UK NIHR health protection research unit: chemical & radiation threats & hazards – biomarkers

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Study Goal: The UK National Institute for Health Research Health Protection Research Unit in Chemical and Radiation Threats & Hazards represents a new collaboration between Public Health England and Newcastle University. Its aims include development, validation and application of existing and new radiation biomarkers to refining uncertainties and individual variations in the response to low doses used in diagnostic and interventional radiology and high doses capable of causing acute health effects.

Abstract: Biomarkers of exposure and effect are important tools in experimental and patient studies of the health effects of medical radiation exposure. Traditional biomarkers of radiation exposure are based on the cytogenetic consequences of DNA damage, with mis-repair leading to the dose-dependent formation of chromosome aberrations. However, in recent years, more sophisticated biomarkers have been developed, for instance based on transcriptional changes or initial DNA damage responses including the formation of gamma-H2AX foci at the site of double strand breaks. Validation of three biomarkers (dicentrics, micronuclei and gamma-H2AX foci), that are already used for routine and emergency response-dosimetry at PHE, has been carried out for large scale, longer term health surveillance studies. Samples from approximately 400 radiotherapy patients, taken with ethical approval and informed consent, were X-irradiated with 0.5, 2, 4 or 6 Gy in order to assess the stability of the responses for dose reconstruction and the ability of scorers to work consistently with large sample numbers. 62,000 dicentrics in 21,000 cells, 146,000 micronuclei in 305,000 cells and 346,000 gamma-H2AX foci in 43,000 cells were analyzed in total. The main output has been the identification of the key challenges for larger scale studies, particularly in terms of practical aspects such as comparison of assay and scorer performance and consumable costs, logistics of sample processing and automation and failure rates. Important information regarding effect modifiers has also been gained, including evidence of inter-scorer variation despite a very high degree of expertise (for all CA, p = 0.008) and assay response ‘drift’ over time (p all < 0.005). In addition the results represent a comprehensive set of data informing inter-individual variation in responses which will provide a benchmark for further radiation biomarker identification and validation going forward.

Conclusion: The dicentric, micronucleus and gamma-H2AX assays have been shown to be suitable for large scale radiation response studies, providing a high degree of quality assurance and quality management is ensured. The results will directly inform further efforts focused on biomarkers of late radiotherapy effects, including through collaboration with the UK Institute of Cancer Research and Royal Marsden NHS Foundation Trust and the Centre Régional de Lutte Contre Le Cancer, France.
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