Radiation and Environmental Biophysics (2020) 59:185–209
https://doi.org/10.1007/s00411-020-00837-y

REVIEW

Individual response of humans to ionising radiation: governing factors and importance for radiological protection

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Received: 15 July 2019 / Accepted: 26 February 2020 / Published online: 7 March 2020

Abstract
Tissue reactions and stochastic effects after exposure to ionising radiation are variable between individuals but the factors and mechanisms governing individual responses are not well understood. Individual responses can be measured at different levels of biological organization and using different endpoints following varying doses of radiation, including: cancers, non-cancer diseases and mortality in the whole organism; normal tissue reactions after exposures; and, cellular endpoints such as chromosomal damage and molecular alterations. There is no doubt that many factors influence the responses of people to radiation to different degrees. In addition to the obvious general factors of radiation quality, dose, dose rate and the tissue (sub)volume irradiated, recognized and potential determining factors include age, sex, life style (e.g., smoking, diet, possibly body mass index), environmental factors, genetics and epigenetics, stochastic distribution of cellular events, and systemic comorbidities such as diabetes or viral infections. Genetic factors are commonly thought to be a substantial contributor to individual response to radiation. Apart from a small number of rare monogenic diseases such as ataxia telangiectasia, the inheritance of an abnormally responsive phenotype among a population of healthy individuals does not follow a classical Mendelian inheritance pattern. Rather it is considered to be a multi-factorial, complex trait.

Keywords Radiation risk · Radiation sensitivity · ICRP · Individual variation · Genetics · epigenetics · Animal models · Modifiable risk factors · Cancer · Tissue reactions

Introduction

Since its foundation some 90 years ago, ICRP has issued recommendations and guidelines on the use of ionizing radiation used worldwide by international organisations and implemented by national bodies in the legal framework of their respective countries. These recommendations have always been based on most recent scientific evidence and additionally include value judgements such as societal and economic aspects, ethics, and experience gained in the application of the system of radiological protection.

As an example, one of the basic recommendations of ICRP is that in planned exposure situations, occupational exposure to ionizing radiation should not result in an effective dose exceeding 20 mSv per year, averaged over defined 5-year periods (100 mSv in 5 years) and 50 mSv in any single year. This dose limit was first introduced in ICRP Publication 60 (ICRP 1991) and confirmed in ICRP Publication 103 (ICRP 2007), and has since been adopted in many countries all over the world. This dose limit was chosen based on contemporary knowledge on the induction of health effects to humans by ionizing radiation such as solid tumours, leukemia, or heritable effects—largely based on knowledge gained from the atomic bomb survivors in Hiroshima and Nagasaki, Japan, and from a number of other human cohorts

The International Commission of Radiological Protection (ICRP) has convened Task Group 111 to review the current science relevant to the topic of individual response to radiation. To begin this effort, ICRP held a series of workshops in December of 2018 with Japanese scientists at the National Institutes for Quantum and Radiological Science, and Technology (NIRS-QST) in Chiba, the Radiation Effects Research Foundation (RERF) in Hiroshima, and the National Cancer Centre in Tokyo to discuss key questions and issues raised. This paper provides summaries of the workshop contributions.

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that were exposed to elevated radiation levels either due to radiation accidents, medical reasons or from natural sources of ionizing radiation. Further knowledge was taken into account on the mechanisms of radiation action obtained by experiments performed at various levels of biological organization, i.e., sub-cellular, cellular, and animal systems. All these studies have suggested that various parameters influence the induction of health effects among humans, including age at exposure, age attained, sex, life-style, etc., just to name a few. Despite these findings, the annual dose limit for occupational exposure as recommended by ICRP does not distinguish between individual characteristics of the exposed workers such as age and sex. While this assumption clearly represents a simplification of the actual scientific knowledge, its implementation allowed—together with other concepts and principles—development of a simple, economical and practical framework of radiological protection to be applicable on a day-to-day basis.

Nevertheless, there are situations where such a generalized approach is too simplistic. For example, the recent development of patient-specific modalities of cancer treatment ("precision medicine") including radiotherapy of both children and adults, require precise dose-delivery regimes with a detailed, daily imaging model of the individual patient's body for diagnostic and therapeutic applications. In such cases, individualized approaches to optimisation of the patients' exposures are at minimum desirable and increasingly required. ICRP has already initiated steps in this direction, and the two male and female adult reference phantoms used by ICRP in calculating effective doses have recently been complemented by a family of phantoms of ages from one to fifteen years and includes a 10th and 90th percentile phantoms (ICRP publications on computational phantoms and radiation transport, paediatric reference computational phantoms, in press). Furthermore, an ICRP publication on the use of dose quantities discusses how estimates of risk from a given effective dose are influenced by age and sex (ICRP publication on the use of dose quantities in radiological protection, in press).

Another example where individualized radiation dose and risk assessment may be important is space travel. Sudden solar activities may lead to an effective dose for an astronaut on a Mars mission greater than 1 Sv (Cucinotta 2006). In an approach to individualizing radiation risk assessment in these situations, NASA has developed a dedicated radiation risk model that explicitly takes into account age and sex-differences in radiation risk (Radiation Risk acceptability and limitations. Cucinotta 2010 https://three.jsc.nasa.gov/articles/AstronautRadLimitsFC.pdf. Date posted: 12-21-2010). Shortly after its May 2019 meeting, the ICRP Main Commission established a new Task Group 115 Framework for Risk and Dose Assessment for Radiological Protection of Astronauts in an effort to explore, among other questions, the degree of individualization needed for the protection of humans exposed to ionizing radiation in space.

For a number of years, ICRP Committee 1 on 'Radiation Effects' and ICRP Committee 3 on 'Protection in Medicine' have identified individual response of humans to ionizing radiation as a topic with growing importance for radiological protection (Rajaraman et al. 2018; Wojcik et al. 2018; Foray et al. 2016; Ferlazzo et al. 2017). (A broader overview on the program of work of both Committees can be found in ICRP (2018). Consequently, at its meeting in October 2018 in Stockholm, Sweden, the ICRP Main Commission approved a new Task Group 111 Factors Governing the Individual Response of Humans to Ionising Radiation, jointly overseen by ICRP Committees 1 and 3. This Task Group is reviewing the currently available information on individual radiation responses with special focus on the following questions and issues: (1) What is the impact of age, sex and other determinants on normal tissue reactions and incidence of cancers and other diseases following radiation exposure? (2) What is the contribution of genetics to individual, normal tissue responses with respect to adverse reactions to varying doses such as given during radiotherapy? Would predictive tests contribute to better radiological protection of radiotherapy patients without compromising cancer cure rates? (3) What is the contribution of genetic and epigenetic factors to tissue responses with respect to cancer induction at relevant doses and dose rates? (4) What is the evidence that modifiable risk factors, such as smoking, diet and exercise for example, can affect the individual risk of radiation-induced cancer, tissue reactions and non-cancer diseases? (5) What are the ways to quantify the potential impact of individual response to radiation on the incidence of cancers, non-cancer diseases and normal tissue reactions? The goal of the Task Group is to develop a report for publication in Annals of the ICRP that presents a review of the current science relevant to the topic of individual response to radiation.

At the end of 2018, Task Group 111 visited Japan from 6 to 12 December and discussed relevant issues with Japanese scientists. During the visit, various meetings took place including a meeting with scientists from the National Institutes for Quantum and Radiological Science, and Technology (NIRS-QST) in Chiba, a Task Group 111 kick-off meeting hosted by the Radiation Effects Research Foundation (RERF) in Hiroshima, a one-day exchange seminar of ICRP members with RERF young scientists, and finally an open workshop entitled "Workshop on Individual Response to Ionising Radiation" in Tokyo at the Japanese National Cancer Centre. This workshop was organized by ICRP, NIRS-QST, and RERF, in collaboration with the National Cancer Centre Japan (NCC), the Japanese Society for Radiation Oncology (JASTRO), the Japan Radiological Society (JRS), the Japan Health Physics Society (JHPS) and the Japanese Radiation Research Society (JRRS).

This paper includes a selection of thirteen summaries of the presentations given at the NIRS-QST meeting in Tokyo, the RERF workshop in Hiroshima, and the open workshop at NCC on the topic of individual response to ionizing radiation. Much of what we know about factors governing individual response to radiation is based on studies of epidemiological cohorts (e.g., LSS) exposed to ionising radiation decades before an outcome (e.g., cancers) was observed. The workshops engaged with researchers performing LSS follow up research as well as animal radiation research studies. In addition, the workshop meetings sought to understand the role of the genetics of individual, normal tissue responses to adverse reactions during radiotherapy. These summaries provide a range of scientific and medical insights that are grouped by cancer risk and normal tissue effects. The order of these summaries begins with a concise but comprehensive overview of both topics and it is followed by presentations related to ionizing radiation-related cancer risks (1 cellular, 2 animal, and 5 human-based). The second summary is a longitudinal analysis of blood samples comparing inflammation and immune status in the LSS population with healthy volunteers. The third and fourth presentations are two summaries of animal studies of radiation effects that may (a) provide mechanistic information and (b) fill gaps in human epidemiological studies by showing the complex interactions between multiple modifying factors (including age, sex, parity, dose rate, radiation quality, and lifestyle). Then follows a series of five epidemiological studies of a variety of radiation-related cancer risks from the LSS. The last group of four summaries focus on the topic of normal tissue effects from ionizing radiation, beginning with the intriguing descriptions of *RadGenomics*, the *Radgenomics Consortium* (RGC) and the use of GWAS to understand genetic variation in individual response to radiation therapy.

The last part of the paper summarizes the open discussion which concluded the Tokyo open workshop with all invited participants, and which gave valuable input to Task Group 111 on the questions posed for the Task Group to review. The conclusion notes key findings and also a few ongoing differences in language and opinion yet it suggests a way forward for the Task Group to investigate the rapidly moving science and medical therapeutic options.

Human individual radiation sensitivity and prospects for prediction

Cancer patients who undergo radiotherapy show different degrees of normal tissue reactions when exposed to the same dose of ionizing radiation and this observation are attributed to differences in individual radiosensitivity (Holthusen 1936). An individually variable response of individuals to radiation is also assumed for stochastic effects (AGIR 2013; Foray et al. 2016; Rajaraman et al. 2018). People who show a strong response to radiation can be described as exhibiting a high radiosensitivity phenotype. It is generally believed that high sensitivity phenotype is genetically determined. The belief is based on the existence of certain rare hereditary conditions such as ataxia telangiectasia or Nijmegen breakage syndrome (Pollard and Gatti 2009). Patients suffering from these diseases lack genes that are essential for the proper repair of DNA damage (Guleria and Chandna 2016). However, these monogenic syndromes are rare and affect only a small proportion of the general population (Rothblum-Oviatt et al. 2016). Heterozygote carriers of the gene defects exhibit a normal radiosensitivity phenotype (Bremer et al. 2003) demonstrating that a monogenic origin of a radiosensitivity phenotype cannot explain the side effects to radiotherapy which are commonly observed among radiotherapy patients. It is more reasonable to assume that for the vast majority of genetically normal individuals, the genetic contribution defining a high radiosensitivity phenotype follows a polygenic model, which predicts elevated risk resulting from the inheritance of an unknown number of low penetrance risk alleles (Barnett et al. 2009). In this way, individual radiosensitivity, both with respect to tissue injury and stochastic effects, can be regarded as a multifactorial trait.

It is well known that multifactorial traits are influenced by the genotype and the environment (Lewontin 2001). Under different environmental conditions, organisms with identical genotypes can express an array of phenotypes over an array of environments. This phenotypic plasticity is referred to as the norm of reaction (Lewontin 2001). Inherent to the multifactorial nature of the radiosensitivity phenotype is that the environment can influence the reaction of patient´s normal tissue to radiation. Indeed, it has been shown that one such factor, surgery, increases the risk of side effects of radiotherapy (AGIR 2013) and that mouth hygiene modulates the risk of mucositis in patients treated by radiation for head and neck cancers (Sroussi et al. 2017). That smoking influences the risk of radiation-induced lung cancer (AGIR 2013) demonstrates that environmental factors also modulate the level of stochastic effects and substantiates the general assumption that risk is conditional (Adams 2000).

More recent investigations show that on top of the genotype and environment, additional factors which impact on the phenotype are non-inherited parental genetic variations, parental environment at the epigenetic level and stochastic molecular variations (Burga and Lehner 2012). These variations can occur at different compartment levels in individuals exhibiting a particular phenotype such as the gene level, the transcript level, the protein level, the metabolite level and the microbiome level (Civelek and Lusis 2014). In consequence, the phenotype is now defined as resulting from the interaction of the genotype, the environment and chance.

With respect to radiation sensitivity, an additional factor contributing to the norm of reaction is the stochastic nature of radiation-induced cell death. When the incidence of normal tissue complication probability (NTCP) is plotted against the dose, a sigmoidal dose response is observed, which is similar to the tumor control probability (TCP) (Fig. 1a). It is intuitive to assume that individuals who develop NTCs in the low dose region are more radiosensitive than those who tolerate higher doses and this explanation was provided by Herman Holthusen who in 1936 was the first to plot the TCP/NTCP dose relationships (Holthusen 1936). However, when cells from a cell line are exposed to increasing doses of radiation and the frequency of inactivated cells is estimated, a similar dose-response curve is observed (Fig. 1b). In such an experiment, the variability of response to radiation cannot be attributed to genetic or environmental factors because the cells are genetically identical and the experiment is carried out under defined laboratory conditions at a defined time point. Moreover, sigmoidal dose-response relationships for adverse side effects to radiotherapy are also observed in inbred laboratory animals (Safwat et al. 1996).

The complex origin of a radiosensitivity phenotype, plus the stochastic nature of radiation-induced cell inactivation make it very difficult to predict an individual's response to radiation exposure. Nevertheless, attempts to find a predictive test have been undertaken over many years (AGIR 2013; Rajaraman et al. 2018). In functional assays, the in vitro radiation response of surrogate tissue samples is used to predict the in vivo response of the organism. Genetic approaches focus on finding a single nucleotide polymorphism (SNP) pattern that characterizes individuals who react strongly to radiation exposure. Not quite unexpectedly, studies of functional assays and candidate SNPs have been largely inconclusive (AGIR 2013; Rajaraman et al. 2018). Apart from the problems described above related to the norm of reaction, there may be other reasons for the lack of success such as the lack of assay standardization, lack of replication and validation studies, heterogeneous patient cohorts and different scales used to quantify adverse tissue effects (AGIR 2013; Rajaraman et al. 2018). Similar problems were encountered when attempting to predict individual sensitivity to stochastic effects. As stated in ICRP Publication 79 (ICRP Publication 79 1998), in vitro human cellular radiosensitivity is not a reliable predictor of in vivo cancer proneness nor, by implication, tumorigenic radiosensitivity.

In summary, it appears very difficult to find a predictive marker of individual radiosensitivity. Although the development of high throughput methods in molecular biology is promising and may provide useful solutions, it is very unlikely that tests can be found that will identify people at a high risk of overreacting to a radiation exposure with 100% specificity and sensitivity.

Radiation-related cancer risk

Longitudinal analyses of clinical data and biosamples

The first of the two topics discussed here involves longitudinal changes, i.e., within-individual variation over many years, in peripheral blood monocytes among atomic-bomb survivors (Yoshida et al. 2019). The Adult Health Study (AHS) has suggested that inflammatory response is augmented in atomic-bomb (A-bomb) survivors several decades after exposure to ionizing radiation. In the AHS, various inflammation markers, measured in peripheral blood, altered in association with radiation dose as well as with aging. However, the cellular and molecular bases for augmented inflammation due to radiation exposure have not been defined. Since previous immunological studies have revealed that aging phenotypes of T-cell immunity were associated with persistent inflammation in A-bomb survivors, this study (Yoshida et al. 2019) investigated whether radiation exposure promoted aging-associated increase in peripheral monocytes—a mediator of prolonged inflammation. Complete blood count tests, performed biannually since

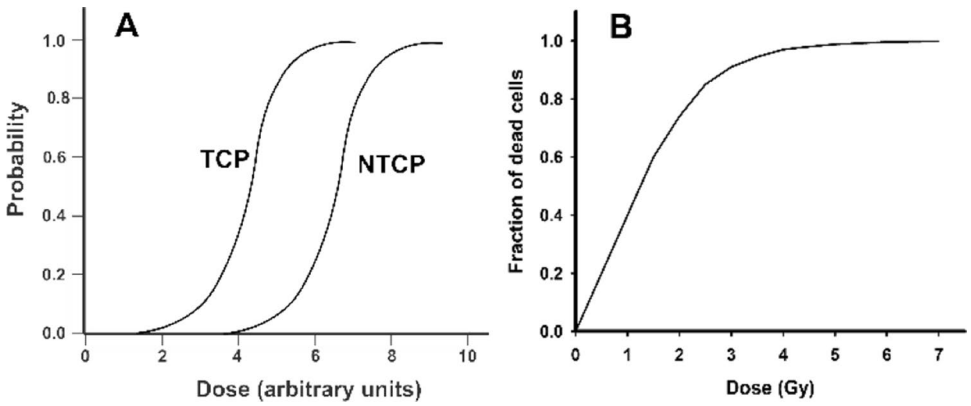

Fig. 1 **a** Dose response relationships for tumor cure probability (TCP) and normal tissue complication probability (NTCP) in patients undergoing external beam radiotherapy. **b** Dose response for clonogenic death of HELA cells exposed to X-rays under in vitro conditions. Graph on **a** drawn based on (Holthusen 1936) and on **b** based on (Puck and Marcus 1956)

1958 in the AHS, provided longitudinal data for the study. In the study including a subset of AHS, 14,000 subjects, a joint regression model composed of a linear mixed-effects model for the hematological endpoints and a proportional hazards regression model for the risk of all-cause mortality was applied. The median follow-up time in the study is 32.8 years (interquartile range 20.6–47.8 years). As a result, the percentage of lymphocytes among leukocytes was found to decrease in both men and women after age 60 at examination, whereas percentages of myeloid cells such as neutrophils and monocytes increased after age 60. There were no significant effects of radiation on lymphocyte or neutrophil percentages; however, significant positive associations were found between radiation dose and monocyte percentages as well as monocyte counts (monocytes increased by 9 cells per 1 uL blood per Gy of radiation dose). Also, increases in monocytes were associated with an increased risk of all-cause mortality. These results suggest that increased production of pro-inflammatory monocytes is involved in persistent inflammation observed long after radiation exposure in A-bomb survivors. The relationship of increased monocytes, along with aging phenotypes of T cells, with the development of inflammatory diseases needs to be investigated in future studies (Kusunoki and Hayashi 2008; Rogacev et al. 2011).

The second topic involved a longitudinal study of the T-cell receptor (TCR) repertoire in healthy adult volunteers (Yoshida et al. 2017), which was not pertinent to AHS studies. The immune system produces a number of T-cell clones with antigen recognition diversity, by rearranging TCR gene segments during T-cell maturation in the thymus. Diverse TCR repertoire is considered essential for effective immune responses in several disease conditions including microbial infection and tumorigenesis. Past studies demonstrated that the decline of TCR repertoire diversity with age is a key aspect of immunological aging; but due to cross-sectional study design, those studies might involve sample selection biases potentially reflecting individual variations in the TCR diversity (Naylor et al. 2005; Britanova et al. 2014; Qi et al. 2014). To more accurately assess TCR repertoire changes with human aging, this longitudinal study (Yoshida et al. 2017) used TCR deep sequencing (sequence depth: 10^6) for analyzing peripheral blood TCRβ repertoire and clonal composition of T cells over 20 years among six volunteers. Results showed that CD4 T cells retained fairly diverse TCR repertoire during middle adulthood up to the age of 65 years, while TCR repertoire diversity in CD8 T cells decreased with aging. Based on the rearranged DNA sequence of TCRβ (*TCRB* CDR3 sequence) that is unique to each T-cell clone and hence usable as a molecular barcode for a distinct T-cell clone, the same T-cell clone was tracked over 20 years and it was observed that many of the most frequent clones persisted, and some of them even expanded. Despite several limitations, antigens could be deduced that are potentially recognized by the most frequent T-cell clones, based on information from literature regarding antigen-specific TCR sequences and HLA types (Brennan et al. 2007; Brennan et al. 2012; Miconnet et al. 2011; Liang et al. 2010; Miles et al. 2005; Lim et al. 2000). A search in the database used [Adaptive Biotechnologies in Seattle, see Brennan et al. (2007) for more information] resulted in several hits for cytomegalovirus and Epstein-Bar virus antigens, suggesting that aging-related changes in human TCR diversity and clonality are somewhat influenced by persistent viral infection, but that almost all top 100 clones (more than 99%) seemed to respond to unidentified antigens. As a whole, the present study established methodologies for TCR deep sequencing that are applicable to a future study in A-bomb survivors investigating relationships between radiation exposure, longitudinal TCR repertoire changes, and the development of age-related diseases.

Further research regarding how ionizing radiation influences T-cell and innate immunity changes during aging and how these changes are involved in the development of diseases will have significant implications for predicting long-term health outcomes in radiation-exposed individuals.

Fetal hematopoietic stem cells are not at all sensitive to radiation for induction of persisting chromosome aberrations. How are the damaged cells eliminated?

It has generally been thought that fetuses are highly sensitive to radiation radiation-related cancer risk. This notion was derived from epidemiological case–control studies which include the Oxford Survey of Childhood Cancer (OSCC) (Stewart et al. 1958; Doll and Wakeford 1997; Boice and Miller 2009) and subsequent studies around the world. The major finding was that those mothers whose children had died of childhood leukemia had slightly higher frequency (~ 15%) of pelvic X-ray exposures during pregnancy than those whose children had not died of childhood leukemia (~ 10%). The X-ray doses to fetuses were later estimated as being around 10 mGy. Therefore, the relative risk (RR) of developing childhood leukemia or cancer was estimated to be around 1.3 to 1.5 at an estimated mean dose of 10 mGy. In other words, the RR at 1 Gy could be about 50 if the increased risks observed were caused by the X-ray exposures and a linear dose response is assumed.

Contrary to the human epidemiological data, however, animal studies have provided no evidence which can support the extremely high sensitivity of fetuses to radiation-related cancer risk (ICRP Publication 90 2003; Upton et al. 1960; Sasaki 1991). Further, cytogenetic studies conducted on atomic bomb survivors revealed that blood lymphocytes from survivors exposed in utero had no record of radiation exposure while their mothers clearly showed such an effect (Ohtaki et al. 2004).

These results were confirmed in subsequent mouse studies using hematologic cells (bone marrow, spleen lymphocytes, and blood lymphocytes) (Nakano et al. 2007). Furthermore, studies on mammary and thyroid epithelial cells in rats and mice, respectively, revealed that 15.5 days old fetuses were equally sensitive to radiation as their mothers for the induction of translocations (Nakano et al. 2014; Hamasaki et al. 2016). Quite importantly, however, the radiation effect seen in mouse thyroid cells became undetectable (disappeared) if mouse fetuses were irradiated before the organogenesis period or if 6.5-day embryos were irradiated (Hamasaki et al. 2016). Thus, the apparent lack of a detectable radiation effect depends not only on the tissues examined but also on their developmental stages at the time of irradiation. Two alternative explanations are possible. Hypothesis 1 is that stem cells before settling in the niche may not be equipped with any system to repair DNA double-strand breaks. As a consequence, aberrant cells should contain unstable-type of damage and are negatively selected through subsequent cell divisions. In contrast, hypothesis 2 is that such stem cells can repair DNA breaks and hence can form exchange-type aberrations which include translocations, but cells bearing those aberrations are selected against by some unknown mechanisms in later stages of the development. It is, therefore, proposed to directly measure the frequency of translocations in cultures of long-term hematopoietic stem cells (LT-HSCs: Lin^{-} $Sca1^{+}$ $c\text{-}kit^{+}$ $CD150^{+}$ $CD48^{-}$) isolated from irradiated fetuses to see if the frequency rapidly declines with time (Hypothesis 1) or persists following multiple cell divisions (Hypothesis 2).

Recent animal studies in QST-NIRS on individual radiation-related cancer risk

Animal experiments can supplement epidemiological studies in contexts where epidemiology has potential issues of inconsistency, bias and/or lack of suitable cohorts. Experimental studies also allow efficient acquisition of mechanistic insights on key events in the adverse outcome pathways leading to radiation-related cancer risk (NCRP 2015). Since 2006, the National Institute of Radiological Sciences (NIRS), a branch institution of the National Institutes for Quantum and Radiological Science and Technology (QST) since 2016, has been conducting a series of animal radiobiology projects related to the effects of age and lifestyle on cancer incidence and life shortening (Shimada et al. 2011). Major findings therein are summarized in Table 1.

Age at the time of exposure is an important individual modifier of radiation-related cancer risk. While ample epidemiological evidence exists on the effect of age at exposure itself, it is more difficult to gain insights on how age interacts with other modifiers (such as dose rate, radiation quality, reproductive factors, etc.) and to understand the biological mechanism underlying the influence of the age at exposure. A series of studies conducted on the rat model of radiation-induced breast cancer indicate that age at exposure influences the dose rate effect and relative biological effectiveness of high-LET radiations (Imaoka et al. 2013, 2017, 2018a, b). Age may also influence the modification of radiation risk by lifestyle factors. For instance, early age of pregnancy is protective against breast cancer in woman (Meier-Abt et al. 2015) but epidemiological studies have indicated inconsistent results on its effect on radiation-related breast cancer (Holmberg et al. 2001; Hill et al. 2005; Brooks et al. 2012; Cooke et al. 2013; Brenner et al. 2018). A study on the rat model (Takabatake et al. 2018) suggests that this protective effect may depend on the age of exposure, advocating a need for a detailed analysis in epidemiology.

Modification of radiation-related cancer risk by age at exposure is heterogeneous among tissues, some tissues having high susceptibility during young age while some exhibiting opposite trends (Preston et al. 2007; Hsu et al. 2013). Experimental studies on animal models have indicated that tissue biology may be a critical determinant of such tissue-to-tissue differences. In mouse models, intestine and liver of young mice show the highest susceptibility to radiation-related cancer risk (Sasaki 1991; Okamoto and Yonekawa 2005; Di Majo et al. 1990). These observations may reflect the refractoriness of intestinal and liver cells of young mice to radiation-induced apoptosis and cell cycle arrest, resulting in survival and proliferation of cells with potential mutations (Miyoshi-Imamura et al. 2010; Shang et al. 2017). An opposite age-related trend has been observed among mice in bone marrow cells and the incidence of myeloid leukemia (Ariyoshi et al. 2014).

It is well known that diet influences cancer risk in the general population (Peto 2001), but it is often difficult to clarify if it also influences radiation-associated cancer risk. Caloric restriction has been shown to reduce the incidence of radiation-induced myeloid leukemia (Yoshida et al. 1997), and more recently it has also been shown to reduce the risk of solid cancers (Tani et al. 2016), in mouse models. A further analysis with a biologically-based mechanistic model (the Armitage Doll multistage model) implies that the reduction in solid cancer risk can be quantitatively explained as an increase in the number of rate-limiting steps in carcinogenesis (Tani et al. 2016). A similar study indicated that obesity accelerates the incidence of radiation-induced rat mammary carcinogenesis (Imaoka et al. 2016).

Part of cancer risk in humans is attributed to various carcinogenic chemicals in diet and environment (Sugimura et al. 2004). In a series of studies on thymic lymphoma of mice, combined exposure to ionizing radiation and a mutagenic chemical exhibits synergistic and antagonistic interactions, at high and low radiation doses respectively, on lymphoma incidence (Kakinuma et al. 2012; Hirano et al. 2013).

Table 1 Major findings of recent animal experiments published from QST-NIRS related to individual radiation-related cancer risk

Individual difference	Endpoint	Major findings	Refs.
Age	Life shortening	Early postnatal mice (females) are more susceptible than fetuses and adults	Sasaki (1991)
	Lung cancer	Juvenile rats are less susceptible than adults	Yamada et al. (2017)
	Mammary cancer	Low dose rate exposure during the peripubertal period leads to higher risk than that in adults	Imaoka et al. (2019)
		RBE of neutrons and carbon ions is higher for rats exposed postpubertally than for those exposed earlier	Imaoka et al. (2013,2017)
		Pregnancies reduce risk related to prepubertal, but not post-pubertal, exposure	Takabatake et al. (2018)
		In young rats, mammary stem cells are susceptible to radiation-induced proliferative cell death, possibly leading to the observed low incidence of cancer	Shimada et al. (1994), Imaoka et al. (2011), Yamada et al. (2017)
		Exposure of fetuses and adults equally leads to persistence of chromosomal aberrations	Nakano et al. (2014)
	Intestinal tumors	Refractoriness to apoptosis of intestinal crypt cells of young mice may render juveniles susceptible to radiation-related cancer risk	Miyoshi-Imamura et al. (2010)
	Liver cancer	Refractoriness to cell cycle arrest of liver cells of young mice may render juveniles susceptible to radiation-related cancer risk	Shang et al. (2017)
	Myeloid leukemia	In young mice, hematopoietic stem cells are susceptible to radiation-induced proliferateive cell death, possibly leading to the observed low incidence of leukemia	Ariyoshi et al. (2014)
	Lymphoma, thymic	Incidence is similar whether mice are exposed in infancy or early adulthood, albeit with a tendency of different genetic mechanisms between the ages	Sunaoshi et al. (2015)
Age and genetics	Medulloblastoma (*Ptch1*$^{+/-}$ mice)	Incidence is highest after exposure during perinatal stages, and the increase of tumors with a 'signature mutation of radiation' was detectable at 50 mGy, in a model of Gorlin syndrome	Ishida et al. (2010), Tsuruoka et al. (2016)
	Kidney cancer (*Tsc2*$^{Eker/+}$ rats)	Perinatal stage has greatest radiation-induced incidence in a model of tuberous sclerosis	Kokubo et al. (2010), Inoue et al. (2020)
	Colon cancer (*Mlh1*$^{-/-}$ mice)	Incidence rates in juveniles and adults are similar following radiation exposure in a colitis-associated, mismatch repair–deficient model	Morioka et al. (2015)
Diet	Myeloid leukemia	Caloric restriction reduces radiation-related incidence of leukemia	Yoshida et al. (1997)

Table 1 (continued)

Individual difference	Endpoint	Major findings	Refs.
	Solid tumors (liver, lung, lymphoma, etc.)	Caloric restriction attenuates radiation-associated risk of tumors in an apparently multiplicative manner; the attenuation fits a model assuming caloric restriction leads to an increase in the number of steps of radiation-related cancer risk	Shang et al., (2014), Tani et al. (2016)
	Mammary cancer	Diet-induced obesity shortens the time to appearance of cancer after radiation exposure	Imaoka et al. (2016)
Exposure to chemicals	Lymphoma, thymic	Radiation and a DNA-alkylating nitroso compound act on different steps of radiation-related cancer risk and result in a synergistic (at higher doses) and antagonistic (at lower doses) combined effect	Kawaguchi et al. (2006), Yamauchi et al. (2008), Kakinuma et al. (2012), Hirano et al. (2013)
	Mammary cancer	Radiation and mutagenic chemicals act in synergy on cancer initiation whereas the observed combined effects on cancer incidence are additive	Imaoka et al. (2005, 2014)

Further studies have indicated that, whereas the chemical is potent in inducing mutations, radiation is more potent, at high doses, in inducing clonal expansion of the cell population in thymus, resulting in synergism (Kawaguchi et al. 2006; Yamauchi et al. 2008); in contrast, lower radiation doses may reduce chemically-induced mutations via induction of DNA repair genes (Kakinuma et al. 2009, 2012). Studies on rat mammary cancer, on the other hand, have indicated additive interaction between radiation and chemical mutagens although evidence supports synergism in the mechanism of cancer initiation (Imaoka et al. 2005; Imaoka et al. 2014). Thus, the combined effects of radiation and chemicals can be varied, possibly depending on the cell and tissue responses to the individual agents.

Animal experiments recently conducted at QST-NIRS thus suggest diverse effects of age and lifestyle factors on radiation-related cancer risk. The studies also point to the involvement of tissue biology in tissue-to-tissue variation in the age dependence of radiation-related cancer risk.

Age-dependence of breast cancer risk

Studies of patients irradiated for diagnostic and therapeutic purposes, atomic bomb survivors, and environmentally exposed populations established a strong association consistent with linearity between breast cancer risk and radiation dose (UNSCEAR report 2013). However, in a pooled analysis of eight cohorts (Preston et al. 2002), no simple unified summary model adequately described the excess radiation risks (excess relative risk [ERR] and excess absolute risk [EAR]) in all groups. The ERR and EAR were found to depend on age at exposure, attained age, and cohort, although the pattern differed. The ERR decreased with increasing age at exposure (Life Span Study [LSS], Tuberculosis Massachusetts Original [TBO], and Benign Breast Disease [BBD] cohorts) and attained age (LSS, TBO, Tuberculosis Massachusetts Extension [TBX], and Rochester Thymus [THY]), while the EAR decreased with age at exposure (LSS, TBO, TBX, BBD) and increased with attained age (all cohorts). Different temporal patterns were observed in BBD and Acute Postpartum Mastitis [APM] cohorts and were likely to be related to the presence of breast disease.

Apart from age at exposure and attained age, epidemiological data on modifiers of radiation risk of breast cancer are sparse and inconsistent. Based on knowledge of human breast tissue development and differentiation, and animal experiments, it was hypothesized that exposure to radiation may be particularly carcinogenic when it occurs during sensitive periods in breast development such as in utero, puberty, and pregnancy, that are characterized by rapid proliferation of undifferentiated cells (Ronckers et al. 2005). Using updated cancer incidence from the LSS cohort of Japanese atomic bomb survivors for the 1958–2009 period,

coupled with data from multiple mailed surveys, radiation risks were evaluated for breast cancer focusing on effect modification pattern by age and reproductive history.

The analyses included 1470 female breast cancers and nearly two million person-years of follow-up with known doses (Brenner et al. 2018). Reproductive history, smoking history, and body mass index (BMI) data were available for 47–62% of the cohort members. Poisson regression methods were applied for grouped survival data to model both the ERR and EAR. The background rates of breast cancer (radiation dose = 0 Gy) were higher in more recent birth cohorts and rapidly increased with age before menopause, slowing around menopause and increasing again thereafter. For the same year of birth and attained age, nulliparous women had about 27% higher risk of breast cancer than women with one child. Each additional birth resulted in 12% reduction of risk, while body mass index (≥ 25 kg/m^2 vs < 25 kg/m^2) was associated with 70% increase in breast cancer risk postmenopause. The risk also increased by 5% per each year closer to menopause and decreased by 4% each year further away from menopause.

Based on a simple linear model without effect modification, there was strong evidence of radiation dose–response. The ERR decreased significantly with increasing attained age and only suggestively with age at exposure. When included in the same model simultaneously, the modifying effect of attained age persisted, while that of age at exposure was attenuated. For EAR, the radiation excess decreased significantly with age at exposure and increased with attained age up to 70 years and then declined slightly. Of all reproductive factors evaluated, significant modification of the ERR and EAR was found with age at menarche, but not with other factors. For the same attained age and radiation dose, both ERR and EAR decreased with older age at menarche (24% and 29% per each year, respectively). Also, independent of modifying effects of attained age and age at menarche, exposure around the time of menarche was found to be associated with the highest radiation risks and that effects of age at exposure before and after menarche were different.

In the LSS, as follow-up increased, the correlation between attained age and age at exposure decreased markedly making possible an examination of age at exposure and attained age as separate effect modifiers. Over time, the evidence and estimated magnitude of a simple monotonic trend in the ERR with age at exposure has lessened, especially when the ERR was allowed to vary with attained age. By contrast, after allowing for attained age effect, the decrease in EAR with age at exposure persisted. The new findings of decreasing trend in ERR and EAR with older age at menarche, coupled with highest radiation risks estimated for exposures near menarche, suggest heightened breast tissue sensitivity to ionizing radiation during puberty. The LSS experience underscores the importance of long, perhaps life-long, follow-up of exposed populations in discerning the complex age patterns of radiation risk.

Intrinsic subtypes of radiation-associated breast cancers among female atomic bomb survivors

A significant dose–response relationship between radiation dose and risk of female breast cancer has been established in the LSS cohort of atomic bomb survivors as well as in medically exposed cohorts. In the latest cancer incidence study of the LSS, the ERR per Gy for breast cancer was 1.12 at age 70 after exposure at 30 years old (95% confidence interval (CI) 0.73–1.59) and risks were significantly higher among women exposed at younger ages, especially around ages at menarche (Brenner et al. 2018). Recently, breast cancer has been thought to be a heterogeneous disease including several subtypes with different molecular profiles (e.g. intrinsic subtypes) (Sorlie et al. 2001). While tumor characteristics, risk factors, responses to therapy, and prognosis in relation to intrinsic subtypes have well been elucidated in sporadic (i.e., non-radiation-associated) breast cancers (Li 2010), little is known about radiation-associated subtypes of breast cancer. Several studies among cancer survivors reported that radiation-associated breast cancer had highly proliferative and more aggressive profiles (Castiglioni et al. 2007; Dores et al. 2010), such as HER2-positive or basal-like, but these studies were based on a relatively small number of cases and analyses of radiation risk were not performed.

At RERF, findings from histological examinations of archival pathological samples were incorporated into epidemiological analyses of atomic bomb radiation and cancers. These studies have provided clues to the pathogenesis of radiation-associated cancers. Currently, radiation risks of breast cancer in the LSS according to intrinsic subtypes have been investigated using pathological samples of atomic bomb survivors.

The analysis included 62,534 LSS females with known radiation dose and no known history of cancer before the start of follow-up in 1958. DS02R1 weighted absorbed breast dose was used as a measure of exposure. Pathological samples of first primary breast cancers ascertained between 1958 and 2005 through population-based cancer registries at Hiroshima and Nagasaki were collected from hospitals and reviewed by study pathologists. Tumors were classified into luminal A-like, luminal B-like, HER2 positive, triple negative or unknown subtype using immunohistochemistry-based definitions of the St. Gallen 2013 Panels (Goldhirsch et al. 2013). Excess relative risks (ERRs) per Gy for each subtype were estimated using Poisson regression methods while allowing baseline rates to vary by city, birth cohort, and attained age. We also evaluated modification of the ERRs by age at exposure, attained age, and age at menarche. At

the workshop, preliminary results were presented and a full manuscript is in preparation.

Thyroid diseases following childhood exposure

Epidemiological and clinical studies of thyroid disease among Hiroshima and Nagasaki atomic bomb survivors have been conducted at RERF and the results have made substantial contributions to the understanding of radiation effects on thyroid. In the following section, thyroid cancer and non-cancer thyroid diseases among atomic bomb survivors exposed in childhood are reviewed.

Thyroid cancer risks among atomic bomb survivors have been studied in the LSS of about 120,000 subjects in Hiroshima and Nagasaki. A recent study analyzed thyroid cancer incidence data among 105,401 members in the LSS cohort between 1958 and 2005 (Furukawa et al. 2013). In that study, the excess relative risk (ERR) of thyroid cancer per 1 Gy of radiation exposure was estimated as 1.28 (95% CI 0.59–2.70) at age 60 years after exposure at age 10 years based on a linear no-threshold dose–response model. In the separate analyses by exposure age (<20 vs. ≥ 20 years), the risk of thyroid cancer for those exposed before age 20 years was significant (ERR/Gy of 1.36, 95% CI 0.59–2.7, $P<0.001$), while no significant dose response was observed for those exposed after age 20 years. Among those exposed before age 20 years, about 36% of the cases were estimated to be attributable to radiation exposure. The attributable fraction has been decreasing over the follow-up years, but it has remained elevated (16%) in the latest decade of the follow-up (1996–2005). This suggests that the excess thyroid cancer risk associated with childhood exposure may persist for more than 50 years after exposure.

The AHS cohort (RERF Adult Health Study) is a subset of the LSS cohort consisting of about 24,000 atomic-bomb survivors who have been invited to biennial health examinations since 1958. Several cross-sectional studies have been conducted to evaluate radiation effects on thyroid cancer and non-cancer thyroid diseases in the AHS since then (Socolow et al. 1963; Parker et al. 1973; Morimoto et al. 1987; Nagataki et al. 1994; Fujiwara et al. 1994; Imaizumi et al. 2006; Imaizumi et al. 2015; Imaizumi et al. 2017). The latest AHS thyroid study including a thyroid questionnaire, ultrasonography and blood tests was conducted between 2007 and 2011 in participants who were younger than 10 years at exposure (Imaizumi et al. 2015; Imaizumi et al. 2017). Data from 2668 participants (mean age of 68.2 years, 1,455 women) were analysed although separate analyses by gender were not possible. The prevalence of thyroid nodules (with a diameter of 10 mm or more or a history of thyroid nodule surgery) was significantly associated with thyroid radiation dose (excess odds ratio per Gy 1.65, 95% CI 0.89–2.64). In the subgroup analysis of thyroid nodules greater than one cm, the prevalence of cancer, benign nodules, and cysts were also significantly associated with thyroid radiation dose. The interaction between age at exposure and dose was significant for the prevalence of thyroid nodules, indicating that the dose effect was higher with earlier childhood exposure. Furthermore, no dose–response relationships were observed for small thyroid nodules (diameter <10 mm). On the other hand, the prevalence of positive antithyroid antibodies (markers of autoimmune thyroiditis), hypothyroidism, and hyperthyroidism (Graves' disease) were not significantly associated with radiation dose. This is consistent with the results of previous AHS thyroid studies (Parker et al. 1973; Morimoto et al. 1987; Fujiwara et al. 1994; Imaizumi et al. 2006).

In summary, longitudinal studies among atomic bomb survivors suggest that the increased risk of thyroid cancer associated with childhood exposure has persisted for more than 50 years after exposure. Furthermore, an increased risk of large thyroid nodules was observed while risks of thyroid dysfunction and autoimmunity were not apparent in the cross-sectional studies performed several decades after childhood exposure. However, careful interpretations are needed because only limited data from cross-sectional studies are available for non-cancer thyroid diseases. Other issues that need to be addressed are risks of in utero-exposed survivors and mechanisms of radiation-associated thyroid cancer. Longitudinal epidemiological and clinical studies (such as those from follow up in radiation oncology patients) as well as basic research using stored bio-samples and/or animal models are needed for a better understanding of radiation effects on thyroid diseases.

Upper gastrointestinal tract cancer among LSS participants

An updated radiation risk analysis for upper digestive cancers was conducted using 11 years of additional follow-up data (1958–2009) as compared to the previous follow-up (Preston et al. 2007) with updated radiation dose estimates (Cullings et al. 2017) adjusted for smoking and alcohol consumption (Sakata et al. 2019). After the exclusion of deceased subjects and subjects who were diagnosed with cancer before 1958, those who were lost to the follow-up and those for whom the DR02R1 dose could not be estimated, 105,444 Life Span Study (LSS) subjects remained for analysis. Cancer incidence information was obtained through Hiroshima and Nagasaki cancer registries. The weighted absorbed dose of radiation was calculated as the sum of the gamma-ray absorbed dose and 10 times the neutron absorbed dose. Dose to the eye was used for analyses of cancers of the oral cavity/pharynx, and dose to the stomach was used for analyses of esophageal and stomach cancer. The excess relative risk (ERR) for radiation exposure was estimated relative

to the background risk adjusted for city, sex, birth year, attained age, and whether in city or not in city at the time of bombing, using Poisson regression. Smoking and alcohol consumption are known risk factors for cancers of the upper digestive tract and were included in the model when necessary. Modifications of the ERR by sex, age at exposure and attained age, and shape of the dose–response curve were investigated. *H. pylori* infection status was unknown.

The analysis was conducted in three anatomic parts, focusing on oral cavity/pharyngeal cancer, esophageal cancer, and stomach cancer. During the 51 years of follow-up from 1958 to 2009, 394 oral cavity/pharyngeal cancers, 486 esophageal cancers, and 5661 stomach cancers were observed. Squamous cell carcinoma was dominant for oral cavity/pharyngeal cancer and esophageal cancer. Most adenocarcinomas in oral cavity and pharyngeal cases were salivary gland cancer. Adenocarcinoma was dominant for stomach cancer. Oral cavity/pharyngeal cancer risk showed significant association with radiation dose. The histological type differed between salivary gland cancer and oral cavity/pharyngeal cancers other than those of the salivary gland. In separating these two groups for analysis, it was found that a significant radiation effect was not observed for oral cavity/pharyngeal cancer excluding salivary gland cancer. On the other hand, salivary gland cancer showed a highly significant association with radiation. The contrast between radiation effects on salivary glands versus other oral cavity cancers is consistent with the results from the first cancer incidence report by Thompson et al. (2005). A decrease in salivary gland cancer risk with age at exposure suggested in a previous study by Preston and co-workers (Preston et al. 2007) was shown more clearly in the current study. Smoking and alcohol consumption both showed a significant association with oral cavity / pharyngeal cancer other than salivary gland cancer, but no association with salivary gland cancer.

A significant increase in ERR with radiation dose was observed for esophageal cancer. In the previous study, (Preston et al. 2007), esophageal cancer risks were estimated using only a linear model. More detailed investigation of dose–response curves was possible with an extended follow-up due to the increased number of cases in the present study. The model fit using a linear in dose was improved significantly by adding a quadratic term in dose. In fact, a purely quadratic model showed the best fit for esophageal cancer. Thus, the dose-response appeared to be non-linear. Although a significant difference according to sex was not observed, to explore the curve, a model was applied allowing for a sex-dependent dose response, because the curvature was only significant for males in all solid cancer models (Grant et al. 2017). As with the study of all solid cancers combined, the dose-response curvature was significant for males but not for females. This means that the curvature observed for esophageal cancer seems to be driven by males. As it is well known, smoking and alcohol consumption showed a strong association with incidence rates of esophageal cancer. However, the radiation effect estimates did not change appreciably after accounting for these factors.

A significantly increased radiation-related risk of stomach cancer was observed in the present study. A linear model exhibited the best fit, and estimated sex-averaged ERR per Gy at attained age 70 was similar to the estimate of 0.34 in the previous study (Preston et al. 2007). The risk significantly decreased with the second power of attained age, i.e. 0.77 times with each ten years increase of attained age. Females showed higher risk than males. Stomach cancer is the predominant cancer among LSS subjects, but although upward curvature for males was significant for all solid cancers combined (Grant et al. 2017), this was only suggested but not significant for stomach cancer in a model that allowed the curvature to differ for males and females. This marginally significant curvature for stomach cancer in males seems to be driven by incidence among subjects whose estimated dose exceeded 4 Gy, and thus were truncated. Smoking was significantly associated with stomach cancer risk. However, the ERR estimates were identical with or without adjustment for smoking.

Lifestyle-related cancer risk: smoking and cancer

Smoking is an established and well-known carcinogen and causes many cancers, especially lung cancers. In Japan, smoking habits became popular rapidly through recovery and development of economy after World War II, peaked around 1970s at which time more than 80% of adult men smoked. Thereafter, smoking prevalence has decreased and reached at a level of 30% in 2010. In women, smoking prevalence has been traditionally low and less than 20% although smoking prevalence among young women had peaked over 20% around the year of 2000. Mortality from lung cancer followed the trend of smoking habits in Japan, i.e., it rapidly increased during the twentieth century, but has decreased thereafter. It has been suggested that the relative risk of smoking for lung cancer observed in the Japanese population might be smaller than that observed in Western countries. The following reasons for the lower relative risk have been suggested: (1) smoking intensity in Japan might have been overestimated by the information from surveys during the rapidly increasing phase of cigarette consumption, i.e., actual cigarette consumption before the survey might have been smaller than that estimated based on the information at the time of the surveys, (2) background incidence/mortality rates of lung cancer among non-smokers might be higher than those among true non-smokers because many non-smokers may have been exposed to ‘second-hand smoke’(i.e., passive smoking) due to high prevalence of

smoking, and (3) Japanese people might be less susceptible to lung cancer due to smoking.

As far as the first reason is concerned, status and risk of smoking were examined in the LSS. Mean number of cigarettes smoked per day in current smokers was larger and mean age of starting smoking in current smokers was younger in later than in earlier birth cohorts. Smokers born before about 1920 smoked on average fewer cigarettes per day than those born later, and many smokers born before 1945 did not start smoking until they reached adulthood. Smokers born after 1920 and started to smoke in early adulthood had smoking habits similar to those of smokers in the UK and the US, and continuing smokers lost about ten years of life as compared to lifelong non-smokers. Thus, previous Japanese studies have probably underestimated the effect of smoking among modern Japanese adults (Sakata 2012). It was also suggested that a cohort born around 1935 had a lower lung cancer mortality compared to neighbouring cohorts probably because they experienced the period just after the war (1945 to 1950) with severely depleted availability of cigarettes in their teenage years (Funatogawa et al. 2013). Second reason was explained by increased risk of lung cancer among non-smoking women with smoking husbands compared to non-smoking women with non-smoking husbands (Hirayama 1981). The third reason might be explained by the finding that lung cancers with mutations in the epidermal growth factor receptor genes (EGFR) are especially frequent among East Asian populations including Japanese (Midha et al. 2015) and that smoking was weakly associated with EGFR-mutation lung cancer, but strongly associated with EGFR-wild-type lung cancer. EGFR-mutation lung cancer is common in adenocarcinoma developed in East Asian non-smoking women (Matsuo et al. 2007).

Smoking risk was high with respect to small cell carcinoma among lung cancer subtypes, then squamous cell carcinoma, while the risk with respect to adenocarcinoma was relatively low. In contrast, radiation risk of squamous cell carcinoma was relatively low compared to that of adenocarcinoma although small cell carcinoma showed the highest radiation risk. Finally, a positive interaction between radiation exposure and smoking on lung cancer was observed among smokers of low smoking intensity. It was the strongest for small cell carcinoma (Furukawa et al. 2010; Egawa et al. 2012).

Radiation damage in normal tissues

Genetic variations in individual radiation therapy adverse response

Radiation therapy effectively treats many cancer types. However, apart from killing/slowing down the growth of cancer cells, ionizing radiation can also affect the nearby healthy cells. Damage to healthy cells can cause side-effects or radiation toxicity. Variable effects are observed in patients receiving the same radiation dose on the same body part by an established standard protocol such that RT causes few/no side-effects in some individuals, while in others the side-effects are more severe. Several factors could contribute to these side-effects of RT. It was recently hypothesized that some genetic variations could, at least in part, influence the risk of radiation toxicity after RT. Therefore, a project called RadGenomics was started at NIRS (in 2001), to look for such genetic variations that correlate with the severity of side-effects.

The strategy for the RadGenomics projects comprises three parts: (1) enrolment of cancer patients who were treated by the standard RT (for example, Iwakawa et al. 2006), (2) selection of the candidate genes that could possibly affect the severity of radiation response of an individual (based on previous comprehensive gene expression analyses) (Iwakawa et al. 2003; Iwakawa et al. 2004; Ban et al. 2004; Noda et al. 2005; and Tsuji et al. 2005; Ban et al. 2005; Ishikawa et al. 2006a, b), and (3) single nucleotide polymorphism (SNP) genotyping using MassArray system (Sequenom, San Diego) and association studies with normal tissue toxicity.

In the RadGenomics project; nearly 3000 patients with cancer(s) of breast, cervix, prostate, lung, head and neck and esophagus were enrolled. Furthermore, selection of about 200 genes and more than 2000 SNPs within or around these candidate genes was carried out. These genes were functionally categorized mainly into processes such as; DNA repair, transcription, and apoptosis. SNPs of the candidate genes were selected from the jSNP database (constructed by analyzing the Japanese population, National Bioscience Database center, NBDC, JAPAN) and the world-wide database, dbSNP (NCBI, USA).

Thus far, multiple SNPs associated with the risk of skin reaction after RT in breast cancer patients (Suga et al. 2007; Seibold et al. 2015; Mumbrekar et al. 2017) and with the risk of urinary morbidity after RT in prostate cancer patients have been identified (Suga et al. 2008). Investigation of cervical cancer patients has associated additional SNPs with the reaction in the gastrointestinal tract after RT (Ishikawa et al. 2011). Furthermore, we have developed a new method for the experimental determination of haplotypes of an individual (Michikawa, Sugahara et al. 2008a, b), and a simple and visible sensor array system that discriminates SNP alleles by allele-specific extension reaction using immobilized oligonucleotide primers and biotin-dUTPs as tags for alkaline phosphatase-mediated precipitation of colored chemical substrates onto the surface of the plastic base, for simultaneous genotyping of the well-selected target SNPs at clinical sites (Michikawa et al. 2008).

The data from the cancer patients indicated an association of multiple genetic factors with an individual's radio-sensitivity, unlike a few Mendelian diseases where hypersensitivity to ionizing irradiation is caused by a single gene mutation e.g., *ataxia-telangiectasia*. Individuals in this study contained different numbers of minor alleles affecting radiation toxicity. Wherein, the contribution of each allele to radiosensitivity was likely to be tissue-specific and the sensitivity strength of one allele to be small and dissimilar to another. This would provide an understanding of the mechanisms underlying the genetic heterogeneity in radiation response among the population, and may also reveal the possibility of risk prediction of the side-effects, prior to RT.

The use of selected genes, however, imposed some limitations on the findings. To move to the next stage, genome-wide association studies (GWAS), which requires several thousands of cancer patients who received radiation therapy, the Radiogenomics Consortium (RGC) was established in 2009 (West and Rosenstein 2010). Namely, the goal of the RGC is to facilitate large-scale collaborative research assessing gene-radiation effect relationships, including GWAS (Rosenstein et al. 2004). The cohorts in RGC have recently become large to have the power to identify genetic variants associated with radiation toxicity. Some of the GWAS have progressed and some results have been published (Kerns et al. 2013, 2019 Barnett et al. 2014, Fachal et al. 2014, Morton et al. 2017). It is anticipated that in the future, knowledge of the genetic variations in cancer patients will be helpful in allowing the patients and their respective doctors to select appropriate treatment protocols using RT that avoid severe side-effects.

Exceptional responders versus tissue effects in radiation therapy

Most oncologists have observed dramatic and unexpected normal tissue responses to cancer treatment in occasional patients, and usually without a plausible explanation. Although there is no clear definition, these patients are called "exceptional responders". These exceptional responders are also seen in the field of radiation oncology. Here, an understanding of exceptional responders in radiation therapy (RT) is outlined.

Regarding the prediction of radiation toxicities in normal organs, dose-volume histogram analyses have been traditionally used (Emami et al. 1991; Bentzen et al. 2010). At the National Institute of Radiological Sciences, carbon-ion radiotherapy (C-ion RT) has been used to treat various adult malignant tumors since 1994. C-ions at the Bragg peak show high linear energy transfer (LET), thereby providing a high density of energy deposition per unit length. This results in a cell-killing effect that is 2–3 times greater than that of X-rays. Several studies relating the dose constraints of C-ion RT have already been published (Okonogi 2018b, Kato et al. 2006, Ishikawa et al 2006a, b). However, sometimes there were patients who developed severe toxicity even if they were treated within the defined dose constraints. Diabetes, collagen vascular disease, smoking, and genetic abnormalities are recognized as possible clinical radio-sensitivity factors. In particular, understanding of genetic abnormalities relevant for radio-sensitivity may help to explain the existence of exceptional responders. Badie et al. demonstrated that aberrant cyclin-dependent kinase inhibitor 1 (CDKN1A) transcriptional response is associated with abnormal acute skin reaction to RT for breast cancer patients (Badie et al. 2008). In this study, higher expression of CDKN1A was shown in severe skin reactors. Thus, CDKN1A may work as a marker of severe early radiation toxicity. By minimizing the irradiated volume of normal tissue, one can reduce the risk of severe toxicities. With regard to this point, C-ion RT (or particle beam therapy) may be the optimal treatment method because it allows for an excellent dose localization.

Regarding radio-sensitivity in tumors, radiation oncologists traditionally estimate tumor response considering the "four R principle" and/or the law of Bergonie and Triboudeau (Bergonie and Triboudeau 1959); success or failure of radiotherapy in clinical settings is determined by the four R's: *r*epair of DNA damage, *r*edistribution of cells in the cell cycle, *r*epopulation, and *r*eoxygenation of hypoxic tumor areas. The radio-sensitivity of a tissue is proportional to its reproductive capacity and inversely proportional to its degree of differentiation. However, there can be differences in tumor response even in cases with the same histology, same tumor size, and same age. A possible reason for this difference in tumor response might be immunogenic reactions induced by RT. Recently, an abscopal effect, which is a reaction of a tumor that has not been directly exposed to radiation but shows tumor regression, has been recognized widely (Dagoglu et al. 2019). To clarify the immunogenic reaction induced by RT, several studies in vitro and in vivo were conducted. A study using mouse tumor models showed that T cell modulation affected the efficacy of RT, and this phenomenon was tumor-specific (Yoshimoto et al. 2014). Another study showed that X-ray or C-ion irradiation-induced high mobility group box 1 protein, which triggered the activation of an adaptive immunity by binding to toll-like receptor 4 on dendric cells (DCs), from cancer cells (Yoshimoto et al. 2015; Onishi et al. 2018). Furthermore, recently the efficacy of a combination of RT and microglia (DCs in brain) in treating malignant glioma in a rat model was demonstrated (Okonogi 2018a). Further understanding of tumor immunity may clarify the reason for the exceptional response of tumors in RT.

Radiosensitivity and radiotherapy

In a pragmatic clinical approach to individual response to ionizing radiation (IR) in patients (Bourguignon et al. 2005, Foray et al. 2016), three abnormal situations can be identified or envisaged: complications and undesirable side effects of radiotherapy with no error in dose delivery which affect the quality of life of patients, cancer proneness, and degenerative diseases after exposures to IR. For the sake of clarity, the corresponding individual states are named here radiosensitivity (Britel et al. 2018), radiosusceptibility, and radiodegeneration respectively (Foray et al. 2016). The text below deals with "radiosensitivity and radiotherapy".

Radiosensitivity was identified at the beginning of the twentieth century but has been forgotten since (Foray et al. 2012). A first major classification of human diseases among individuals exhibiting radiosensitivity was made on the basis of the cell survival fraction in vitro after exposures to IR at 2 Gy (SF2) and found to be in good agreement with the clinical response to IR (Deschavanne and Fertil 1996). Radiosensitivity is clearly related to an excess of cell death after IR exposure even though the tissue response is important as well in vivo. A more recent classification into two subcategories can be made on a clinical basis: hyper-radiosensitivity and moderate radiosensitivity.

Hyper-radiosensitive patients who present the most severe response after radiotherapy (CTCAE/EORTC grade 4–5) have a SF2 ranging from 1 to 10% and rare homozygous mutations of genes resulting in the loss of protein function that lead to an alteration of DNA DSBs recognition and repair. These patients are called group III hyper-radiosensitive patients in the frame of the radiation-induced ATM nucleo-shuttling (RIANS) model (Berthel et al. 2019).

Moderately radiosensitive patients with CTCAE/EORTC grade 2–4 have a SF2 ranging from 10 to 50% and are observed in more frequent genetic syndromes associated with high cancer proneness and in many neurodegenerative diseases. They are patients group II in the RIANS model.

Recently, cohorts have been constituted with hundreds of cancer patients exhibiting clinical radiosensitivity, e.g., the Copernic cohort (Granzotto et al. 2016; Ianuzzi et al. 2002). Most of these cancer patients exhibit moderate radiosensitivity since the patients with a homozygous genetic mutation are usually not treated by radiotherapy because of the very high risk.

Finally, clinical radiosensitivity is observed in 5 to 20% of patients treated by radiotherapy: less than 5% show hyper-radiosensitivity with severe tissue reactions grade 4 and 5, and up to 15% show moderate but significant radiosensitive tissue reactions grade 2 and 3 as identified by the patients and including but not limited to 'dermatitis radiation, skin fibrosis, and proctitis'. (Bruheim et al. 2010). These grades demonstrate some continuity between normality and severe syndromes.

Clonogenic survival, cytogenetic, DSB repair and gene expression assays have been proposed to predict radiosensitivity but these tests are difficult to use in routine practice mostly because of the delay in response for obtaining the results. Among the most recent assays, CD8 T-lymphocyte apoptosis has been proposed to predict late toxicity after radiotherapy (Seibold et al. 2015) but the inverse correlation with IR dose is surprising and still not understood. Gene expression assay of CDKN1A is also promising to identify severe early radiation toxicity (Badie et al. 2008). Numerous immunofluorescence assays are nowadays available and allow to follow the cell kinetics of proteins in space (cytoplasm/nucleus) and time and thus to perform cell functional assessment. The kinetics of ATM have been modelled and it appears that the aforementioned neurodegenerative diseases exhibit an absence or a delay of translocation of ATM from the cytoplasm where it resides as dimers in the direction of nucleus as pATM monomers after exposure to IR (Granzotto et al. 2016, Vogin et al. 2018). In the absence or in case of a delayed appearance of pATM in the nucleus the DNA DSBs are not properly repaired, and this is the first time that a second clear mechanism of radiosensitivity, i.e., an indirect abnormal DDR has been identified. Subsequently, a pATM ELISA assay has been successfully developed in skin fibroblasts and lymphocytes for clinical use (Pereira et al. 2018). The observation of an absence or a delay of translocation of ATM from the cytoplasm to the nucleus raises a new interesting concept regarding cell function: the right protein has to be present in the right amount at the right place at the right time (Gomolka et al. 2019).

At this stage, it appears that radiosensitivity is clearly a public health issue since about 10 Mio. of patients benefit from radiotherapy worldwide every year and certainly more than 500,000 of them have an enduring altered quality of life after their treatment. To make progress in the prediction of radiosensitivity with the hope to avoid such poor clinical outcomes, international collaboration is necessary. Cross comparisons of assays in different international cohorts of patients are certainly a good way to make significant progress, and thus should be initiated.

Finally, about 8% of patients treated for cancer by radiotherapy exhibit a second cancer (Cosset et al. 2018). Although the issue is to know if it is a metastasis of the primary cancer or a second primary cancer caused by the therapeutic exposure, these patients may be radiosusceptible and such a status of cancer proneness needs to be explored in the future with pertinent biomarkers.

In conclusion, radiosensitivity, radiosusceptibility and radiodegeneration are key issues of the individual response to ionizing radiation and will be addressed by ICRP Task

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Normal tissue responses after exposure to low doses of ionizing radiation

In children diagnosed with cancer, the DNA damage foci approach was applied to identify patients with double-strand break (DSB) repair deficiencies, who may overreact to DNA-damaging radio- and/or chemotherapy (Rübe 2010a, b). The results obtained show that DNA damage foci analysis of blood and tissue samples allows detection and characterization of DSB repair deficiencies and enables identification of patients at risk for high-grade toxicities (Schuler et al. 2014).

To give an example, a child with Li–Fraumeni syndrome (LFS) was reported to develop genomic instability during craniospinal irradiation for metastatic choroid plexus carcinoma (CPC). Li–Fraumeni syndrome is a cancer predisposition disorder characterized by germline mutations of the p53 tumor-suppressor gene. In response to DNA damage, p53 activities lead to protective cellular processes including cell-cycle arrest and apoptosis, to prevent aberrant cell proliferation. Current cancer therapies involve agents that damage DNA, which also affect non-cancerous hematopoietic stem/progenitor cells. It was demonstrated that a patient with LFS receiving craniospinal irradiation involving large volumes of bone marrow developed progressive genomic instability of the hematopoietic system (Schuler et al. 2017). In other words, during DNA-damaging radiotherapy, genome-stabilizing mechanisms in proliferating stem/progenitor cells are perturbed by p53 deficiency, increasing the risk of cancer initiation and progression.

There is increasing evidence that genetic factors regulating the recognition and/or repair of DNA DSBs are responsible for differences in radiosensitivity among patients. Genetically defined DSB repair capacities are supposed to determine patients' individual susceptibility to develop adverse normal tissue reactions after radiotherapy. For example, in a preclinical murine model, the impact of different DSB repair deficiencies on the cumulative DNA damage in normal tissues during the course of fractionated irradiation was analysed (Rübe et al. 2008a, b, 2010a). Different strains of mice with defined genetic backgrounds (SCID(−/−) homozygous, ATM(−/−) homozygous, ATM(±)heterozygous, and ATM(+/+) wild-type mice) were subjected to single irradiation (2 Gy), fractionated irradiation (5 × 2 Gy), or fractionated low-dose irradiation (5×, 10×, 15×, 20 × 0.1 Gy). By enumerating γH2AX- and 53BP1-foci, the formation and rejoining of DSBs were analyzed in organs representative of both early-responding (small intestine) and late-responding tissues (brain, lung, kidney, and heart) (Flockerzi et al. 2014). In repair-deficient SCID(−/−) and ATM(−/−) homozygous mice, large proportions of radiation-induced DSBs remained unrepaired after each fraction, leading to the pronounced accumulation of residual DNA damage after fractionated irradiation, similarly visible in early- and late-responding tissues. The slight DSB repair impairment of ATM (±) heterozygous mice was not detectable after single-dose irradiation but resulted in a significant increase in unrepaired DSBs during the fractionated irradiation scheme at both the 0.1 Gy and 2 Gy fractions.

Radiation-induced DSBs accumulate similarly in early- and late-responding tissues during fractionated irradiation, whereas the whole extent of residual DNA damage depends decisively on the underlying genetically defined DSB repair capacity (Flockerzi et al. 2014). Moreover, data indicate that even minor impairments in DSB repair lead to excess DNA damage accumulation during fractionated irradiation (by comparison with acute single dose irradiation) and thus may have a significant impact on normal tissue responses in clinical radiotherapy (Lorat et al. 2016). For pre-therapeutic testing of individual radiosensitivity in clinical radio-oncology, isolated blood lymphocytes of patients are generally irradiated ex-vivo with single-doses and radiation-induced DNA damage foci are counted at different time-points to measure individual DSB repair capacity (Schuler et al. 2014; Rübe et al. 2010a, b). This can mean that after single-dose exposure slight DSB repair deficiencies of patients can easily be overlooked, but may have profound effects in terms of normal tissue toxicities in clinical radiotherapy.

Discussion

At the end of the Tokyo workshop, the last session was dedicated to a discussion of a number of questions raised by Task Group 111 members with the experts present in the audience. The following provides a summary of the five issues that were discussed during this session.

What is the impact of age, sex and other determinants on normal tissue reactions, on incidence of cancers and on incidence of other diseases following radiation exposure?

The radiation and tissue weighting factors recommended by ICRP are rounded values and deliberately do not depend on any individual parameters such as age and sex. Moreover, in calculating effective dose, organ equivalent doses are calculated separately for males and females but are then averaged over sex to provide numerical values for effective dose that are, consequently, only valid for averaged ICRP reference persons/populations. This simplification is on purpose because it has been felt that any individualization in the radiological protection quantities would make the

system too complicated to apply, and legally and ethically problematic. Nevertheless, ICRP has developed and provided some tools that would allow for a more individualized assessment of radiation-related issues if needed. For example, ICRP has developed a family of voxel phantoms that can be used for more individualized dose estimates after exposure to ionizing radiation, such as for dose estimates in paediatric radiotherapy. The detriment is further elaborated in a recent ICRP publication on the use of effective dose as a risk-related radiological protection quantity, where sex and age influence the estimated risk per unit effective dose (ICRP Publication 2020, in press).

Having said this, it is important to realize that individual response to ionizing radiation will depend on the endpoint considered, be it a stochastic effect or tissue reaction. For example, normal tissues are characterized by differences in structure and composition that might influence the radiation response of that tissue. Further, there is an entire field of research on the effect of ionizing radiation on stem cells (Joiner and van der Kogel 2018). A similar example holds for radiation and type of cancer incidence. It has often been stressed that children are more sensitive than adults, and there is compelling evidence that, for example, for leukemia, brain, breast cancer, thyroid cancer, and skin cancer, there is a significant age-at-exposure effect (UNSCEAR 2013 report). In contrast, however, colon, liver, lung and bladder cancer do not show a pronounced age-at-exposure effect (UNSCEAR 2013). These findings may suggest that depending on the endpoint considered the tissue weighting factors proposed by ICRP could be age-dependent. While the mission of Task Group 111 is to review the current scientific evidence, it should be stressed again that ICRP's role is to apply the available scientific information to practical approaches to be used in radiological protection.

What is the contribution of genetics to individual, normal tissue responses with respect to adverse reactions to varying doses such as given during radiotherapy? Would predictive tests contribute to better radiological protection of radiotherapy patients without compromising cancer cure rates?

Recently efforts have been intensified to predict individual responses of patients to ionising radiation with the rationale to decrease therapy doses to exceptional responders and thereby reduce the incidence of any adverse side effects while increasing therapy doses ("dose escalation") for less-sensitive patients and so improve therapy outcome/tumour control. Another benefit would be that, with a bio-indicator for sensitivity, patients may have a better basis for judging the likely benefits and risks of a proposed therapy modality and giving informed consent.

The opinion was expressed that genetics alone will probably not explain the whole variety of responses observed among individuals. DNA damage repair among certain cell lines might be promising and could be seen as an outcome of genetic factors. However, looking at such end points among fibroblasts or lymphocytes and then making predictions of other tissues might be too simplistic.

Much of what we know about factors governing individual response to radiation is based on studies of epidemiological cohorts exposed to ionising radiation decades before an outcome (e.g., cancers) was observed. To quantify any effects among high-risk populations such as children, long-term follow-up is needed. Medically exposed cohorts could offer a promising option to study side effects after radiotherapy among cancer survivors. This would require a thorough quantification of all sources of doses from diagnostic procedures and radiotherapy modalities including not only doses to the target volume but also out-of-field doses. In Europe, several working groups of the European Radiation Dosimetry Group (EURADOS) are currently working towards this goal (Rühm et al. 2018). Indeed, there are already studies on cancer survivor cohorts in the US, UK, and Netherlands (Opstal-van Winden et al. 2019), and studies involving CT scans in children (Bernier et al. 2018). The study of issues relevant for the radiological protection of patients is indeed very important; however, this is not an easy task and complicated by the fact that (a) the cohort members are patients who got their radiation doses for certain reasons leading to the potential for confounding dues to indication bias and/or reverse causation, and (b) associations with radiation dose if there are any, are not very strong.

What is the contribution of genetics and epigenetic factors to tissue radiation response with respect to cancer induction at relevant doses and dose rates?

In this context, the observation that women with early menarche show a higher susceptibility to breast cancer as compared to women with later menarche (see above) was considered important. Thus, age at menarche can be considered as an effect modifier to both spontaneous and radiation-induced breast cancer risk. This is not surprising because the reproductive period is also a surrogate for estrogen exposure, and estrogens play a role for sporadic breast cancer. In addition, menarche corresponds to a peak in breast proliferation with high proliferation of breast stem cells. Whether this is also relevant for radiation-induced breast cancer is hard to say. Interestingly, a recent paper by Utada et al. on uterine cancer among A-bomb survivors shows that the uterine corpus is especially sensitive to the carcinogenic effect of radiation exposure occurring during the mid-pubertal period preceding menarche (Utada et al. 2019). This radiosensitive period

is somewhat earlier in puberty as compared to breast cancer risk, and may be explained by the fact that the uterus matures somewhat earlier than the breast. The contribution of genetics and epigenetic factors to tissue radiation response with respect to cancer induction is difficult to assess but obviously varies with the type of cancer. For breast cancer, the genetic basis of cancer risk is about 25% (Czene et al. 2002, Pomerantz and Freedman 2011). Twin studies have provided estimates of heritability of cancer risk that range from 42% (95% CI 29, 50) to 27% (95% CI 4, 41) (Lichtenstein et al. 2000).

What is the evidence that modifiable factors can affect the individual risk of radiation-induced cancer, tissue reactions and other non-cancer diseases?

There is some evidence that one can indeed reduce the risk of secondary cancer after radiotherapy (e.g., Imaoka et al. 2016). Epidemiological studies found associations of cancer risk with lifestyle factors such as, for example, smoking (considering light smokers, heavy smokers and non-smokers for lung cancer), UV exposure (for skin cancer), and reproductive factors (for breast cancer). While evidence for such associations seems to be convincing, their use for risk prediction seems less clear, partly because of the lack of dedicated randomized trials to study those effects. In this context, animal experiments could fill the gap suggesting, for example, positive effects of calorie-restricted diet (Yoshida et al. 1997), although there is not much evidence from such experimental studies on lifestyle factors influencing cancer risk. Furthermore, there is some indication that even for genetically identical animals a distribution of effects can be observed suggesting also some stochastic processes to contribute to the investigated outcome. Nevertheless, animal studies could be considered and performed as predictive tests are investigated.

While sound scientific evidence on the issue is desirable, however, it was also mentioned that it might not always be needed for medical decisions. In reality, if there is indication *ex-vivo* that a certain diagnostic or therapeutic modality does not turn out as beneficial or useful as originally believed, alternative strategies would be implemented even without the availability of perfect scientific information.

Of course, although the above considerations relate mainly to patients and radiotherapy, they similarly are relevant at lower doses and dose rates typical for the radiation exposure of the general (healthy) population.

What are the ways to quantify the potential impact of individual response to radiation on the incidence of cancers, non-cancer diseases and normal tissue reactions?

Based on recent findings on the correlation of radiation exposure at the time of menarche and later breast cancer incidence (Brenner et al. 2018), it appears that the time of menarche could serve as an individual marker for breast cancer risk. Analyses on uterus cancer among A-bomb survivors suggest a similar possibility for cancer of the uterus (Utada et al. 2019). However, for the time being a generalized picture is still missing.

As for cancer patients undergoing radiotherapy, it was again stressed that a complete assessment and documentation of all sources of radiation doses to an individual patient is important. Along these lines there are guidelines to quantify doses and, as an example, the Image Gently campaign in paediatrics in the US (imagegently.org) aims at optimizing diagnostic protocols for children.

As far as normal tissues and low doses are concerned, animal experiments at low doses and with fractionation schemes are important, because one can observe in nearly any tissue some changes if sensitive detection methods are available. In contrast, for humans there is much less evidence on individual non-cancer response to radiation. This might be due to the fact that, for example, for cardio-vascular diseases there are many more contributory risk factors other than ionizing radiation, and there is perhaps not sufficient information available in the life span study (LSS) of the Atomic bomb survivors. For example, the impact of smoking on radiation-induced cardiovascular diseases in the LSS has not yet been investigated. It was noted though, that for some benign endpoints there is modification due to age-at-exposure, and benign brain tumours show a strong interaction with ionizing radiation.

Conclusions

The goal of the workshops was to share current scientific knowledge and opinion from around the world on individual response to ionizing radiation. At times, there were differences of opinion about (a) definitions and (b) the state of science of biomarkers for tissue effects for radiation therapy patients. Perhaps some of this may be due to language translations and the effect of scientific silos, i.e., the knowledge and evidence perspectives of radiation epidemiology, radiobiology, and radiation therapy.

The topics presented during Task Group 111's time in Japan and the discussions with Japanese scientists demonstrated that there are very many factors that might play a role in the individual response of humans to ionizing

radiation. Should robust and consistent evidence be found, one consequence might be that some of the key elements in the current system of radiological protection as developed by ICRP such as the radiation and tissue weighting factors used to calculate effective dose might need reconsideration. The lessons learned during the meetings described might serve as a good starting point.

One should keep in mind, however, that the issue of individual response of humans to ionizing radiation represents just one piece in a broader picture. This is reflected for example in the ICRP Task Group 79 draft report "The Use of Dose Quantities in Radiological Protection" (ICRP Publication 2019, in press), and in the current work programme of ICRP Committee 1 including Task Group 91 Radiation Risk Inference at Low-dose and Low-dose Rate Exposure for Radiological Protection Purposes, Task Group 102 Detriment Calculation Methodology, and a number of working parties on: cardiovascular disease; non-radiation related parameters of detriment"; hereditary and trans-generational effects; and, cancer risk models for detriment calculation. The discussions in Japan have provided insights into some of the factors that are implicated in modifying individual responses to ionizing radiation. These include non-modifiable (fixed) factors such as age, sex and genetic factors; but there is clearly increasing evidence for a role of modifiable factors (or potentially modifiable factors) such as diet, smoking status and co-exposure to chemical agents. Most evidence comes from studies of normal tissue reactions to radiotherapy and studies with cancer as an endpoint. There appears to be less information available on the factors modifying individual response to radiation- associated non-cancer diseases such as circulatory diseases and cataract. The fact that some cellular assays are providing evidence that the severity of normal tissue reactions may to an extent be predictable is encouraging, but clearly further work, including international multi-centre studies are needed before such predictive tests become part of routine practice widely. It is moreover notable that relevant evidence comes from a wide range of approaches, including epidemiological investigations, animal studies and cellular studies; examples of all these are included in this summary report. In several important areas there are mixed findings and differing interpretations of the available data, this will present a challenge to the Task Group but it is important to reach sound judgements on the relative importance of fixed as opposed to modifiable factors that govern individual responses to radiation, and the robustness of predictive tests.

An individual approach for radiological protection purposes might not only be useful for patients but could also apply for emergency workers and astronauts. Nevertheless, for the system of radiological protection, a generalized approach is probably, at this time without alternative.

A majority of the diseases of concern in radiological protection are common within the populations (cancers, but potentially circulatory diseases and cataracts). Generally, exposure to radiation at the levels commonly experienced in occupational and public situations are low and consequently, the additional risk due to exposure is low and outweighed by that from 'spontaneous' causes and other risk factors. There is as noted in this report evidence that radiation can act either additively, synergistically or antagonistically with other risk factors, including smoking, diet, and co-exposures. Further work is required to document and quantify these interactions. Understanding the extent to which variation in radiation responses are modifiable independently from other risk factors will be an important consideration. In situations where radiation is not a major contributory risk factor (ie when exposures are low), variations in radiation response are likely to have a similarly small role on individual risk, keeping in mind the exceptions where there are strong genetic influences such as in Ataxia telangiectasia cases. In the medical area though, radiotherapy exposures are high and, therefore, this contribution of radiation exposure to diseases or tissue reactions is much greater. It is in this area that understanding of the range of radiation response amongst individuals in the population, and reliable methods to predict an individual's response that practice and approaches to radiological protection may well be influenced. Similar considerations are possible in the case of long duration deep space travel, where exposures could be substantial.

ICRP Task Group 111 members learned a great deal in the course of the discussions and workshops in Japan, and we are very grateful to all those who participated and shared their knowledge and information. The Task Group will now be exploring the scientific literature on individual response to radiation in depth and in a systematic manner, taking into consideration the main endpoints of concern noted previously—cancers, normal tissue reactions and non-cancer diseases. The outcome of this review will be published in Annals of the ICRP, and it will be a substantial but worthwhile task.

Acknowledgements The workshop participants and members of ICRP Task Group 111 thank Christopher Clement, the ICRP Scientific Secretary for his support and participation at these workshops and his review and comments on this article. The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the US Department of Energy (DOE). The research was also funded in part through DOE award DE-HS0000031 to the National Academy of Sciences and contract HHSN261201400009C through the U. S. National Cancer Institute (NCI). The views of the authors do not necessarily reflect those of the two governments. The study by A Sadakane is based on a collaboration with researchers outside RERF, Dr. Shuji Yonehara of JA Onomichi General Hospital, Dr. Takashi Nishisaka of Hiroshima Prefectural Hospital, Dr. Masahiro Nakashima of Nagasaki University, Dr. Dale L. Preston of HiroSoft International Corporation, and Dr. Kiyohiko Mabuchi, Dr. Xiaohong

R. Yang, and Dr. Amy Berrington de Gonzalez of the US National Cancer Institute. This study is supported by the contract with US NCI (HHSN261201400009C) and by JSPS KAKENHI Grant Number JP23590839, in addition to the usual funds from Japanese and US governments.

Author contributions Human Individual Radiation Sensitivity and Prospects for Prediction (AW); Longitudinal analyses of clinical data and biosamples (KY); Fetal hematopoietic stem cells are not at all sensitive to radiation for induction of persisting chromosome aberrations. How are the damaged cells eliminated? (KH); Recent Animal Studies in QST-NIRS on Individual radiation-related cancer risk (TI, MN, SK, YS); Age-dependence of breast cancer risk (AB); Intrinsic subtypes of radiation-associated breast cancers among female atomic bomb survivors (AS); Thyroid diseases following childhood exposure (MI); Upper gastrointestinal tract cancer among LSS participants (RS); Lifestyle-related Cancer Risk: Smoking and Cancer (KO); Genetic Variations in Individual Radiation Therapy Adverse Response (TI); Exceptional responders versus tissue effects in radiation therapy (NO, TK); Radiosensitivity and radiotherapy (MB); Normal tissue responses after exposure to low doses of ionizing radiation (CER).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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