Letter to the Editor
Diagnostic Genetics

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Correspondence: Response to "Evaluating the Cumulative Impact of Ionizing Radiation Exposure With Diagnostic Genetics"

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Dear Editor,

We appreciate the opportunity to respond to the Letter to the Editor by Professor Wang [1] regarding our article reporting dose estimation curves following *in vitro* X-ray irradiation using blood from four healthy Korean individuals [2]. Professor Wang raises an important scientific issue in the original research paper, namely, clinical application of cytogenetic dosimetry for low-dose exposure to ionizing radiation (IR) <100 mGy.

Except for accidental overexposure, most human exposure to IR, including natural background radiation, diagnostic medical tests, and occupational exposure, is typically at low doses [3]; thus, evaluating risks at this dose range is important. Although the effect of low radiation doses on cancer risk is less well established than that of high doses [3], related studies have recently been published [4, 5]. A study on 262,573 individuals who had been exposed to <100 mGy IR reported that the relative risks of acute myeloid leukemia and acute lymphoblastic leukemia were 2.56 and 5.66, respectively, with an excess risk also apparent for cumulative doses <50 mGy [4]. The report by the Committee on the Biological Effects of Ionizing Radiation concluded that the cancer risk would continue in a linear trend at lower doses of IR, without a threshold, and that the lowest dose has the potential to cause a small increase in risk to humans [5].

However, to date, there is no standard method specifically designed for detecting chromosomal abnormalities following exposure to doses ≤100 mGy, and the accuracy of estimation methods using dose-response curves remains unclear [6]. According to the guidelines of the International Atomic Energy Agency (IAEA) [6], dicentric chromosome (DC) and FISH translocation (TR) assays are typically used following radiation exposure >100 mGy and >250 mGy, respectively. In our study, the curves for DC and TR induced by X-ray irradiation showed good radiation dose responsiveness [2]. However, at doses ≤50 mGy, the increase in the number of DCs observed did not correlate with the radiation dose [2]. This might be due to confounders such as age, smoking, and polymorphisms in DNA repair genes [7].

To reduce the influence of these confounders on the fitted curve, IAEA guidelines recommend that a sufficient number of cells be analyzed, between 3,000 and 5,000 per dose-point [6]. Based on an analysis of more than 5,000 cells for each data point, a prior study reported a strong correlation between radiation dose and DC frequency, even at a low dose of 20 mGy [8]. Another study using multicolor FISH for all 23 homologous pairs found that it served as a good alternative method for improving the identification of chromosome aberrations due to low-dose exposure [9]. In addition to these studies, other approaches for

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increasing discriminative power at low doses are being examined; however, further studies examining whether these can be clinically applied are needed.

Professor Wang also suggests the necessity of in-depth research for IR-induced genomic sequence alterations/mutations, using next-generation sequencing (NGS) [1]. IR is known to induce a broad range of DNA damage, including base-pair substitutions, single strand breaks, deletions, DNA-protein cross-links, and double strand breaks (DSB) [6]. DSB are critical in the formation of chromosome aberrations, such as DC or TR, which can be estimated by standard cytogenetic dosimetric methods [6]. However, at a higher molecular resolution, the genome-wide consequences of radiation insult are thus far poorly understood. A recent study using exome sequencing showed that NGS is a good tool to advance research on genomes and help identify IR-induced DNA variants [10]. The authors analyzed 10 exomes from human gingiva fibroblasts with five different irradiation dose-points and found that increases in IR-induced sequence variants with increasing radiation dose were highly statistically significant [10]. In addition, they suggested that certain chromosomal regions are more prone to preferentially accumulate IR-induced variants, which might be due to structural and/or functional chromatin domain differences [10]. Molecular assays based on the sequence data are expected to elucidate the mutational effects of IR, in addition to its related mutation rate and spectrum at the molecular level.

As substantial evidence demonstrates an association between IR exposure and increased adverse health effects [3-5], ongoing improvements and studies of diagnostic methods are needed to overcome limitations such as low statistical power, dosimetric uncertainties, deficiencies in confounder control, and other biases.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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