



Review

Ionizing radiation biomarkers in epidemiological studies – An update



Janet Hall^{a,*}, Penny A. Jeggo^b, Catharine West^c, Maria Gomolka^d, Roel Quintens^e,
Christophe Badier^f, Olivier Laurent^g, An Aerts^e, Nataša Anastasov^h, Omid Azimzadeh^h,
Tamara Azizovaⁱ, Sarah Baatout^{e,j}, Bjorn Baselet^{e,k}, Mohammed A. Benotmane^e,
Eric Blanchardon^g, Yann Guéguen^g, Siamak Haghdoost^l, Mats Harms-Ringhdahl^l,
Julia Hess^h, Michaela Kreuzer^d, Dominique Laurier^g, Ellina Macaeva^{e,j},
Grainne Manning^f, Eileen Pernot^m, Jean-Luc Ravanat^{n,o}, Laure Sabatier^p, Karine Tack^g,
Soile Tapio^h, Horst Zitzelsberger^h, Elisabeth Cardis^{q,r,s,**}

^a Centre de Recherche en Cancérologie de Lyon, INSERM 1052, CNRS 5286, Univ Lyon, Université Claude Bernard, Lyon 1, Lyon, F-69424, France

^b Genome Damage and Stability Centre, School of Life Sciences, University of Sussex, Falmer, Brighton, BN1 9RQ, United Kingdom

^c Translational Radiobiology Group, Institute of Cancer Sciences, The University of Manchester, Manchester Academic Health Science Centre, Christie Hospital, Manchester, M20 4BX, United Kingdom

^d Federal Office for Radiation Protection, Department of Radiation Protection and Health, D-85764 Neuherberg, Germany

^e Radiobiology Unit, Belgian Nuclear Research Centre, SCK-CEN, B-2400 Mol, Belgium

^f Cancer Mechanisms and Biomarkers group, Radiation Effects Department, Centre for Radiation, Chemical and Environmental Hazards, Public Health England, Chilton, Didcot, United Kingdom

^g Institut de Radioprotection et de Sécurité Nucléaire, F-92260 Fontenay-aux-Roses, France

^h Helmholtz Zentrum München, German Research Center for Environmental Health GmbH, Institute of Radiation Biology, D-85764 Neuherberg, Germany

ⁱ Southern Urals Biophysics Institute, Clinical Department, Ozyorsk, Russia

^j Cell Systems and Imaging Research Group, Department of Molecular Biotechnology, Ghent University, B-9000 Ghent, Belgium

^k Pole of Pharmacology, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, B-1200 Brussels, Belgium

^l Centre for Radiation Protection Research, Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, SE 106 91 Stockholm, Sweden

^m INSERM U897, Université de Bordeaux, F-33076 Bordeaux cedex, France

ⁿ Laboratoire des Lésions des Acides Nucléiques, Univ. Grenoble Alpes, INAC-SCIB, F-38000 Grenoble, France

^o Commissariat à l'Énergie Atomique, INAC-SYMMES, F-38000 Grenoble, France

^p Commissariat à l'Énergie Atomique, BP6, F-92265 Fontenay-aux-Roses, France

^q Barcelona Institute of Global Health (ISGlobal), Centre for Research in Environmental Epidemiology, Radiation Programme, Barcelona Biomedical Research Park, 08003 Barcelona, Spain

^r Universitat Pompeu Fabra (UPF) (MTD formerly), Barcelona, Spain

^s CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

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ABSTRACT

Recent epidemiology studies highlighted the detrimental health effects of exposure to low dose and low dose rate ionizing radiation (IR): nuclear industry workers studies have shown increased leukaemia and solid tumour risks following cumulative doses of <100 mSv and dose rates of <10 mGy per year; paediatric patients studies have reported increased leukaemia and brain tumours risks after doses of 30–60 mGy from computed tomography scans. Questions arise, however, about the impact of even lower doses and dose rates where classical epidemiological studies have limited power but where subsets within the large cohorts are expected to have an increased risk. Further progress requires integration of biomarkers or bioassays of individual exposure, effects and susceptibility to IR. The European DoReMi (Low Dose Research towards Multidisciplinary Integration) consortium previously reviewed biomarkers for potential use in IR epidemiological studies. Given the increased mechanistic understanding of responses to low dose radiation the current review provides an update covering technical advances and recent studies. A key issue identified is deciding which biomarkers to progress. A roadmap is provided for biomarker development from discovery to implementation and used to summarise the current status of proposed biomarkers for epidemiological studies. Most potential biomarkers remain at the discovery stage and for some there is sufficient evidence that further development is not warranted. One biomarker

* Corresponding author.

** Corresponding author at: ISGlobal, Radiation Programme, Barcelona Biomedical Research Park, 08003 Barcelona, Spain.

E-mail addresses: janet.hall@inserm.fr (J. Hall), elisabeth.cardis@isglobal.org (E. Cardis).

identified in the final stages of development and as a priority for further research is radiation specific mRNA transcript profiles.

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1. Introduction

It is well known that exposure to IR¹ increases the risk of cancer and, at higher doses, diseases such as cardiovascular diseases and

cataracts [1,2]. However, there are important unanswered questions that need addressing to increase our understanding of the impact of low dose (below 100 mSv)/dose rate exposure (0.1 mSv min⁻¹) [3]. These include: Do tissues differ in their

¹ Abbreviations: ³H: tritium; 8-oxodG: 8-oxo-7,8-dihydro-2'-deoxyguanosine; AT: Ataxia telangiectasia; ATM: Ataxia telangiectasia mutated; ATR: Ataxia telangiectasia and Rad3 related; BER: base excision repair; bp: base pair; CBMN: cytokinesis block micronuclei; ccfDNA: Cell-free circulating DNA; CNV: copy number variant; Cs: cesium; CT: computerized tomography; CURE: Concerted Action for an Integrated (biology-dosimetry-epidemiology) Research project on Occupational Uranium; CV: coefficient of variation; CVD: cardiovascular diseases; DC: dicentric; DDR: DNA damage response; DRC: DNA repair capacity; DNA: deoxyribonucleic acid; dNTP: deoxyribonucleotide triphosphate; DoReMi: European project towards Low Dose Research towards Multidisciplinary Integration; DSB: double strand break; EPI-CT: Epidemiological study to quantify risks for paediatric computerized tomography and to optimise doses; EPR: electron paramagnetic resonance; FDXR: Ferredoxin Reductase; GWAS: genome-wide association study; HO[•]: hydroxyl radicals; HPLC-MS: Liquid chromatography-mass spectrometry; HCR: Host cell reactivation; HRR: homologous recombinational repair; HRS: hyper radiosensitivity; I: iodine; IR: ionizing radiation; IRR: increased radiation resistance; LDR: low dose rate; LET: linear energy transfer; LFS: Li-Fraumeni syndrome; lncRNA: long-non-coding RNA; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; miRNA: micro RNA; MN-RET: Micronucleated reticulocytes; MS: mass spectrometry; mRNA: messenger RNA; mtDNA: mitochondrial DNA; NBS: Nijmegen Breakage Syndrome; ncRNA: non-coding RNA; NHEJ: non-homologous end joining; NLCS: Netherlands Cohort Study; NMR: nuclear magnetic resonance; OPERRA: Open Project for European Radiation Research; PBL: peripheral blood lymphocytes; PCC: Premature Condensed Chromosome; PTC: papillary thyroid carcinoma; Pu: plutonium; qRT-PCR: quantitative reverse-transcriptase PCR; RENEB: Realising the European Network of Dosimetry EU Coordination action; RNA: ribonucleic acid; ROS: reactive oxygen species; RT: reverse transcription; SNP: single nucleotide polymorphism; SOPs: standard operating procedures; Sr: strontium; STROBE-ME: STrengthening the Reporting of OBServational studies in Epidemiology-Molecular Epidemiology; TC-FISH: telomere/centromere-fluorescence in situ hybridization; TL: telomere length; U: uranium; UNSCEAR: United Nations Scientific Committee on Effects of Atomic Radiation.

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