



# Radiation Effects on Cognitive Function Among Atomic Bomb Survivors Exposed at or After Adolescence

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## ABSTRACT

**BACKGROUND:** The objective of this study was to investigate radiation effects on longitudinal pre-dementia cognitive decline among participants who developed dementia as well as on those who did not develop dementia during follow-up.

**METHODS:** Measuring cognitive function with the Cognitive Abilities Screening Instrument approximately every 2 years, we followed 1844 atomic bomb survivors participating in the Adult Health Study of the Radiation Effects Research Foundation from 1992 to 2011. Participants were adolescents or older when exposed to between 0 and 4 Gy. Approximately 15% and 40% of participants were exposed to  $\geq 1$  Gy and  $< 5$  mGy, respectively. At study start, participants were dementia-free and between 60 and 80 years old. Three-quarters of the participants returned after baseline, averaging 8.4 years of follow-up. During follow-up, 313 developed dementia. We used cognitive scores before dementia onset for analysis and a mixed-effects model to estimate radiation effects on longitudinal change of cognition, adjusting for dementia occurrence, age, sex, and education.

**RESULTS:** Cognition level was significantly associated with age, education, and dementia occurrence but not with radiation dose or sex. Cognitive decline accelerated with increasing age, especially among participants who developed dementia. Neither radiation nor education was significantly associated with the degree of deterioration with age. Radiation did not modify the different cognitive decline by dementia occurrence.

**CONCLUSIONS:** Radiation did not significantly affect cognition among atomic bomb survivors exposed at or after adolescence.

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The improved survival rates over the last decades among those who received radiation therapy for childhood cancer has resulted in the detection of neuropsychological dysfunction in adulthood.<sup>1,2</sup> Findings as to neurocognitive function among adult cancer survivors, however, are conflicting, except for the well-known occurrence of radiation encephalopathy as an acute reaction in patients receiving conventional high-dose radiation therapy.<sup>3-6</sup> Separating the adverse effects of radiation from those of chemotherapy and the malignant disease itself is often difficult.<sup>3</sup>

Since 1958, the Adult Health Study (AHS) of the Radiation Effects Research Foundation (RERF), consisting of

atomic bomb survivors who were within 2000 m of the hypocenter at the time of bombing (approximately two-third of subjects) and age- and sex-matched subjects who were beyond 3000 m (approximately one-third of subjects), has conducted biennial examinations to investigate the health effects of exposure to ionizing radiation from the atomic bombings, up to now.<sup>7</sup> Atomic bomb radiation doses were lower than those used in radiation therapy, and they were single and external. Individual doses were estimated by some dosimetry systems introduced later. In April 1992 in Hiroshima, we initiated the study of cognitive function<sup>8</sup> and dementia occurrence<sup>9,10</sup> for AHS participants who at that time were  $\geq 60$  years old (those  $\geq 13$  years old at the atomic bomb). Our previous cross-sectional study on cognition at baseline examination (1992-1996 in Hiroshima and 1993-1998 in Nagasaki) found no radiation effect.<sup>8</sup> Neither the prevalence of dementia between 1992 and 1996<sup>9</sup> nor the incidence of dementia between 1992 and 2003 after excluding prevalent cases<sup>10</sup> among Hiroshima AHS subjects showed radiation effects on dementia occurrence.

Although some reports investigate change of cognitive function over a relatively long period (eg, 10-15 years),<sup>11</sup> we could only find 2 covering radiation-exposed subjects by radiation therapy for malignant tumor.<sup>12,13</sup> In this study, we investigate the effects of radiation on longitudinal cognitive decline before dementia onset while accounting for age, sex, and education. Subtle physiologic changes in the brain possibly induced by radiation may be more evident before dementia onset than after; for this reason, we consider cognitive decline before dementia onset. Participants included those who developed dementia during follow-up and those who did not.

## METHODS

In Hiroshima, from 1992, we initiated a study of cognitive function and dementia incidence among AHS participants who at that time were  $\geq 60$  years old.<sup>14</sup> The RERF institutional review boards (Research Protocol Review Committee and Human Investigation Committee) reviewed and approved this study, and all participants provided informed consent.

### Assessment of Cognitive Function and Dementia Occurrence

We assessed cognitive function at baseline using the full Cognitive Abilities Screening Instrument (CASI).<sup>15</sup> The score range is 0-100, and typical administration time is 15-20 minutes. To reduce the total time required for the health checkup,

we selected domains that showed large aging effects in previous CASI analyses<sup>16</sup> and used it as "CASI-short" (CASI-s) with a score range of 0-49. The CASI-s tests language (repeat 3 words, name 5 objects), short-term memory (recall 3 words, recall 5 objects), recall digits backward, serial subtraction, orientation (age, time, place), and verbal fluency of animal names. From the baseline full CASI, we then used only the aforementioned items to obtain a baseline CASI-s score. Using CASI-s scores from baseline and follow-up, we assessed the trajectories of cognitive function.

To determine whether the participants had dementia,<sup>14</sup> we used the 2-phase procedure (screening and detail check) established in a US-Japan cross-national study.<sup>17</sup> The consensus panel evaluated the presence of dementia and subtypes based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and other diagnostic criteria.<sup>9,10</sup> For participants with dementia, the onset date was determined by caregiver information or as the midpoint between the date of first dementia diagnosis and the date of the previous disease-free examination. Details are described elsewhere.<sup>9,14</sup>

## CLINICAL SIGNIFICANCE

- Little is known about the effects of radiation exposure on trajectories of pre-dementia cognitive function.
- In this analysis of survivors exposed to atomic bomb radiation at or after adolescence, radiation did not significantly or substantially affect cognition during long-term follow-up.
- These findings provide no reason to believe exposure to lower doses of radiation at or after adolescence has a deleterious effect on late-life cognitive function.

## Study Participants

The participants in this study were part of the original AHS cohort. The makeup of this subset was very similar to the full cohort with respect to distance from hypocenter and radiation dose: approximately one-third were beyond 3000 m, and most of their radiation doses were 0 or almost 0 (less than 5 mGy). We started with 7585 CASI-s observations from 2367 participants, excluding observations made after dementia onset. We excluded 867 observations from 260 participants who were missing radiation dose information, 51 observations from 25 participants who were missing education (23) or birthdate (2) information, 464 observations from 229 participants who were more than 80 years old at study start, 76 observations from 50 participants who were more than 90 years old at the time of observation, and 29 observations taken within 6 months of a previous measurement from the same participant. Finally, we eliminated 24 observations from 9 participants who had very little education ( $\leq 5$  years), which preliminary analyses showed to have substantial impact on inferences involving education.<sup>18</sup> Our final data set had 6074 observations from 1844 participants. Of those, 443 (24%) supplied only 1 CASI-s measure, whereas the remaining 1401 participants supplied 2 or more observations, contributing 11,733 person-years. Dementia was found in 313 participants who contributed 882 observations (with 70 or 22% of these participants

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