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Commentary

Radiobiological Implications of Fukushima Nuclear Accident for Personalized Medical Approach

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On March 11, 2011, a devastating earthquake and subsequent tsunami caused serious damage to areas of the Pacific coast in Fukushima prefecture and prompted fears among the residents about a possible meltdown of the Fukushima Daiichi Nuclear Power Plant reactors. As of 2017, over six years have passed since the Fukushima nuclear crisis and yet the full ramifications of the biological exposures to this accidental release of radioactive substances remain unclear. Furthermore, although several genetic studies have determined that the variation in radiation sensitivity among different individuals is wider than expected, personalized medical approaches for Fukushima victims have seemed to be insufficient. In this commentary, we discuss radiobiological issues arising from low-dose radiation exposure, from the cell-based to the population level. We also introduce the scientific utility of the Integrative Japanese Genome Variation Database (iJGVD), an online database released by the Tohoku Medical Megabank Organization, Tohoku University that covered the whole genome sequences of 2,049 healthy individuals in the northeastern part of Japan in 2016. Here we propose a personalized radiation risk assessment and medical approach, which considers the genetic variation of radiation sensitivity among individuals, for next-step developments in radiological protection.

Keywords: Fukushima Daiichi Nuclear Power Plant; low-dose radiation; precision medicine; radiation sensitivity; radiation-induced bystander effect
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Commentary

In March of 2011, the northeastern part of Japan was devastated by the triple disasters of an earthquake, a tsunami, and the Fukushima Daiichi Nuclear Power Plant (FNPP) accident (Shibahara 2011), leaving local residents fearful about the long-term health risk of low-dose radiation because of radioactive substances released from the FNPP (Ishigaki et al. 2013; Fukunaga and Kumakawa 2015). As of 2017, unfortunately, the ramifications of biological exposure to low dose radiation remains unclear (Hosoda et al. 2016).

Previous epidemiological data indicate a clear increase in the long-term risk of cancer from exposure to radiation at doses exceeding 100 mSv. For this reason, following Japan's worst ever radiation accident at FNPP, radiation doses have been measured in the Fukushima residents, using both personal dosimeters for external exposure and whole-body counters for internal exposure (Yasumura et al. 2012). Several studies have indicated that the radiation exposure levels of Fukushima residents are much lower than predicted (Hayano et al. 2013; Kamiya et al. 2016). Furthermore, Harada et al. (2014) showed that the mean annual radiation dose rate in 2012 associated with the accident was 0.89-2.51 mSv/y and the mean dose rate estimates for 2022 are comparable with the variations of the average 2 mSv/y background radiation due to exposure to natural radionuclides in Japan. These findings suggest that the extra lifetime integrated dose after 2012 will increase the estimated lifetime risk of cancer incidence by a factor of 1.03 to 1.05 at most, which is unlikely to be epidemiologically detectable (Harada et al. 2014).

In 2013, the World Health Organization (WHO) reported that the estimates of radiation-induced health risks in Japan for the lifetime risk for some cancers may be somewhat elevated above baseline rates in certain age and sex groups among residents of the areas most affected by the FNPP accident (WHO 2013). Also, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) published a report suggesting that a general

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radiation-related increase in the incidence of health effects among the exposed population would be indiscernible over the baseline level; however, it could not rule out the possibility of excess cases of disease due to irradiation, nor to the possibility of detection of a biomarker for certain types of cancer in certain subgroups being identified in the future that could be associated with radiation exposure (UNSCEAR 2014, 2015). In addition, the dose-response relation for cancer at low doses is assumed, for purposes of radiological protection, to be linear and without a threshold, but this has not been definitively confirmed for all exposure scenarios. An appropriate dose-response relation for the effects of low doses of radiation therefore remains to be established (Kamiya et al. 2015).

The knowledge accumulated concerning the risks of low-dose radiation exposure to humans appears to be insufficient at this time because of important radiological issues arising at low doses due to inhomogeneous dose distribution in living systems. In general, the energy deposition of radiation is localized along its track, resulting in a heterogeneous distribution of exposed or unexposed cells in an organ. A Monte Carlo track simulation study reported that roughly 50% of the cell nuclei in a cell population receive a "hit" from a radiation track produced by an acute exposure of 270 μGy of ^{137}Cs γ-rays (Watanabe 2012). This situation differs substantially from that in higher dose regions when analyzed by the concept of "absorbed dose." Instead, an "elemental dose," given by a single radiation track to a target volume, as developed by microdosimetry, should be used in the analysis of low-dose effects (ICRU, International Commission on Radiation Units and Measurements 1983). This dose was estimated as 0.87 mGy for ^{60}Co γ-rays by Booz and Feinendegen in 1988 (Booz and Feinendegen 1988). In this low-dose situation, two groups exist in a cell population: one consists of cells that received the elemental dose from a single track, and the other consists of cells that did not receive any dose. Although several papers reveal the clinical utility of inhomogeneous dose distribution in tissue-based level such as micro-slit-beam radiation therapy using synchrotron-generated X-ray beams (Mukumoto et al. 2017), to our knowledge, the radiation risk assessment of such inhomogeneous dose distribution in a living system has not yet been determined. Thus, two main factors are recognized as governing the biological influences of low-dose irradiation. The first is the radiation-induced bystander effect (RIBE) at the cell or tissue levels (Nagasawa and Little 1992; Prise and O'Sullivan 2009; Blyth and Sykes 2011), and the second is radiation sensitivity at the individual or population levels (Fukunaga et al. 2016; Fukunaga and Yokoya 2016).

A simple definition of RIBE is that "a cell responds to the fact that its neighbor(s) have been irradiated" (Fig. 1), and a key characteristic of RIBE, in contrast to direct irradiation effects, is the dose-response relationship. Instead of an increased response with an increasing radiation dose, the RIBE becomes saturated at relatively low doses (typically less than 1 Gy) (Prise and O'Sullivan 2009). Since the first report of RIBE by Nagasawa and Little (1992), low-dose radiation research, pursued in a variety of experimental systems that have focused on cultured cells, has suggested that DNA damage and genetic instability due to RIBE are responsible for some of the effects of low-dose radiation on cells (Prise and O'Sullivan 2009; Blyth and Sykes 2011). However, the underlying biological mechanism has yet to be clarified, thereby maintaining the assessment of radiation risks at low doses in a very controversial status. To our knowledge at this time, the data accumulated concerning the cancer risks of RIBE at individual levels appears to be insufficient (Blyth and Sykes 2011). The radiation exposure levels of local residents have truly been extremely low after the FNPP accident; however, the future effects on people's health remain in doubt because of the lack of knowledge of

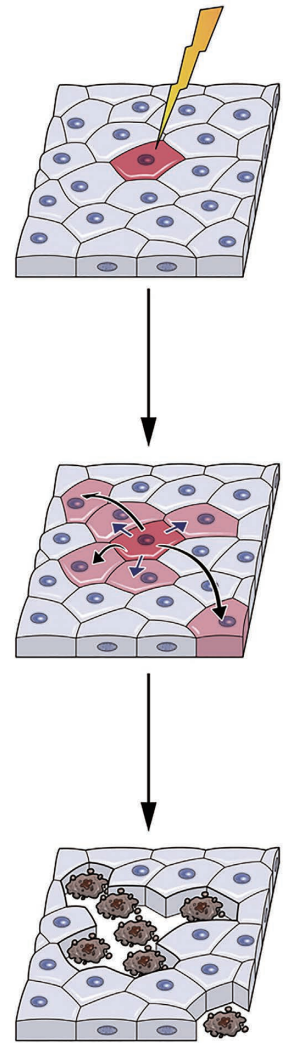

Fig. 1. Radiation-induced bystander effect.
Cells that did not directly receive radiation doses but did receive signals from nearby or neighboring irradiated cells behave as though they have been exposed, showing genomic instability and other abnormalities. The effect is mediated either through gap junctions or via soluble factors released by irradiated cells.

the underlying mechanism of the biological effects of low-dose radiation, including RIBE.

Severe reactions to radiation therapy have been reported in clinical practice in individuals suffering from DNA damage response (DDR) defective disorders, such as ataxia-telangiectasia (AT), Nijmegen breakage syndrome, Fanconi anemia, and DNA ligase IV deficiency (Pollard and Gatti 2009). These patients, and other heterozygous carriers, can be associated with radiation hypersensitivity, as well as with cancer predisposition, although the underlying mechanism of radiation-induced carcinogenesis in these individuals remains to be determined (Jongmans and Hall 1999). Additionally, several single nucleotide polymorphisms (SNPs) have been reported as potential biomarkers for predicting the development of radiation pneumonitis (RP), one of the adverse effects of radiation therapy. These SNPs in genes related to DDR, cell signaling, and inflammation have a statistically confirmed association with RP, suggesting their direct or indirect involvement in radiation sensitivity (Zhang et al. 2010; Yin et al. 2011, 2012; Edvardsen et al. 2013; Tang et al. 2016). In 2016, we reported the estimated prevalence of heterozygous careers of major DNA repair disorders in Fukushima, such as AT, Werner syndrome, and hereditary breast ovarian cancer syndrome (Fukunaga and Yokoya 2016).

We used the Integrative Japanese Genome Variation Database (iJGVD, available at https://ijgvd.megabank.tohoku.ac.jp/) in 2016 to investigate the variations in these radiosensitivity-related gene in a large population. This is an online database released by the Tohoku Medical Megabank Organization, Tohoku University that covered the whole genome sequences of 2,049 healthy individuals in the part of northeastern Japan that was seriously damaged in the 2011 disaster (Nagasaki et al. 2015; Yamaguchi-Kabata et al. 2015). We found that a large number of individuals have SNPs associated with the risk of developing RP, indicating a greater than expected genetic diversity of radiation sensitivity (Fukunaga et al. 2016). We also investigated the frequency of mutations in the *WRN* gene among residents in the northeastern part of Japan to determine the presence of Werner syndrome (WS) patients and/or *WRN* heterozygous carriers. This syndrome is a rare genetic disorder that causes deficiency of the WRN protein and presents with features suggestive of accelerated aging and radiation hypersensitivity (UNSCEAR 2011). Genetic instability has been observed in WS patients and in *WRN* heterozygotes, suggesting an association between *WRN* gene mutations and radiation hypersensitivity, as well as cancer predisposition, in these persons (Moser et al. 2000). To our knowledge, our result is the first evidence of a direct link between the presence of heterozygous carriers with genetic instability and radiation hypersensitivity in the northeastern part of Japan after the 2011 FNPP accident (data not shown). Consideration of these patients and heterozygous carriers with other radiation sensitivity disorders would give a much wider than expected individual variation in radiation sensitivity.

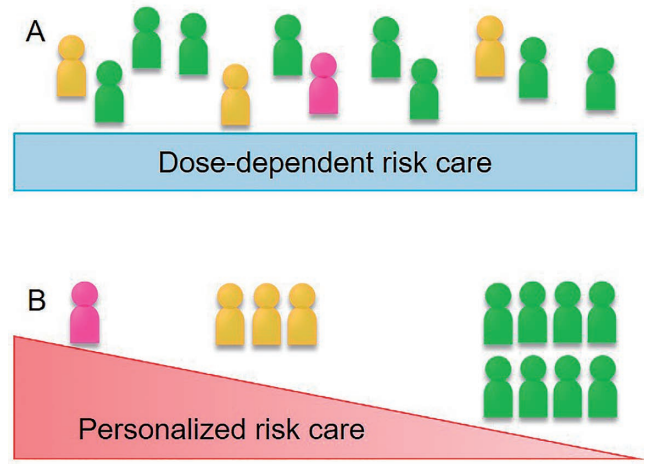

Fig. 2. Personalized radiation risk assessment and care system in the large-scale nuclear accident management.
There are two radiation risk assessment and care systems after the nuclear accident: the dose-dependent (A) and the personalized (B). High, moderate, and low radiation-induced health risk parson are shown in red, yellow, and green, respectively.

The target of current medical approaches has shown a gradual change from the "average person" to "each person." However, in the matter of radiation protection, this approach has not been sufficiently developed (Fukunaga et al. 2016). Using the iJGVD and other databases, we are now investigating the heterozygous carriers of these disorders in the northeastern part of Japan including Fukushima; however, because of the sample size we cannot significantly detect such high-risk individuals, with the exception of the *WRN* heterozygous mutation carriers. Other diseases including Cockayne's syndrome are extremely rare; therefore, heterozygous carriers could not be significantly detected because of methodological limitations. It is true that the iJGVD has great potential for future innovations from the view point of precision medicine, but the present sample size is too small and needs to be urgently expanded. As previously mentioned, several genomic studies have recently determined a wider than expected variation in radiation sensitivity among individuals, indicating an inadequacy in the conventional approach to radiological protection. As shown in Fig. 2, we need a personalized radiation risk assessment and care approach that considers the genetic variation of radiation sensitivity in individuals to replace the current dose-dependent risk assessment approach. Appropriate actions are expected in Fukushima health facilities for the coming era of precision medicine.

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Conflict of Interest

The authors declare no conflict of interest.

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