the topic important?

Although much is known about radiation risks, still considerable uncertainty exists in their quantification (UNSCEAR 2012b). In order to reduce these uncertainties, it is important to improve and continue epidemiological studies of health effects from exposures to ionizing radiation, and to develop methods to quantify and combine the various sources of uncertainties. Such uncertainties include for example, impact of population selection, exposure assessment, health outcome assessment, study design, confounding factors, statistical methods and model uncertainty and hypothesis of baseline stability over time (UNSCEAR 2019). ICRP recognizes variation in sensitivity and variability in radiation-related health risk. In 1999, the ICRP issued publication ‘Genetic susceptibility to cancer’ (ICRP 1998). In UK, the Advisory Group on Ionising Radiation published a report on human radiosensitivity (HPA 2013). At present, there is insufficient information on the influence of individual radiation responses on health risk estimates. In particular, sound data on responses to radiation at different dose levels, dose rates and with radiation of different qualities are often not sufficient to estimate risk without substantial uncertainties in many exposure situations. Thus, a well-integrated multidisciplinary research (including mechanistic studies) is

required to elucidate the extent of variation of radiation-related sensitivity and susceptibility and the factors contributing to this variation. The individual response to ionizing radiation has been identified by MELODI and subsequently also by EURAMED as an important issue because of the high probability that the people concerned by an abnormal response deserve more attention and radiological protection than normal responders. The abnormal response was initially named ‘radiosensitivity’ and mentioned as a priority in the SRA of MELODI. Implications for radiation protection are not straightforward and include several ethical considerations. The first question is how to identify those that might be sensitive to radiation, how large is the variation in sensitivity in population and who might be in need of additional protections. The identification of variability in the response to ionizing radiation raises public health, socioeconomic and ethical issues which should be addressed. Radiosusceptibility is unlikely to be characterized by a single modifying factor within a multivariate risk model, nor exist as a trait dividing the population into simple radiosusceptible and radioresistant groups. Tailoring of medical treatments and radiation protection strategies at an individual level is a current trend. However, testing of individual IR responses of low-dose occupationally exposed individuals is questionable (Hamada et al. 2018). In the clinical context, translating the results into clinical practice will require decision support to guide radiation oncologists. The goal is not to strictly specify treatment, but to indicate possible options, help guide decision-making and confirm eligibility for enrollment in clinical trials. Individuals identified with severe radiation sensitivity will be exceedingly rare, such that the most relevant subgroup is the larger population of patients with moderate sensitivity and a less-certain outcome. One of the areas defined by the MELODI Strategic Research Agenda that requires further research is the development and validation of biomarkers for exposure, early and late effects for cancer and non-cancer diseases. This part including the biological mechanisms is summarized by Gomolka et al. (2019) and Averbeck et al. (2019) in this Special Issue.

Up to 20% of patients treated with radiotherapy will develop moderate to severe adverse health effects after treatment, also because of their radiation sensitivity status, which may affect their quality of life. Modern radiotherapy techniques require frequent imaging for the accurate patient positioning. The imaging dose adds to the radiotherapy dose to the normal tissue. In a Finnish study, the maximum cumulative doses from radiotherapy imaging ranged from <20 to 106 mGy. The authors showed that cumulative radiation organ doses from radiotherapy imaging can vary by a factor of ten or more, depending on the frequency (e.g. daily vs. weekly) and the imaging technique used (Siiskonen et al. 2017). With increasing interest in personalized medicine worldwide, the identification of radiation sensitive and susceptible individuals using a screening tool would allow to change the management of these individuals. The goal of the radiosensitivity biomarker assays elaborated on the basis of mechanisms of radiosensitivity is to give the radiation oncologists prior to the beginning of the treatment the

warning that undesired reactions may occur during or after the radiation treatment.

In the following, we will illustrate the current situation in radiation exposure research and conclude with recommendations for the way forward in the research in this field.

## 2. What is known so far?

### 2.1. Clinical observations

The aim of radiotherapy is to eradicate the tumor and prevent recurrences with minimal impairment of the quality of life of the cancer patients. Adverse effects related to ionizing radiation comprise acute and long-term effects such as vascular damage, heart complications, digestive bowel injury or fibrosis. The Quantitative Analyses of Normal Tissues Effects in the Clinics (QUANTEC) (Bentzen et al. 2010; Jackson et al. 2010; Marks et al. 2010) updated the Emami data from the early 1990s (Emami et al. 1991) on recommendations how to protect organs to un-attempted effects of radiotherapy. With advancement of radiotherapy techniques, the rates of side effects decreased over the last decades. For example, the use of the CT scanner allowed improved delineating the healthy organs as well as the tumor volumes. Dose-volume histograms (DVHs) enabled the comparison of dose distributions, but lack spatial information. To help physicians in the treatment decision, equivalent uniform dose (EUD) (Niemierko 1997) and normal tissue complication probability (NTCP) (Lyman 1985; Lyman and Wolbarst 1987; Kutcher et al. 1991) models were developed and are regularly used (e.g. Henríquez and Castrillón 2011; Chaikh et al. 2018; Liang et al. 2019). However, the algorithmic calculation is not incorporated in the treatment planning systems. Concomitantly to these improvements in delineation, complication analysis and improvement of dose calculation, physicians tried to decrease the dose and irradiated volumes. Hodgkin disease was the main example to keep the same tumor control and decrease of side effects although the dose was reduced by one third and no prophylactic node irradiation was required (Raemaekers et al. 2014; Aznar et al. 2017; Thomas et al. 2018). New techniques such as stereotactic irradiation, intensity modulated radiation therapy or use of protons helped to decrease the volume of irradiated healthy tissue and led to improved dose distributions. However, there are still ongoing discussions on long-term effects of new techniques and fractionation schedules, in particular given the increased life expectancy of patients and the challenge with re-irradiation. Furthermore, modern treatment devices are not always available or affordable.

### 2.2. Sensitivity

Adverse effects related to ionizing radiation comprise acute and long-term effects. Radiosensitivity is in particular relevant in the high dose radiation field such as radiotherapy. Acute effects occur within a few weeks of radiation exposure

in fast proliferating tissue and include dermatitis, mucositis or hair loss. Long-term effects can emerge years, and even decades, after radiation exposure and include vascular damage, rectal dysfunction or fibrosis (e.g. Bentzen and Overgaard 1994; Barnett et al. 2009). The relationship between acute and late effects still remains unclear.

There are some situations where radiosensitivity has already been taken into account by radiation oncologists:

- rare hyper-radiosensitive syndromes like ataxia-telangiectasia homozygotes, Nijmegen breakage syndrome homozygotes, Fanconi anaemia patients;
- a few more frequent diseases, for example, neurodegenerative diseases, systemic sclerosis, Behçet's disease and diabetes, that are associated with some degree of radiosensitivity;
- paying attention to a family history of cancers because it could also predispose to radiation-induced second cancers and clinical hyper-radiosensitivity; and
- being particularly careful with children with cancer.

In such patients, radiation oncologists commonly adapt the total dose delivered. Guidelines for such a dose adaptation in radiosensitive patients on the basis of appropriate assays still need to be elaborated, together with the rules of clinical follow-up, taking into account the benefit as well as potential harm for the patients. In case it would be feasible to elaborate radiation sensitivity on an organ base, it would be also possible with today's planning and treatment systems (intensity modulated radiotherapy, IMRT) to adjust the application scheme while maintaining the target dose as close as possible to the prescribed dose. This approach could even be followed when indications arise for organs of an individual being more sensitive than expected to ionizing radiation during the radiation treatment.

It is necessary for the radiation oncologists or the interventional radiologists to inform the patients of the strategy of screening of radiosensitivity and radiosusceptibility and of the consequences in terms of:

- adaptation of radiation therapy dose or the interventional therapeutic approach and follow-up since the decreased risk of adverse events may, for example, be associated with an increased risk of cancer recurrence as a consequence of a delivered dose lower than the conventional standard protocols;
- a conventional fractionation scheme can be considered instead of hypofractionation;
- if the risk of adverse effects from radiotherapy is high, alternative treatment options should be discussed;
- avoid concomitant therapies that increase the risk of adverse treatment effects (chemotherapy, hormonal therapy) if possible; and
- if the risk of recurrence is low, partial irradiation, for example, of the breast can be considered.

Markers of radiation sensitivity are urgently required to adapt the radiotherapy, total dose, dose per fraction,

technique, beam to personalize radiotherapy. Today, some biomarker tests are available to detect patients at risk of side effects (e.g. Azria et al. 2015; Granzotto et al. 2016), but no consensus was developed for their usefulness and independent validation is essential.

Also, radiation exposure to low (up to 100 mGy) to moderate dose (100 mGy to 1 Gy) may have possible negative health effects. Cardiac doses from breast cancer radiotherapy were previously associated with increased cardiovascular mortality (Darby et al. 2013). Further, there are hints that low dose exposure might be associated with circulatory diseases (e.g. Darby et al. 2010; Kreuzer et al. 2015) with excess relative risks per Sv of 0.1–0.2 in a meta-analysis by Little et al. (2012) and Little (2016), although additional research better considering potential confounding factors such as hypertension or body mass index is warranted to confirm these results (Kreuzer et al. 2015). Doses <0.5 Gy to the lens of the eye were shown to increase the risk of cataracts (Cucinotta et al. 2001; Neriishi et al. 2007; Worgul et al. 2007; Chodick et al. 2008; Chylack et al., NASA study of cataract in astronauts (NASCA) 2009; Azizova et al. 2018; Little et al. 2018), as summarized by Kitahara et al. (2015).

### 2.3. Susceptibility

A serious health effect of low dose radiation is an increase in cancer incidence, which has been demonstrated in many studies, including the Life Span Study of Japanese atomic bomb survivors (Grant et al. 2017). The extent of this effect is however not entirely elucidated. Some studies showed a small increase in cancer risk after low dose exposure; for example, gamma radiation from natural background has been suspected to contribute to childhood leukemia as shown in the UK childhood cancer case-control study (Brenner et al. 2003; Kendall et al. 2013). Also, occupational radiation doses (e.g. Muirhead et al. 2009; Leuraud et al. 2015; Richardson et al. 2015) and exposure to radioactive waste as in the Techa River Cohort in the 1950s (Schonfeld et al. 2013) were positively associated with increased risk of solid tumors and non-CLL leukemia.

In the 1980s, the predominant source of radiation exposure (>80%) was from natural background radiation in the USA. By the mid 2000s, the estimated per capita annual dose almost doubled from 3.6 mSv to 6.2 mSv, mainly due to higher medical radiation exposure, in particular from diagnostic procedures such as CT scans or X-rays (summarized by Kitahara et al. 2015). A number of studies found elevated cancer risks (in particular leukemia and brain tumors) after multiple CT scans in children and adolescents (e.g. Einstein 2012; Pearce et al. 2012; Mathews et al. 2013).

Pooled analyses showed that frequency of chromosomal aberrations and the number of micronuclei in peripheral blood lymphocytes as biomarker for chromosomal damage may predict cancer risk (Bonassi et al. 2006; 2008).

It is today not possible to screen all individuals in general before any medical diagnostic examination involving ionizing radiation as no reliable marker for susceptibility is known. Susceptible individuals for whom screening would

be notably relevant include those (especially, children, and young adults) in whom repeated especially three- or four-dimensional diagnostic examinations are necessary, for example, for scoliosis and in particular if the breast is in the field of view. In such persons, the cumulated dose over the years may reach a few tens up to 100 mSv.

In these individuals, the identification of radiosusceptibility could have the consequence to minimize exposures to ionizing radiation and to favor other modalities of investigation (echography, MRI) in order to minimize the risk.

A number of studies reported an increased cancer risk after radiotherapy in organs outside the radiation field (e.g. Little 2001; Suit et al. 2007; Tubiana 2009; Friedman et al. 2010; Dracham et al. 2018). For example, Berrington de Gonzalez et al. (2011, 2013) estimated 5 excess secondary cancers per 1000 patients treated with radiotherapy by 15 years after diagnosis.

### 2.4. Factors that may play a role in radiation sensitivity and susceptibility

As mentioned in the MELODI strategic research agenda (Kreuzer et al. 2018a) and the HLEG report (HLEG 2009), differences in radiation susceptibility between individuals, or groups, may relate to genetic constitution (determining sex and other phenotypic features), but also to other characteristics such as age at exposure, attained age, health status and comorbidity, epigenetic factors, lifestyle, and co-exposures to other (non-radiological) stressors.

Age at exposure clearly affects the radiation-induced risk of certain cancers, such as for instance leukemia (Wakeford 2013) or thyroid cancer (Cardis et al. 2005), for which exposure at younger ages are associated with higher radiation related-risks (expressed as excess relative risk per Gy). Whether such patterns apply to all cancer types is, however, uncertain (UNSCEAR 2013).

Sex may, beyond obvious differences between males and females in organs and tissues (which can show different radiation-induced cancer risk per unit dose), influence radiosusceptibility to cancer in other organs and tissues through other pathways (e.g. hormonal). Females tend to be at greater risk of cancer from a given whole-body dose of radiation than males (Wakeford 2012; Grant et al. 2017).

Epidemiological evidence on the effects of genetic variants is still scarce. Some studies suggest higher radiosusceptibility to breast cancer risk in *BRCA* mutation carriers (Pijpe et al. 2012; Colin et al. 2017). In the U.S. Radiologic Technologists cohort, *IL1A* A114S significantly modified the dose-response relationship between cumulative personal diagnostic radiation and breast cancer risk (Sigurdson et al. 2007). The radiation-associated breast cancer risk also varied significantly by linked markers in chromosome 5p12 in the mitochondrial ribosomal protein S30 (*MRPS30*) gene (Bhatti et al. 2010). A recent study in uranium miners suggests an interaction between radon exposure and the genomic region 15q25 on lung cancer risk (Rosenberger et al. 2018). However, because of the possibility of a chance finding, these preliminary results call for confirmation in other

populations. A few genetic markers of late toxicity after radiotherapy were identified for prostate and breast cancer so far, such as *ATM* (e.g. Fachal et al. 2014; Andreassen et al, International Radiogenomics Consortium (RgC) 2016; Kerns et al. 2016). There are a few rare hereditary disorders with increased sensitivity to radiation such as Nijmegen breakage syndrome or ataxia telangiectasia (e.g. Taylor et al. 1975). However, it is more likely that a number of common low risk markers account for (at least a proportion of) the genetic contribution to radiosensitivity, following a polygenic model with each genetic marker contributing a small effect rather than a few contributing high risks as discussed, for example, by Andreassen and Alsner (2009), Kitahara et al. (2015), and Andreassen et al, International Radiogenomics Consortium (RgC) (2016).

Interaction of ionising radiation with co-exposures to other stressors (e.g. tobacco smoke, heavy metals, medication) on disease risk is also important (HLEG 2009; Kreuzer et al. 2018a).

Smoking is among the most studied lifestyle factors in the radiosusceptibility studies. Studies in uranium miners internally exposed to radon and its progeny (NRC 1999; Schubauer-Berigan et al. 2009; Leuraud et al. 2011; Kreuzer et al. 2018b) and in Mayak workers internally exposed to plutonium (Gilbert et al. 2013) have reported interactions ranging from supra-additive to multiplicative on lung cancer risks, whereas the largest domestic radon studies investigating this question identified multiplicative interactions (Krewski et al. 2005; Darby et al. 2006; Turner et al. 2011). For external radiation exposure, analyses in atomic bomb survivors data revealed a complex pattern: the excess relative risk of lung cancer per Gy was higher for low-to moderate smokers than for non-smoker or for heavy smokers (Cahoon et al. 2017). It needs to be taken into account that radiation risks are calculated as a lifetime risk and that smoking also reduces the lifespan. So there is a competing risk in a multiplicative risk model because of the higher background cancers for smokers versus additional radiation risk due to longer lifespan in never smokers which was shown in the NASA model (Cucinotta et al. 2012). Information on effect modification of radiation effects by other lifestyle aspects such as alcohol consumption or dietary patterns remains limited (e.g. Turner et al. 2011; Grant et al. 2012).

Very little is known on the joint effects of co-exposures to radiation and other environmental stressors. Recently, several studies have begun to investigate such questions, in line with the rapidly expanding interest for studies of the human exposome (Wild 2005). This includes effects of co-exposure to radon and ultraviolet radiation on skin cancer risks (Vienneau et al, SNC Study Group 2017), radon and electromagnetic fields from power line on childhood leukemia (Pedersen et al. 2014), radon and urban air pollutants on lung cancer and leukemia risks (Bräuner et al. 2010; Turner et al. 2011; Bräuner et al. 2012), radon and asbestos (Darby et al. 2006), or incense burning (Tse et al. 2011) on lung cancer risks.

Beyond environmental exposures, interactions with chemicals have also been investigated in the field of radiation therapy studies, where interactions between radiation treatment and chemotherapy (in particular anthracyclines) are an issue of importance for patient care (e.g. van Nimwegen et al. 2017).

Also, importantly, radiation exposure of two individuals under the same radiation setting can result in different dose patterns (e.g. in terms of absorbed doses to organs and tissues) in these individuals because of inter-individual variations in their characteristics. Such characteristics notably include morphology (e.g. body mass index and organ size) which can influence the relation between external exposure and organ doses (e.g. Bentzen and Overgaard 1994; Lilla et al. 2007; Barnett et al. 2009), but also other aspects of physiology (e.g. breathing rates (Marsh et al. 2014), airway morphology variability), metabolism, diseases impacting the function of organs and tissues or even alimentary deficiency (Cardis et al. 2005), which can modulate the relationship between intakes of radionuclides and internal dose distribution through their influence of biokinetics (Schwarz and Dunning 1982; Klein and Breustedt 2014). As several physiological characteristics (e.g. height, weight, and breathing rates) are associated with age, dose coefficients can vary according to age (Kendall and Smith 2005). In case of internal contamination, some aspects of lifestyle can also influence the relation between exposure and dose. For instance, there is greater retention of insoluble forms of plutonium in the pulmonary tissues of smokers (leading to higher absorbed doses to the lungs) by comparison with non-smokers (Suslova et al. 2009).

Throughout such influences on dosimetry, individual characteristics can modulate relationships between exposure and risk, therefore contributing to radiosusceptibility. This must be considered, especially, when radiation protection standards are defined in terms of exposure levels. Therefore, individual radiosusceptibility can be considered as a function of exposure and not only dose, and the study of radiosusceptibility should consider the dimensions of dose inhomogeneity, radiation quality, and internal versus external exposures (Kreuzer et al. 2018a).

### 3. What are the difficulties in radiation epidemiology?

In 2017, UNSCEAR published its Principles and criteria for ensuring the quality of the Committee's reviews of epidemiological studies of radiation exposure (UNSCEAR 2017b). Reflecting these principles, we will discuss the major challenges with epidemiological studies in radiation research such as power problems when assessing small low dose effects, bias and confounding, the need for long follow-up times, heterogeneity in radiation exposure assessment among studies and in particular with endpoint definitions, collection of biological material and ethical consequences of individual response to ionizing radiation.

### 3.1. Power and methodological considerations

As the effect sizes in radiation exposure are often small, in particular in the low dose field, large sample sizes are needed. For example, given a cumulative disease incidence of 0.1, exposed vs. non-exposed of 50% and power of 80%, about 5500 cases and 5500 controls would be required to detect a relative risk (RR) of 1.10. If the relative risk is only 1.05 (=half), then the required sample size would be four-fold higher. When evaluating differences between subgroups, this requires even larger sample sizes to achieve adequate statistical power than analysis of the overall average effect size because of the smaller subgroups (UNSCEAR 2017a): Given radiation exposure doubles the risk (RR = 2.0), a cumulative risk of 0.1, the modifying risk factor is 10%, a power of 80%, and 50% received radiotherapy, the required sample size would be 7.261. If the cumulative risk is only 0.01 instead of 0.1, then the required sample size would be tenfold higher. Very obviously, the required sample size depends strongly on the risk difference: the larger the contrast, the smaller the sample size needed to demonstrate it.

The sample size requirement has major implications for effect modification analysis. To achieve a reasonable statistical power, large enough numbers of radiation-induced outcome events are required. This means large sample sizes, and large effect sizes in relatively frequent endpoints. In practice, the optimal choice for studies of effect modification would be common cancer types in large patient cohorts with high doses followed up at ages when cancer incidence is high. Children treated for cancer have higher relative risk coefficients per dose unit, but lower cancer incidence rates than adult patients. Also, childhood exposures to behavioral factors that may modify cancer risk from radiation differ from adult, and they have no occupational exposures, are no active smokers or alcohol drinkers. Further, comorbidity is less common in childhood.

It is important to notice that detecting differences in cancer risk becomes exceedingly difficult when the radiation-induced risk diminishes. This means that evaluating effect modification in low-dose studies is extremely challenging. Excess risk due to radiation could be observed as additional cancer cases to those occurring due to other factors ('spontaneous' cases). However, epidemiological studies do not have enough power to estimate those effects directly, and the radiation-induced cases cannot be distinguished as there are no established 'signatures' that would reveal radiation as a cause of the malignancy. Therefore, an effect of radiation can be shown only at group or population level.

Focusing on differences in late effects of high-dose radiation is therefore less difficult. Only when the determinants of radiation-induced risk have been well established in such studies, efforts should be directed toward low-dose studies, where detecting any potential differences in radiation-induced risk is less likely. However, this presumes that at higher doses similar processes act as at low doses. Radiotherapy studies relate to selective populations with previous cancer and a specific radiation exposure (local, fractionated, etc.), and may thus not be entirely transferable to the general population and other exposures (potential bias).

The most common cancer types that also have high radiation-induced excess risks include breast, lung, stomach, and colon cancer. A secondary consideration is the extent of confounding, that is the impact of other risk factors that need to be controlled to obtain a valid (unbiased) estimate of the radiation-induced risk. For instance, smoking is the major determinant of lung cancer risk, and without accurate and detailed information on smoking history, the radiation-induced risk cannot be estimated with confidence. The need to control for the effect of smoking also decreases the statistical power for assessment of modification due to other factors. However, information on smoking and other (potential) risk factors is often not available, although data on socioeconomic status often provide a reasonable proxy for it. However, this information should be collected if possible. On the other hand, for leukemia and thyroid cancer that have high excess relative risk from radiation, but few strong and common risk factors (potential confounders) other than age and sex, this issue might be less problematic.

### 3.2. Radiation exposure assessment

The radiation exposure assessment is challenging for epidemiology. However, individual doses are needed for good dose-response analysis which are cost and labour intensive to collect. Especially, when assessing environmental background radiation exposure, there is usually no dosimetry information available. For medical radiation exposure, the calculation of the imaging doses is not trivial and detailed dosimetry information from physics data (DVHs/Dose-volume-histograms, DICOMs/Digital imaging and communications in Medicine) is often not available in patient cohorts. Low to moderate radiation doses from imaging procedures also contribute to the total amount of radiation dose and can have negative health effects. Awareness and optimization of the diagnostic and interventional radiation exposure (e.g. imaging dose in image-guided radiotherapy) should be strengthened. Misclassification of radiation exposure can yield bias for risk estimates often to the null.

### 3.3. Uncertainties

One of the biggest challenges are uncertainties. First of all, there is uncertainty even about the phenomena and concepts, illuminated by the heterogeneity in the definitions and use of the concepts of sensitivity and susceptibility. Assessing the modifying factors that affect the probability of developing a radiation-induced malignancy involves also uncertainty, as soon as the focus is on anything more complicated than age and sex. Reconstructing exposure history to co-carcinogens such as smoking history, not to mention occupational or environmental exposures is also subject to error. Biological assays always involve some element of uncertainty, with magnitude highly dependent on the complexity of the method, and reliability is also affected by the degree of experience of the staff and standardization of the assay. It is unclear, whether it is possible to apply within legal considerations if uncertainties remain too large (e.g.



the proof of a 95% confidence interval that one worker is more sensitive than another). A study on variability on organ dose estimated relative uncertainties in the range of 10%–30% (Zvereva et al. 2018). Other publications discussed various aspects of uncertainties in risk estimates (UNSCEAR 2012b; Fisher and Fahey 2017; Ulanowski et al. 2019) including competing risks and effective dose.

In order to reduce the uncertainties, it is important to improve and continue epidemiological studies of health effects from exposures to ionizing radiation, and to develop methods to quantify and combine the various sources of uncertainties, such as impact of population selection, exposure assessment, health outcome assessment, study design, confounding factors, statistical methods, and model uncertainty and hypothesis of baseline stability over time (UNSCEAR 2019).

### 3.4. Study design

To reliably assess adverse health effects after ionizing radiation exposure, long follow-up times over several years (or even decades) for both low and high dose research are needed. This includes also long-term funding, often collaborative and multinational.

Thorough validation of findings is essential because small studies can lead to false-positive or false-negative findings. This is in particular relevant when studying small risk associations such as genetic effects. In previous studies, however, there was often substantial heterogeneity between the studies in terms of sample size, study design, location, quality of dose estimates and classification of endpoints (e.g. Kitahara et al. 2015). In particular, using retrospective study designs requires careful assessment of potential biases such as selection bias or recall bias when estimating radiation exposure doses, for example.

### 3.5. Heterogeneity in endpoint definitions when assessing health effects

To reliably assess radiation-related adverse effects, it is essential to have standardized scoring systems to compare health effect rates and to identify sensitive subjects. To date, three scoring systems are commonly used to assess adverse effects after radiotherapy:

1. the Common Terminology Criteria for Adverse Events (CTCAE; Trotti 2002);
2. the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer criteria (RTOG/EORTC; Cox et al. 1995); and
3. the Late Effects in Normal Tissue – Subjective, Objective, Management, Analytic criteria (LENT-SOMA; Rubin et al. 1995; Seegenschmiedt 1998).

The scoring systems range from grade 0 = no adverse effects, grade 1 = mild, grade 2 = moderate, grade 3 = severe to grade 4 = very severe symptoms (and grade 5 = lethal). The RTOG/EORTC criteria are more commonly used in

Europe, while CTCAE, published by the National Institute of Health, now seems to have become the international standard in classification of cancer treatment related adverse effects (Zhen et al. 2017). For statistical analysis, toxicity is often dichotomized as grade 2 or higher. One hint for radio-sensitivity is that severe adverse reactions occur early during the course of radiotherapy. Usually, the radiotherapy is then interrupted before the symptoms reach grade 3 or 4 until the reactions attenuate. Therefore, it would be useful to also assess interruptions of radiotherapy due to complications.

When pooling studies that used different scoring systems, the scoring needs to be harmonized to ensure comparability across studies (e.g. Hoeller et al. 2003; van der Laan et al. 2008). The Standardized Total Average Toxicity (STAT) score may be an alternative metric for combining different toxicities endpoints and enables pooling of data from different studies (Barnett et al. 2012).

Due to improvements in radiotherapy techniques (such as intensity-modulated radiotherapy, image guided radiotherapy) and treatment planning, the rate of related toxicity has decreased in the last decades. However, it is still estimated that up to 20% of the cancer patients develop radiotherapy-related adverse effects of grade 2 or higher, with about 5% experiencing grade 3 or 4 toxicities (e.g. Marks et al. 2010). It also should be assessed whether specific late adverse effects are more common with certain regimens/techniques such as hypofractionation.

Also, patient reported outcomes are of high relevance to capture the whole spectrum of radiosensitivity and its adverse health effects, for example, using the PRO-CTCAE (Dueck et al. 2015). This involves also (subjective) health-related quality of life, which can be assessed, for example, using the EORTC QLQ C30 (Aaronson et al. 1993) or the FACIT (Functional Assessment of Chronic Illness Therapy, Cella et al. 1993) questionnaires, as well as disease specific symptoms. For prostate cancer, for example, these include EPIC (Expanded prostate cancer index composite, Wei et al. 2000), FACT-P (Functional Assessment of Cancer Therapy – Prostate, Esper et al. 1997) or EORTC QLQ PR25 (van Andel et al. 2008) questionnaires.

In oncology, standard definitions of adverse effects are more internationally accepted. However, similar problems are faced when comparing studies that are investigating non-cancer effects such as cataract or cardio-vascular diseases. In a meta-analysis by Scholz-Kreisel et al. (2017) on cardiovascular effects after childhood cancer, more than 100 cardiovascular endpoint definitions were found. Furthermore, consensus is needed on what type of endpoints can be combined, for example, for cancer types such as leukemia, lymphoma, or brain tumors.

### 3.6. Collection of biological material

Although it has long been emphasized to include biological samples in epidemiological studies, there are major obstacles for the collection. It needs to be defined what to collect, for example, blood, urine, hair, nails, tissue. In particular for the latter, the willingness to provide, for example, skin

samples is limited. Another issue is the timing of sample collection which should preferably be before radiation exposure. This is however not always feasible. Many biomarker assays were analyzed retrospectively and not validated in independent populations. Only a few compared pre- versus post-exposure. If the measured radiosensitivity is genetically determined though, then it should be less relevant when the sample is taken. Also, the limited sensitivity and specificity of the assays imply a source of misclassification (as discussed in Gomolka et al. 2019 in this Special Issue). Recently, Schofield and colleagues discussed the issue of big data in radiation biology including biomaterial archives (Schofield et al. 2019).

### 3.7. Ethical issues

When we are faced with the question, whether susceptibility testing should be offered prior to radiotherapy or employment in a job involving radiation exposure, a broad evaluation of the issue is needed. Important publications on this topic include Beauchamp and Childress (2013), Cowley (2016), Offit and Thom (2007), Perko et al. (2019), Salerno et al. (2019), ICRP (2018), Brandl and Tschurlovits (2018), Malone and Zölzer (2016), and NCRP (2010). The obvious ethical justification for seeking evaluation of susceptibility is the potential to reduce adverse effects of radiation exposure (beneficence), but other ethical issues also need to be considered including autonomy and justice.

Before susceptibility testing is used outside research purposes, its scientific basis has to be comprehensively elaborated and established. First, the extent and robustness of the research findings must fulfil the most stringent validity criteria – do we have sound enough knowledge as a basis for interventions? A real causal effect must be demonstrated, including confirmation and replication to preclude false-positive/-negative findings (chance results, serendipity, and false discovery). For complex diseases, such as any major non-communicable disease, confounding and other biases need to be well controlled. Ideally, also adequate understanding of mechanism of action is required to improve plausibility. Second, the interpretation of a test result should convey a practical meaning and bear some real-life impact. Susceptibility is nearly always a matter of degree, not absence versus presence of hazard. The finding should have a substantial effect on the health outcome in question, which can be shown in terms of frequencies of outcomes in those with and without the susceptibility, for example,  $P(\text{outcome}|\text{exposure and susceptibility})$  versus  $P(\text{outcome}|\text{exposure and no susceptibility})$ . This would give a precise estimate of the excess absolute risk conferred by the susceptibility.

The ethical principles that need to be evaluated include autonomy and dignity, including privacy and confidentiality, justice, as well as beneficence and non-maleficence (e.g. Cho et al, Authors on behalf of ICRP 2018).

Besides firmly established scientific evidence, an equally important prerequisite for susceptibility testing is that it

should benefit the person, and those benefits should outweigh any harms.

Justice means that people should be treated equally, unless there is a legitimate and justifiable reason for different treatment. Generally, characteristics that are outside the control of people themselves such as age, gender or ethnicity are not legitimate results for unequal treatment. This clearly applies also to genetic traits. All of these features are potential determinants of susceptibility and hence relevant here.

If it is established that a certain constitution or trait renders some people more liable to develop disease following radiation exposure, those people are vulnerable, and it is not only a medical issue, but bears also major ethical and social implications. There is also a clear potential for misuse of susceptibility information, for example, stigma and discrimination. In the social sphere, such information could limit opportunities at work, availability of insurance, result in discrimination and stigmatization. Psychologically such vulnerability can induce fear, anxiety, fatalism, or loss of self-efficacy.

Autonomy and informed consent entail the right to know but also the right to remain in ignorance. It should be up to the person to decide whether he or she wants to know the susceptibility status. A further issue is the potential impact of other people such as family members in the case of hereditary traits.

Informed consent requires provision of information, individual assessment of capacity for judgment and decision-making, and opportunity to consider and decide. Besides facts, the decisions should be compatible with the person's own values and priorities relevant for the context.

An established framework for application should exist to guide practice. Decision-making should not take place only on a case-by-case basis, but regulation to protect the subject is needed. Such guidelines should be developed by multidisciplinary expert groups, probably under auspices of governmental organizations or professional societies. Also, clear options should be defined as the basis of decision-making, whether related to the susceptibility of the effects of radiation at work or in therapeutic applications. Alternative course of action should be clearly outlined with reduced radiation exposure and pertinent risks (as well as potential loss of treatment benefits). Guidance or counselling with sufficient expertise about the nature and meaning of susceptibility should be available to support decision-making both before and after susceptibility testing. Just providing information about existence of susceptibility is not ethically justifiable and can be regarded as abandonment.

Besides the ethical issues related to the development of this type of predictive medicine, the identification of radiosensitivity/radiosusceptibility also raises the legal issue who is responsible for the results of the assay(s) especially, if they include the exposure to ionizing radiation of a tissue sample (lymphocytes, fibroblasts...). One can imagine that clinical laboratory technologists would be authorized to practice for such assays. Additional questions regarding the legal as well as the ethical aspects arise if artificial intelligence would be used to evaluate assays or other markers, and such results

should be used for personalizing diagnostic approaches and/or therapeutic applications of IR.

The ethical aspects of the individual response evaluation to ionizing radiation are also covered in a separate paper by Kalman and Oughton (2019) in this Special Issue.

#### **4. How to overcome these difficulties in the next years: recommendations for the way forward in radiation research**

##### **4.1. Need for large prospective cohort studies**

These prospective cohorts (with other epidemiological research questions) need sufficient long-term follow-up and sufficient sample size because radiation-related effects often emerge years after exposure. Adequate exposure measurement, standardized health effects assessment, repeated measurements and identification of sources of uncertainty is needed. Realistic drop-out rates need to be considered. Small studies can lead to false-positive/false-negative findings. Therefore, international collaborations are highly needed, including international funding opportunities for long-term follow-up which is very limited at the moment. The data sources should be made accessible to the research community.

##### **4.2. Find existing radiation research cohorts**

Existing European cohorts for radiation epidemiology research can be identified via the newsletter ([http://www.concert-h2020.eu/en/Concert\\_info/Access\\_Infrastructures/Bulletins](http://www.concert-h2020.eu/en/Concert_info/Access_Infrastructures/Bulletins)) and the <http://www.concert-infrastructures.eu/home> website from the CONCERT initiative, for example. In addition, there are several cohorts on childhood cancer patients (e.g. Hawkins et al. 2008; Rugbjerg et al. 2014; Schwartz et al. 2014; Asdahl et al. 2015; Winther et al. 2015; Teepen et al. 2017; Grabow et al. 2018). Their follow-up for subsequent neoplasms is a promising approach to study effects and effect modification in organs exposed to both high and low doses. Nevertheless, the effect of non-radiation risk factors underlying the first tumor and the effects of chemotherapy and other treatment for the first primary tumor need to be controlled for.

There is a number of radiotherapy patient cohorts established worldwide, for example, approachable through the Radiogenomics Consortium with members at more than 100 institutions (RgC; West et al. 2010; Rosenstein et al, Radiogenomics Consortium 2014; <https://epi.grants.cancer.gov/radiogenomics/>) or the RTOG/EORTC trials. Biosamples might be available for some radiotherapy cohorts such as the COPERNIC cohort (Granzotto et al. 2016). Further in 2013, a large international cohort with over 4400 RT patients with prospective and standardized data collection, the REQUITE project ([www.requite.eu](http://www.requite.eu)), was established in Europe and the USA with at least two years of follow-up (e.g. West et al. 2014; Seibold et al. 2019).

A systematic review on existing cohorts for radiation research is encouraged and currently being undertaken by

Cardis et al. based on a DoReMi survey. The heterogeneity of the study populations in these studies needs to be investigated. Challenges in combining data from various sources include data harmonization, data quality and data handling.

##### **4.3. Use data from well-defined cohorts with good exposure assessment and biological material already collected**

Many cohorts have been established during the last years in Europe and elsewhere such as the UK biobank, Scandinavian biobanks such as the Biobank of Eastern Finland, CONSTANCES in France, the German National Cohort (NAKO), the Gutenberg Heart Study and many others. Although not intended for radiation research, some of them have already collected biological material and some may even have basic information on radiation exposure. Smart designs, such as nested case-control studies in a defined cohort and use of record linkage (e.g. with publicly available environmental databases) should be developed to use this large valuable source of data. It should also be assessed which quality of dose reconstruction and which prevalence of radiation exposure can be expected.

##### **4.4. Focus on study quality with standardized data collection and reporting**

Endpoints to be studied for radiosensitivity and radiosusceptibility need to be clearly defined upfront using standardized endpoint definitions. Adverse effects from ionizing radiation should be routinely documented using a standardized scoring system. Toxicity evaluation at different time points is preferable to detect undesired effects early. The radiation quality needs to be taken into account. When publishing the study findings, existing reporting guidelines such as CONSORT (Begg et al. 1996), PRISMA (Moher et al, PRISMA-P Group 2015), STROBE (von Elm et al, STROBE Initiative 2014), or STROGAR (Kerns et al. 2014) should be applied.

For radiotherapy cohorts: If possible, the situation before radiotherapy should be documented and interruptions of radiotherapy due to complications should be recorded as well. Also untreated similar locations such as the contralateral breast could be compared with. Both medical doctor diagnosed and patient self-reported outcomes should be collected. Both objective and subjective assessment like quality of life are of relevance. Information on secondary cancers after radiotherapy should be collected. Comprehensive radiotherapy dosimetry data is of great importance for effects at remote sites from the target tissue. Radiotherapy techniques have improved over time and keeping the old software and hardware for evaluating physics data of long-term studies is needed. Photos of the irradiated organ pre- and post-radiotherapy can be compared to assess cosmesis.

#### 4.5. Improve statistical analysis

Power calculations are crucial: Evaluating differences between subgroups requires substantially large sample sizes. Statistical analysis should be conducted based on a statistical analysis plan. Multivariate models should take known influencing factors into account that may explain variation in radiation response. It should be clear which results are hypothesis driven vs. exploratory. To avoid false-positive and false-negative findings, adjustment for multiple testing and (if possible) validation of findings in independent populations should be aimed for. Thorough assessment of any type of bias, confounding and misclassification should be part of the statistical analysis.

#### 4.6. Cooperation between radiobiology and epidemiology

Identify which types of samples are most relevant for a biomarker assay of individual response to radiation (e.g. blood, tissue, saliva, and urine). If possible, sample collection should cover both pre- and post-radiation exposure. Take into account logistic issues of sample collection (e.g. timing, transport, skin tissue, fresh sample, etc.). Develop and validate a biomarker (and/or signature) for radiation exposure, early and late health effects. Assess gene-environment interactions with radiation exposure. It is likely that a combination of assays is needed rather than one single test to assess radiosensitivity (see also Gomolka et al. in this Special Issue). It is encouraged to make use of experienced laboratory networks (e.g. RENEB) with inter-comparisons, other established infrastructures and outside-the-field expertise as stated in the MELODI Strategic Research Agenda 2018 (Averbeck et al. 2018).

#### 4.7. Take into account consequences of radiosensitivity and radiosusceptibility

Develop fast, affordable and reliable tests for the identification of radiosensitive/radiosusceptible individuals and come up with recommendations and guidelines for the implementation and use. For acceptance, the risk assessment tools needed to be easily useable and interpretable, such as nomograms. For a more detailed discussion on ethical aspects, please see Kalman and Oughton (2019) in this Special Issue.

### 5. Summary

There remains a long way ahead before a somewhat more individualized approach will be implemented in the radiation protection system, but discussions towards individualized strategies are useful, such as for protection of medical patients, emergency workers, and astronauts, among which medicine will lead the way. Strategies to incorporate the individualized approach need to be considered, along with further developments of scientific knowledge and ethical foundations.

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