authors obtained from the analysis. Whereas they noted increased risk from low-dose radiation for a subset of leukaemias (ie, leukaemias excluding chronic lymphocytic leukaemia), in the summary statement they linked low-dose radiation exposure to leukaemias without any qualification. In making this statement, they neglected to mention that a negative association was noted between radiation dose and chronic lymphocytic leukaemia mortality. This type of variation in dose–response between leukaemia types—that low-dose radiation risks for specific subsets of leukaemias increase while decreasing for others—is to be expected because of statistical fluctuations, and the increased risk for one or more subsets might meet the statistical criterion for significance, especially when the lower 90% CI is used. Use of such subset data to imply overall increase in leukaemias due to low-dose radiation is misleading.

Finally, neglecting to consider the medical radiation doses of the workers in the process of assessing dose response can also affect the results of the study. In the early years of the study, cumulative medical radiation doses of the workers were small and could be neglected in comparison with cumulative occupational radiation doses. However, in later years, medical radiation dose per head is known to have increased many times over in the general population, whereas the occupational doses of radiation workers had decreased substantially. This would make cumulative medical radiation dose a significant part of the overall cumulative radiation dose of the workers, even if the workers had a somewhat reduced number of diagnostic studies per head in comparison with the general population. The neglect of cumulative medical radiation dose would therefore affect the lower dose data of later years in a major way while not affecting significantly the higher dose data of earlier years, thereby introducing a major error in the radiation exposure assignments and therefore the calculated shape of the dose–response relationship. Although the authors state that they had considered the model stratified by calendar year, data were not presented showing that the estimated radiation leukaemia risks were consistent between the entire study and the earlier and later years of the study period.

In view of these concerns, the conclusion of the publication, that the study provides strong evidence of an association between protracted low dose radiation exposure and leukaemia mortality, is not supported.

I declare no competing interests. The opinions expressed in this Correspondence are those of the author and do not necessarily represent the views of his employer.

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Authors' reply

We thank Shigenobu Nagataki and Fumiyoshi Kasagi, and Mohan Doss for their interest in our study on leukaemia risk among radiation-monitored nuclear workers in France, the UK, and the USA.[1] The authors ask for additional details on the way the study was done and raise several issues that, they suggest, seriously limit our conclusions. In the following, we address their points to clarify why we disagree with that suggestion.

Nagataki and Kasagi pose three questions. First, why was the study conducted on the basis of three countries from the 15-country study? Because of the need for efficiency in project coordination, INWORKS included three major partners from the previous 15-country study (France, the UK, and the USA); however, less than 20% of deaths from leukaemia had been contributed by the other 12 countries. The cohorts included in INWORKS were predominantly externally-exposed, had the most complete and up-to-date information on cohort eligibility and occupational dose, and were each updated for mortality since the 15-country study.[2] As a result, the INWORKS analysis yields much more precise estimates of association than the earlier 15-country study. Second, why were workers with neutron exposure and internal contamination included in our study contrary to the 15-country study? A concern raised regarding exclusion of these workers in the previous 15-country study was that the practical effect was to exclude a large number of workers with high cumulative external photon doses.[3] Therefore, in INWORKS we included these workers and then evaluated the impact of their inclusion on associations of interest; we found little evidence of potential bias due to neutron exposure or internal contamination on the estimated radiation dose–leukaemia mortality associations. Third, Nagataki and Kasagi asked how we dealt with potential confounders such as medical exposures and smoking. Although we could not directly adjust for individual histories of medical exposures or smoking histories, we controlled for temporal trends in leukaemia risk factors, such as diagnostic x-ray exposure, in the analysis. In addition to covariate control, we note that it is unlikely that smoking is a strong

confounder in view of its relatively weak association with leukaemia.

Doss also raises three concerns. First, he argues that use of a linear model for analysing dose–response associations in this study is not justifiable and he advocates for a model in which low dose radiation would reduce cancer. We did not simply assume that the data fit a linear model. We examined the relative risk of leukaemia (excluding chronic lymphocytic leukaemia) across categories of cumulative dose, observed that the trend in the excess relative risk of leukaemia (excluding chronic lymphocytic leukaemia) with dose was well described by a linear function of cumulative dose, and noted that a higher order polynomial function of dose did not substantially improve the model fit. Second, Doss notes that, in our summaries of our findings, we report that radiation exposure was associated with leukaemia. We agree with Doss that the summary statements in our abstract and conclusion could be modified to clarify that our main finding pertains to leukaemia (excluding chronic lymphocytic leukaemia); however, we expect most will correctly infer this because we clearly refer to results for leukaemia (excluding chronic lymphocytic leukaemia) in the preceding sentence of the Summary and in the Discussion. Third, Doss contends that another concern is the absence of information on doses from medical procedures, which on a population level varied over time. Individual information on radiation doses from medical procedures is unavailable in INWORKS, as is the case for most occupational epidemiology studies. However, as noted above in our response to Nagataki and Kasagi, our analyses estimate the association between occupational radiation dose and mortality within strata defined by the cross-classification of country, attained age, sex, and calendar period. Thus, for confounding to occur, medical radiation exposures would need to be associated with occupational doses, within strata defined by these adjustment factors, which is unlikely to be the case. Doss incorrectly asserts that we stated that we had considered the model stratified by calendar year. We fit no such model. Rather we fit a model that adjusted for calendar period (using a statistical method known as background stratified Poisson regression), yielding a summary estimate of the excess relative rate per gray that represents the average association over the calendar periods, which was the parameter of interest. As pointed out by Doss, INWORKS did not evaluate dose effect modification by calendar period, but we note that an analogous evaluation (for birth cohort–dose interaction) in a component cohort found no evidence of effect modification for leukaemia excluding chronic lymphocytic leukaemia.[4]

In summary, the INWORKS study (like most observational epidemiology studies) has limitations, which we believe have been adequately described in our Article, and which, in our opinion, do not greatly affect its conclusions.

We declare no competing interests.

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