Title

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Journal

Radiation and Environmental Biophysics, 52(1)

ISSN

0301-634X

Authors

Little, Mark P
Azizova, Tamara V
Bazyka, Dimitry
et al.

Publication Date

2013-03-01

DOI

10.1007/s00411-012-0453-6

Peer reviewed

Comment on "Dose-responses from multi-model inference for the non-cancer disease mortality of atomic bomb survivors'" (Radiat. Environ. Biophys (2012) 51:165–178) by Scho¨llnberger et al.

Mark P. Little,[1, 2] Tamara V. Azizova,[3] Dimitry Bazyka,[4] Simon D. Bouffler,[5] Elisabeth Cardis,[6] Sergey Chekin,[7] Vadim V. Chumak,[4] Francis A. Cucinotta,[8] Florent de Vathaire,[9] Per Hall,[10] John D. Harrison,[5] Guido Hildebrandt,[11] Victor Ivanov,[7] Valeriy V. Kashcheev,[7] Sergiy V. Klymenko,[4] Olivier Laurent,[12, 13] Kotaro Ozasa,[14] Soile Tapio,[15] Andrew M. Taylor,[16] Ioanna Tzoulaki,[17] Wendy L. Vandoolaeghe,[17] Richard Wakeford,[18] Lydia Zablotska,[19] Wei Zhang,[5] Steven E. Lipshultz[20]

[1]Radiation Epidemiology Branch, National Cancer Institute, Rockville, MD, USA
[3]Southern Urals Biophysics Institute, Ozyorsk, Russia
[4]Research Center for Radiation Medicine, Kyiv, Ukraine
[5]Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards, Chilton, UK
[6]Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
[7]Medical Radiological Research Center of Russian Academy of Medical Sciences, Obninsk, Russia
[8]NASA Johnson Space Center, Radiation Health Office, Houston, TX, USA
[9]Radiation Epidemiology Group, INSERM Unité U1018, Institut Gustave Roussy, Villejuif, France
[10]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[11]Department of Radiotherapy and Radiation Oncology, University of Rostock, Rostock, Germany
[12]Program in Public Health, College of Health Sciences, University of California Irvine, Irvine, CA, USA
[13]Laboratoire d'Epidémiologie, Institut de Radioprotection et de Sûreté Nucleaire (IRSN), PRP-HOM, SRBE, LEPID, Fontenay-aux-Roses, France
[14]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima City, Japan
[15]Helmholtz Zentrum München, German Research Centre for Environmental Health, Institute of Radiation Biology (ISB), Radiation Proteomics, Oberschleissheim, Germany
[16]UCL Institute of Cardiovascular Sciences & Great Ormond Street Hospital for Children, London, UK
[17]Department of Epidemiology and Biostatistics, Imperial College Faculty of Medicine, London, UK
[18]Dalton Nuclear Institute, University of Manchester, Manchester, UK
[19]Department of Epidemiology and Biostatistics, University of California San Francisco School of Medicine, San Francisco, CA, USA
[20]Department of Pediatrics, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA

[2]Corresponding author
Mark P. Little
Radiation Epidemiology Branch
National Cancer Institute, Executive Plaza South,
6120 Executive Boulevard MSC 7238, Rockville, MD 20852-7238 USA
Tel +1 301 402 9138 (office) / +1 301 875 3413 (mobile)
Fax +1 301 402 0207
E-mail mark.little@nih.gov

We read with interest the recent paper of Scho¨llnberger et al. (2012), which assesses the nature of the dose response for blood circulatory system diseases following exposure to ionizing radiation during the atomic bombings of Hiroshima and Nagasaki. They reach the conclusions that for cerebrovascular disease, risk estimates are compatible with no risk below a threshold dose of 0.62 Gy, while for cardiovascular disease, risk estimates are consistent with no risk below a threshold dose of 2.19 Gy. Clearly, this is pertinent to the current scientific deliberations as to whether low-level exposure to ionizing radiation increases the risk of circulatory disease.

The conclusions of a recent meta-analysis of ours of circulatory disease risk following moderate and low-dose radiation exposure (Little et al. 2012) have some bearing on the conclusions of Scho¨llnberger et al. (2012). The biology of radiation-associated atherosclerosis has been subject to several extensive and recent reviews (Advisory Group on Ionising Radiation 2010; Little et al. 2008, 2010). As we state in our paper (Little et al. 2012), there are ‘‘biological data suggesting that many inflammatory end points potentially relevant to circulatory disease may be differentially regulated below and above about 0.5 Gy (AGIR 2010), emphasizing the importance of assessing risks associated with exposures of <0.5 Gy.’’ It was for this reason that in attempting to assess low-dose and low-dose rate circulatory disease risk, we chose to study groups with ‘‘exposures [with] moderate- or low-dose (cumulative mean <0.5 Sv) whole-body exposure, or exposures at a low dose rate (i.e., <10 mSv per day)’’. It should be emphasized that even though cumulative doses >0.5 Gy were of importance in generating the dose response in the occupational studies that we considered, these cumulative doses were, in general, received at a low-dose rate over many years, in contrast to the brief exposures experienced by the Japanese atomic bomb survivors.

Scho¨llnberger et al. (2012) suggest a novel method for assessing low-dose circulatory disease risk based on the established statistical technique of multi-model inference (MMI) (Burnham and Anderson 1998; Claeskens and Hjort 2008), used also in other contexts. Although not explicitly Bayesian, MMI is somewhat related to Bayesian model averaging and similar Bayesian techniques (Wang et al. 2012); these Bayesian methods have the advantage of assessing the parameter uncertainty distribution more thoroughly, albeit at somewhat greater computational cost. In particular, we are concerned that the method of Scho¨llnberger et al. may not adequately assess the uncertainties in model parameters, which Bayesian techniques can better address (Wang et al. 2012), although clearly better than what can be obtained using just a single model.

However, we doubt that models incorporating thresholds as employed by Scho¨llnberger et al. (2012) should be fitted to the Japanese atomic bomb survivor Life Span Study (LSS) cohort’s circulatory disease endpoints or any other data of this sort. There are no biological data to persuasively suggest the existence of a threshold (below which there is no modulation of effect) for inflammation or other markers relevant to circulatory disease (Advisory Group on Ionising Radiation 2010; Little et al. 2008, 2010), and so the statistical fits, while of interest, could be misleading as to the nature of the underlying dose response.

Moreover, Scho¨llnberger et al. (2012) do not analyze the current version of the LSS data (Shimizu et al. 2010) employed elsewhere (Little et al. 2012), instead using the older Preston et al. (2003) data, and restricting attention to deaths in proximal survivors from 1968 onwards, due to possible ‘‘healthy survivor’’ selection effects (Scho¨ llnberger et al. 2012). However, the evidence for these selection effects (absence of, or negative, dose response in the pre- 1968 data) is only manifest in relation to certain categories of non-cancer disease apart from circulatory disease, so that there is little justification for applying such restrictions for circulatory disease (or cancer). Also, although the later paper (Shimizu et al. 2010) has only six more years of follow-up, there is a substantial increase in numbers of deaths, so that with the more current data and removing the restriction to proximal survivors from 1968 onwards, for stroke, the total goes from 3,954 to 9,622 (12,139 if contributing causes are included) deaths, and for heart disease from 4,477 to 8,463 (14,018 if contributing causes are included). This means that their analysis loses considerable statistical power, and some of the inferences are we suspect inconsistent with the later data (e.g., the suggested threshold of 2.19 Gy for cardiovascular diseases) (Scho¨ llnberger et al. 2012).

The efforts of Scho¨llnberger et al. (2012) are to be applauded in attempting a more quantitative strategy for determining the shape of the dose response for circulatory disease, and thereby making inferences on low-dose risk. However, Scho¨llnberger et al. (2012) apply models that do not have a biological basis, fitted to a

single (LSS) data set. As such, Scho¨llnberger et al. (2012) effectively ignore the evidence that can be gleaned by comparison of radiation- induced circulatory disease risks in a number of different populations with moderate and low cumulative doses, exposed at a low-dose rate, as carried out elsewhere (Little et al. 2012). It is the broad range of scientific evidence, epidemiological and experimental, that will eventually provide an answer as to whether low-level ionizing radiation increases the risk of circulatory disease rather than an exercise of statistical fits to the data from one, albeit important, population briefly exposed to ionizing radiation

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