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＜ Review ＞

Lessons learned from radiation biology: Health effects of low levels of exposure to ionizing radiation on humans regarding the Fukushima accident

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Abstract

Herein we summarize the important issues for radiation health effects on humans based on the reliable scientific literature. Radiation effects are categorized "tissue reactions" and "stochastic effects". The former are previously called "deterministic effects" which have a threshold below which the effect does not occur. The tissues and organs-threshold doses of local exposure has been estimated at around 100 mSv for fetal abnormalities, temporary infertility of the male and 120～200 mSv for severe mental retardation among the atomic bomb survivors of Hiroshima and Nagasaki who were exposed in utero. Whole body irradiation >1000 mGy causes acute radiation syndrome (ARS), including erythema, nausea, vomit, headache, diarrhea, fever and confusion. On the other hand, stochastic effects consist of cancer and genetic effects. Cancer risks for human exposure to radiation are estimated by epidemiological study among the atomic bomb survivors of Hiroshima and Nagasaki. Radiation risks below around 100 mSv are not capable to be estimated directly from this epidemiological data. Although all the epidemiological data do not support the linear nonthreshold (LNT) model, the model is useful for the purpose of radiation protection but not for risk assessment. In order to understand radiation effects on humans, we explain the essential terms relative biological effectiveness, equivalent dose, effective dose, dose and dose-rate effectiveness factor in this manuscript.

We hope that this review paper facilitates the knowledge acquisition of the radiation effects on humans and may help administrative officers and public health nurses to implement public health actions against future nuclear disasters or radiological accidents.

keywords: low-dose radiation, health effects, cancer risk, Fukushima nuclear accident, radiation biology

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I. Introduction

We have had a severe radiological disaster after the Great East Japan Earthquake and Tsunami of 2011. A large amount of radioactive materials was released into the environment from the damaged Fukushima Daiichi Nuclear Power Plant [1]. The health-related hazards for human exposure to ionizing radiation (hereafter shortened to 'radiation') are estimated by using the Life Span Study Cohort data from the atomic bomb survivors of Hiroshima and Nagasaki [2]. According to this epidemiological study, incidence of leukemia and solid cancer increased among those who received higher doses. Radiation risks below ～100 mSv are not able to be determined directly from the epidemiological data because of the requirement of a very large sample size. In the Fukushima accident, the World Health Organization (WHO) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) reports indicated that doses of radiation to the public are at low levels [3, 4]. The public health actions for radiation protection, such as

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evacuations from the radiation affected areas and control of the distribution of various food products, remarkably reduced external and internal radiation exposures [5]. However, there are mental health issues such as psychological distress from fear of radiation exposure, especially in long-term low-dose rate irradiation [6].

The main biological target for radiation is the DNA molecule. DNA double-strand breaks (DSBs) cause harmful effect such as cell death and chromosomal aberrations in irradiated cells [7, 8]. Radiation biology research has focused on DNA damage responses and has elucidated the mechanisms such as DNA repair, cell cycle checkpoint, and apoptosis in mammalian cells [9]. The effects of long-term radiation exposure are generally milder than for an acute exposure under the same total dose by repairing damaged DNA. The health risks associated with low-dose long-term radiation remain to be elucidated and are currently being investigated intensively to understand the Fukushima case [10, 11].

We previously summarize the public health actions taken to mitigate the public exposures to radiation after the Fukushima accident in order to provide valuable lessons learned for disaster preparedness [5]. We also introduced governmental action of several occupational health interventions for Radiation Workers including the emergency workers and the decontamination workers in the Fukushima accident [12]. In this review paper, we described the reliable scientific knowledge about radiation biology to help to understand health effect of radiation exposure in humans. In addition, we explain the terms relative biological effectiveness, equivalent dose, effective dose, dose and dose-rate effectiveness factor in this manuscript.

II. Methods

The Ministry of the Environment, Government of Japan published "The universal textbook regarding health effects of radiation" to provide the basic knowledge of radiation effects after the Fukushima accident (http://www.env.go.jp/chemi/rhm/kisoshiryo/pdf_h28/2016tk1whole.pdf). The aim of this text is for the avoidance of confusion when using various sources for the explanations of the radiation effects. Therefore, we mainly collect the information from this text and also use the WHO and UNSCEAR reports. The other papers which we reviewed were searched from the PubMed electronic library databases [13].

III. Results

1. External and internal radiation exposure

A large amounts of Iodine-131 (I-131), Cesium-134 (Cs-134), and Cesium-137 (Cs-137) were released into the environment during the Fukushima event [14]. There are two main pathways of exposure to radiation in humans: radiation is externally exposed from outside the body due to contaminated soil or internally exposed by consuming foods containing radioactive materials and inhalation of contaminated materials. For external exposure, X- and γ-rays penetrate deeply enough into the body to reach living tissue. However, alpha particles can be absorbed within the stratum corneum of the skin and do not reach to basal cells as the radiation target. In contrast, the alpha-emitter nuclide with accumulative property and long half-life is the most potent in the case of internal exposure. Radiation exposure is generated when radioactive nuclides physically decay in the body. However, some of them are excreted from the body without physical decay so that it no longer is a source of radiation exposure to the organism. Taking into consideration the elimination of a substance from a living organism, the biological half-life, is an important factor for consideration of internal exposure in addition to the physical half-life.

Insoluble Cs-bearing particles were identified in aerosol samples following the Fukushima accident [15]. Such Cs-bearing particles are thought to have persisted for a long time on the land surface, longer than those of the water-soluble Cs particles. The health effects of these particles are being investigated based on the particle sizes and insolubility in water.

2. Radiation effects on human

Radiation effects on humans are usually classified into two categories: "tissue reactions " and "stochastic effects" (Figure 1) [16]."Tissue reactions" are previously called "deterministic effects" which have a threshold below which the effect does not occur. Stochastic effects do not always occur even if it receives a certain amount of radiation. The influences are increasing as exposure increases. Stochastic effects consist of cancer and genetic effects. The effect of radiation on tissues is not severe in low- or moderate-doses of radiation (below threshold), despite the small amounts of cells which die. Surviving cells maintain the tissue and organ function in this dose range. Radiation induces transient loss of the tissue and organ function with an increase in the radiation dose. Proliferation and differentiation of tissue stem cells contributes to their recovery from radiation injury. In contrast, high doses of radiation irreversibly damage the tissue stem cells by radiation-induced cell death and they never recover. The tissues and organs-threshold doses of local exposure has been estimated at around 100 mSv for fetal abnormalities, temporary infertility of the male and 120～200 mSv for

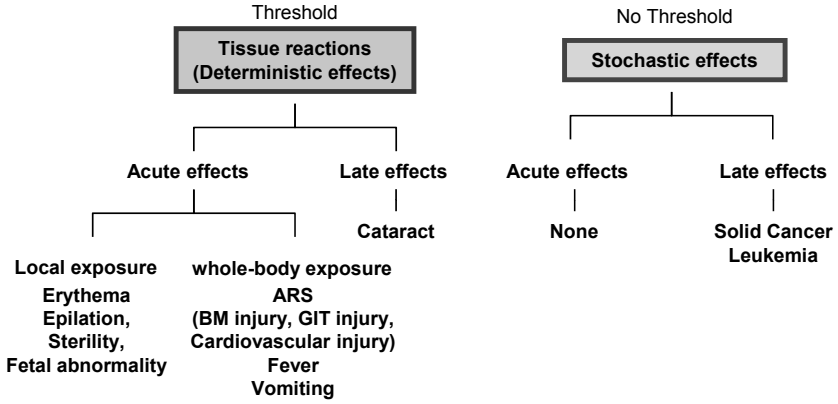

Figure 1 Tissue reactions and Stochastic effects

severe mental retardation among the atomic bomb survivors of Hiroshima and Nagasaki who were exposed in utero [17]. Exposure >500 mGy to bone mallow transiently decreases the number of blood cells with a reduction of hematopoietic capacity [18]. The radiation exposure threshold for cataracts is initially estimated as 1500 mGy and this value was recently revised to a lower 500 mGy according to the Life Span Study Cohort from the atomic bomb survivors of Hiroshima and Nagasaki [18]. There is no evidence of a significant increase in trans-generational genetic effects following radiation exposure in the atomic-bomb survivors of Hiroshima and Nagasaki, and the patients who received radiotherapy [19, 20].

Whole body irradiation >1000 mGy causes acute radiation syndrome (ARS). In the Chernobyl accident, ARS was confirmed in 134 of the emergency workers (28 died within the first four months) [21]. In JCO accident in 1999, two workers died of ARS due to exposure to >6~7 Sv of high doses of radiation [22, 23]. In the case of local radiation exposure on the body, high doses of radiation causes erythema, epilation, and sterility etc. We summarized characteristic symptoms and treatment modality regarding ARS according to the radiation doses in Table 1. The prodromal phase of ARS usually occurs in the first 48 hours and represents erythema, nausea, vomit, headache, diarrhea, fever and confusion [16]. Hematopoietic disorders, gastrointestinal disturbances and cardiovascular disorders appear after 3 weeks in the latent phase of ARS. No ARS was reported in the Fukushima accident, because of radiation exposure due to the Fukushima accident is below 1000 mSv among emergency workers [12].

3. Cancer risks associated with radiation exposure

Radiation is known as a carcinogen that causes leukemia and solid cancer in humans. There is no threshold for stochastic effects, such as cancer induction and mutations which are thought to depend on the absorbed dose. There are major concerns about cancer risks for human exposure

Table 1 Characteristic symptons and treatment modality of ARS

Dose (Gy)	Below lethal dose	Therapeutic range			Lethal range	
	0~1	1~2	2~6	6~10	10~15	>50
Therapeutic needs	None needed	Clinical observation	Effective therapy	Possible therapy	Palliative	Therapy
Main targeted organ	–	Blood-forming tissue			Gastrointestinal tract	Central nervous system
Characteristic symptoms	–	Moderate Leucopenia	Heavy leucopenia, purpura,haemorrhage,infection, epilation(more than 3Gy)		Diarrhoea, fever, electrolytic imbalance	Cramps, tremor ataxy, lethargy
Appearance of vomiting	No	1Gy:5%, 2Gy:50%	>3Gy:100%			
Time of delay of nausea+vomiting	–	3h	2h	1h	30min	
Therapy	Psychotherapy	Psychotherapy, haematological observation	Transfusion of blood, antibiotics	Transplantation of bone marrow is possible and white	Support of electrolytic balance	Symptomatic
Prognosis	Excellent		Guarded		Poor	Hopeless
Lethality (Time of death)	0		0-80% (2 months)	80-100% (2 months)	90-100% (2weeks)	100% (2 days)
Cause of death	–		Haemorrhage-infection		Enterocolitis	Irreversible circulatory collapse, cerebral oedema

to radiation after the Fukushima accident [3, 4]. The Life Span Study Cohort from the atomic bomb survivors of Hiroshima and Nagasaki revealed an increase in incidence of leukemia a few years after the bombing and peaked at 6～7 years after. Cancer risks for human exposure to radiation are estimated by this epidemiological study among the atomic bomb survivors of Hiroshima and Nagasaki. The radiation-associated excess leukemia risks are evident even 55 years after the bombings [24]. On the other hand, the solid cancer risks increased in persons over the age of 40, the so-called cancer-prone age [2]. The cancer risks associated with internal radiation exposure was reported in the epidemiological study of Chernobyl victims. Internal exposure to I-131 from contaminated milk in childhood caused an increased risk of thyroid cancer after the Chernobyl nuclear crisis [21, 25, 26]. Fortunately, the absorbed doses to the thyroid of younger people were limited in the Fukushima accident [4]. Details are described in other papers in this special issue. Cancer risks from natural radiation has been investigated among residents who live in the high natural background radiation area in Kerala, India [27] and Yangjiang in Guangdong Province, China [28]. Increased risk of cancer due to the high natural background radiation has not been observed in these areas. The other study of the risk of childhood cancer also showed no evidence of an association [29]. In contrast, a nationwide cohort study of the risk of childhood cancer due to background radiation in the Swiss National Censuses suggested a positive association [30]. So far, radiation risks below around 100 mSv are not capable to be estimated directly from these epidemiological data. International organizations such as World Health Organization (WHO) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) reported that increased risk of disease associated with radiation exposure from the Fukushima accident will not be expected besides the possibility of thyroid cancer because of the limited radiation exposure among public [31]. Dr. Boice from National Council on Radiation Protection and Measurements commented that the linear nonthreshold (LNT) model is used for the purpose of radiation protection but not for risk assessment in the low-dose range because of all the epidemiological data do not support the model [32]. Some scientists have been suggested utilizing the beneficial effect of radiation such as hormesis and adaptation to low-doses of radiation for risk assessment [33]. However, the cancer risks associated with low-dose radiation are uncertainties because of insufficient scientific evidence.

4. Radiation signatures associated with radiation-induced tumorigenesis

The elucidation of the mechanism of radiation-induced tumorigenesis is indispensable to clarify the cancer risks of low-dose radiation [34]. Identification of DNA mutations associated with radiation-related carcinogenesis, so-called radiation signature, may help to understand the characteristics of radiation-induced tumorigenesis [35, 36]. The transcriptional factor acute myeloid leukemia 1(AML1) is indispensable for hematopoiesis. It was reported that AML1 mutations were found in myelodysplastic syndrome patients among atomic bomb survivors [37]. Radiation is thought to contribute to the transformation of hematopoietic progenitors via AML1 mutations. RET/PTC rearrangements are frequently observed in adult-onset papillary thyroid cancer (PTC) of A-bomb survivor [38]. RET/PTC is considered as radiation signature for IR-induced thyroid cancer. However, others claim that the mutation also appears in sporadic PTC [39]. Thus, the radiation signatures are still argued among various cancers. Epigenetic effects may also be involved in radiation-related cancer. However, little science is available currently on the epigenetic effects [35, 36].

The biological model of carcinogenesis based on scientific evidence may help people understand their risk from radiation exposure [34]. For instance, the Amitage and Doll multistage model of carcinogenesis in which several successive changes in the cell are required before cancer appears as a clinical manifestation [40]. They further developed a two-stage theory of carcinogenesis. Healthy cells have acquired growth advantages by the faster rate of multiplication to form intermediated cells at the first stage. Then, the second discrete event occurs to transform malignant cells at the second stage [41]. This model is applied to the understanding of the risk of radiation-related carcinogenesis by using human epidemiological data.

5. Relative biological effectiveness, equivalent dose and effective dose

Radiation includes diverse particles such as photons, electrons, protons, and neutrons which produces ionized and/or excited atoms in irradiated materials. The linear energy transfer (LET) differs depending on the type and energy of the incident radiation. Alpha particles consist of two protons and two neutron (charged helium nuclei), are less penetrating and are classified as high-LET radiation. The biological target of ionizing radiation is DNA. High-LET causes more severe unrepairable DNA damage in the nucleus (so-called clustered DNA damage [42]) than other radiation. On the other hand, X- and γ -rays belonged to low-LET and are less effective to the organelle by the repair

of damaged DNA. Thus, the biological effect of radiation is influenced by radiation dose, dose rates and radiation quality. Relative biological effectiveness (RBE) of radiation is estimated as the ratio by using the X-ray as a standard.

Equation 1: $RBE = D_X / D$

In Equation 1 D_X is a reference absorbed dose of X-rays, and D is the absorbed dose of tested radiation that causes the same biological effect. The RBEs have been estimated as the effectiveness of various endpoints, such as cell survival, mutation rates and incidence of apoptosis. The value of RBE varies according to radiation dose, dose rates, division of irradiation and cell type. Since RBE is so complicated, it cannot simply apply for radiological protection. The radiation weighting factor W_R is conservatively defined to connect with LET on a basis of acknowledgement of the experimental RBEs. W_R is 20 for alpha particles, while it is 1 for X-, γ -and β -ray. Equivalent dose H (Sv) is calculated as the mean absorbed dose to a tissue or organ D (Gy) multiplied by the radiation weighting factor W_R.

Tissue weighting factor W_T is considered the radiation sensitivity of each tissue or organ. Bone marrow, lymph tissue and testis are particularly susceptible to radiation, whereas brain and bone are shown to be low radiation sensitivity [16]. This value applies to determine the effect of partial body irradiation or local irradiation. For instance, the target organ for internal exposure to I-131 is the thyroid. It is important to estimate absorbed dose to the thyroid to elucidate the effect of I-131. Effective dose E (Sv) is determined by the tissue-weighted sum of the equivalent doses multiply by W_T. Thus, the absorbed dose Gy converts to Sv in consideration of the RBE.

6. Dose and dose-rate effectiveness factor

In the case of fractionated radiation and chronic exposures, the health effects are typically milder than those of acute high-dose rate irradiation at the same total dose [43]. Cells can eliminate the DNA damage induced by low dose rate radiation through protective mechanisms of DNA repair and show adaptive responses to long-term exposure [44]. The International Commission of Radiological Protection (ICRP) proposes that a dose and dose rate effectiveness factor (DDREF) of 2 accounts for the reduced effectiveness of low-dose rate radiation [45]. However, the radiobiological studies were the main argument in numerical value of DDREF [46, 47]. The German commission on radiological protection (Strahlenschutzkommision:SSK) recommended not to use of the DDREF in radiological protection due to uncertainty about the value of DDREF. WHO did not use DDREF in the global report on the Fukushima nuclear accident regarding health risk assessment [3].

IV. Discussion

The aim of this review paper is to learn from the Fukushima experience and help practitioners to implement radiation protection actions against future nuclear disasters or radiological accidents. After the Fukushima accident, people believed that the exposure exceeding 1 mSv/year causes increase in cancer risks and genetic effect in the progeny. However, radiation risks below around 100 mSv are not capable to be detected from current epidemiological data. Trans-generational genetic or epi-genetic effects due to radiation exposure have not been reported in humans. We have to know that we know what we know, and to know that we do not know what we do not know. ICRP recommends 1 mSv/year as the dose limit for the general public based on the fact that the difference level of natural radiation background between low and high areas in order to not suffer the disadvantage of radiation exposure among the public [48].

It is minimally required to know the units of radiation dose to understand the radiation effect on humans. Radiation absorbed dose and effective dose uses Gy and Sv, respectively. We mentioned the difference between Gy and Sv by interpreting the terms of RBE, equivalent dose and effective dose.

Many researchers are working on various issues regarding uncertainty for radiation effects, such as the accuracy of radiation dose estimation, cancer risk of low-dose and low-dose rate radiation and the health effects of insoluble Cs particles. These investigations may contribute to obtain more reliable scientific evidences for radiation protection in the future.

V. Conclusion

There is the issue of anxiety from radiation exposure after the Fukushima accident even though radiation exposure among the public is limited. Continuous support to overcome this issue, together with the local community, is important to protect the public health during the recovery from the nuclear disaster.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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放射線生物学から学ぶ低線量放射線による人の健康影響について

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抄録

本総説論文では，人の放射線影響研究について，どこまでわかっているのかを科学的根拠を基に紹介する．ヒトの放射線影響は，組織反応と確率的影響に分類される．組織反応は，以前は確定的影響とよばれ，しきい値があり，しきい値以下の線量の被ばくでは影響が観察されない．胎児の異常や男性の一時的不妊のしきい値は100 mSvで，胎児期の被ばくによる精神発達遅延のしきい値は，広島・長崎原爆被爆者の疫学解析から120~200 mSvと報告されている．1000 mGy以上の高線量の全身被ばくでは，急性放射線障害といわれる，紅斑，吐き気，嘔吐，頭痛，下痢，発熱，混乱等の症状がみられる．一方，確率的影響には，がんと遺伝的影響がある．ヒトの放射線による発がんリスクの科学的根拠には，広島・長崎の原爆被爆者の寿命調査の疫学データが用いられる．もっとも精度が高いと言われるこの調査によっても100 mSv以下の低線量放射線による発がんリスクの増加があるかどうかを評価することはできない．しきい値なしの直線モデルは，全ての人の放射線発がんに関する疫学データの結果を反映しているわけではないが，放射線防護を考える上で有用ではある．しかし，このモデルを使って放射線リスク評価をすることはできない．

本論文では，ヒトの放射線影響を理解する上において重要な生物効果比，等価線量，実行線量，線量・線量効果値について，説明する．本総説論文が，放射線事故の際に，放射線対策に関わる実務者の放射線基礎知識の向上に活用されることを期待する．

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