

## **The impact of unobserved heterogeneity and competing risks with shared frailty in radiation risk assessment**

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Unobserved heterogeneity, or *frailty*, in survival data can bias estimation of the associations of interest due to selection of the subjects over follow-up. While frailty, which could potentially exist in any analysis including randomized controlled trials, is likely to have a large impact through a long follow-up, accounting for frailty is still uncommon in epidemiological risk assessments.

As a motivating example, this study focuses on analysis to evaluate the effects of radiation exposure on incidence of multiple types of cancers in a long term follow-up of an exposed population. Generally, cancer occurrence is affected by a number of factors other than the exposure of interest, e.g., lifestyle, socio-economical, and genetic background, and missing any of them may introduce frailty in analysis of the study population. In addition, it is plausible that subjects might be heterogeneous in sensitivity to radiation exposure (i.e., some might be more resistant to radiation than others), which is, however, not measurable. Under such a circumstance, the study population is expected to become less and less frail (i.e., those who are less prone to cancer and/or more resistant to radiation exposure gradually become dominant in the risk set) as the follow-up proceeds. This shift is likely to proceed more quickly in the exposed than in the unexposed, which would affect estimation of the time-varying risk coefficients. Furthermore, if such a source of frailty for an endpoint (incidence a cancer type) is shared by a competing risk event (incidence of another cancer type), this type of selection bias will become even larger and complicatedly distort the dose response estimation with a conventional approach of treating censoring due to such a competing risk event as non-informative.

The main objective of the current study is to evaluate the extent to which risk estimates might be biased when a competing risk of shared frailty is present but not appropriately accounted for in a cohort study of Japanese atomic bomb survivors (Grant et al., *Radiat Res*, 2017; Ozasa et al., *Radiat Res*, 2012). In particular, simulation studies are conducted to show that the dose response estimation of a late-onset radiation associated cancer can be largely distorted by not accounting for informative censoring of an early-onset cancer with a shared frailty. This might partly explain the observed variations in radiation-associated risk estimates and their apparent dependences on time-scale factors among the cancer types.