Response to Invited Commentary

Richardson et al. Respond to “Missing Doses in the Life Span Study”

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The Life Span Study of Japanese atomic bomb survivors is a landmark cohort study and serves as a quantitative basis for radiation protection worldwide. In the Life Span Study, proximity to ground zero was a determinant of dose level and whether the dose was missing. Ten percent of cohort members who were within 3 km of ground zero are missing a dose; 0% of cohort members who were more than 3 km from ground zero are missing a dose. In our article in this issue of the Journal (1), we showed that a missing dose is associated not only with proximity to ground zero but also with all-cancer and leukemia mortality, particularly during the first years of follow-up.

This is of concern because recent major analyses of radiation dose-mortality associations excluded people with a missing dose, an analytical approach sometimes referred to as complete-case analysis (2). Simply excluding cohort members with a missing dose may lead to biased estimates of dose-mortality associations (2–4).

Ozasa et al. (5) reported that records held by the Radiation Effects Research Foundation provide shielding information for many people with a missing dose. Curiously, given this information, they do not see the need for a change in how they handle missing doses in their analyses. We do. In fact, the information reported by Ozasa et al. reinforces our concern that a missing dose is associated with mortality. In our article, we noted that bias in risk estimates would occur if there were unmeasured common causes of missing doses and mortality. We provided the examples of post-war migration or morbidity as causes of missing doses and mortality. Ozasa et al. enriched this discussion with additional details about important determinants of dose, number of participants with a missing dose, and mortality. They noted that people who reported being on trams or trains when the bombs were dropped are almost always missing information on the level of dose, whereas people who were at home inside wooden houses are seldom missing dose. People with disabilities or disease would be less able to ride trams and trains and therefore more frequently at home. Disability and disease related to location in trams or homes at the time of bombing are specific examples of the variables represented by “U” in our Figure 3 (1). Ozasa et al. also noted that location in concrete buildings in the city centers and bomb shelters were common reasons for a missing dose. Thus, people who were healthy enough to be employed in commercial buildings and able to move to bomb shelters were protected from radiation exposure more than people who were not. This is an example of variables represented by “V” in our Figure 3. The information that Ozasa et al. used to create their table on location at time of bombing provides additional information on common causes of exposure, mortality, and missing doses.

Ozasa et al. argued that much was known about the shielding status of survivors before the start of follow-up in 1950. Such information was used in analyses of mortality with respect to distance from ground zero, symptoms, and shielding. However, more recent quantitative dose estimates often required more detailed shielding information. Although 180,000 interviews were conducted as part of a 1949 radiation census, these interviews did not always produce sufficient information for calculating a dose. Although we clarified this point later, our initial reference to survivors having a missing dose “for reasons including a lack of interview” (1, p. 562) did not make clear that this was sometimes an additional interview with survivors who had been interviewed previously. A substantial effort to conduct shielding interviews continued into the 1960s. In current analyses, cohort members begin to contribute person time on October 1, 1950, regardless of whether sufficient information was available on that date to assign a dose to a person.

By providing interview dates and a flag for the interview that resulted in sufficient information to allow the computation of the dose metric of interest, the Radiation Effects Research Foundation could clarify the history of this important study and provide a basis for quantifying the amount of
immortal person-time that results from entering everybody into follow-up on October 1, 1950 (including survivors whose shielding information was incomplete on October 1, 1950, for the purposes of calculating dose of interest). It would be useful if this information would be shared in a structured format that is available to all interested parties.

Ozasa et al. did not discuss the relationship between dose and missing dose introduced by the decision to require shielding interviews for proximal survivors but not distal survivors. Assignment of all distal survivors to the lowest dose group induces a relationship between dose, missing dose, and potential for immortal person-time for survivors whose shielding information was incomplete on October 1, 1950. This relationship leads to biased risk estimates because immortal person-time, which causes underestimates of death and incidence rates, can only occur among proximal survivors (6).

In summary, Ozasa et al. (5) do not show that a complete-case analysis approach to missing data is an appropriate method for analysis of this cohort. However, there is the possibility for future work to draw on the information that the Radiation Effects Research Foundation has at their disposal for addressing the problem of missing dose. When extra detailed information on subsets of cohort members exists, it can be used to improve the validity of the estimates for the entire cohort. Ozasa et al. are impressed by the “remarkable achievements” of the early surveys of atomic bomb survivors, as are we. However, remarkable achievements may still be imperfect. Such imperfections are common in observational research and pose both challenges and opportunities for investigators.

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REFERENCES