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"Interaction between a Single Exposure and Age in Cohort-based Hazard Rate Models Impacted the Statistical Distribution of Age at Onset"

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Study Findings

This research showed that the standard practice of assessing interaction between age and exposure to infer risk modification (how the magnitude of risk depends on other factors related to age that are not directly measured) also impacts the statistical distribution of age at onset of the outcome. The implication is that two phenomena—effect modification by unmeasured variables correlated with age, and distribution of onset-age among exposed persons—are both affected by a single interaction parameter in the statistical analysis model. Hence, there is confounding of that parameter by two effects that cannot be distinguished without further information. We therefore recommend that either 1) additional data on specific age-related effect modifiers be obtained and included as covariates in the analysis or 2) biological information about the effect of exposure on the onset-age distribution be incorporated into the analysis model.

Explanation

This methodological research was carried out to elucidate the particular form of exposure-by-age interaction reported by Sakata et al. in their analysis of radiation effects on age at menopause in the RERF Life Span Study (LSS) (*Radiation Research* 2011; 176:787–795). In an additive (excess absolute rate) model, they reported that radiation risk was modified by a log-linear function of (log of age)-squared. Because biological considerations predict that some, but not all, exposed women may experience accelerated onset of menopause, we sought to assess how the reported age modifier impacted the onset-age distribution.

1. Study purpose

Interaction between exposure and various age-time scales is commonly studied in epidemiologic risk analyses. Age at exposure, time since exposure, and age at risk (or attained age, the advancing age throughout follow-up) are frequently tested for interaction with radiation dose in follow-up studies of risk. The primary motivation for examining such interactions is that underlying, but unmeasured, biological factors that are correlated with these age-time scales may be modifying the radiation risk. Because the actual modifying factors are not measured, the interactions are assessed using the age-time scales as surrogates. For example, risk for exposure may be modified by growth leading to carcinogenic promotion; hence, there may be an age-at-exposure effect on risk. Aging may lead to genomic instability, allowing past mutations to be expressed; hence there may be an effect of advancing age on risk. Carcinogenesis is known to be a multi-stage process, so that accumulation of multiple exposures may increase risk; hence, there may be a time-since-exposure effect. However, because age is the underlying time scale used for comparing rates between exposed and non-exposed persons, it is apparent that if increased risk is not constant with age, some statistical interaction between age and exposure may be required to adequately capture the effect of exposure on the age at onset. We therefore undertook to study how exposure-by-age interaction impacts the statistical distribution of age at onset.

2. Study methods

Based on the data of Sakata et al. (2011), we performed statistical analyses using various forms of exposure-by-age interaction for both additive (excess absolute rate) and multiplicative

(excess relative risk) models. We noted that the menopause onset-age distribution in non-exposed women could be approximated by a normal distribution. We then derived the resulting onset-age distributions among exposed women using statistical theory that relates the risk and survival functions to the density function (distribution of onset age).

3. Study results

We discovered that the form of interaction between exposure and age, including the basic model (whether a relative or absolute risk model) has a substantial impact on the estimated distribution of age at onset of outcome among exposed persons. For the type of onset-age distribution seen with menopause, an interaction between radiation dose and the square of log age, after dividing by age 50, on the absolute risk scale was most consistent with what would be expected from biological and clinical considerations. In other words, risk was stochastic, meaning that some exposed women experienced early menopause whereas other exposed women did not, such that the distribution of onset age spread out towards younger ages. Other forms of age modification, such as using the log of age (rather than the square of log of age) or no modification at all, or using age modification with a relative risk model, produced unnatural shapes of onset-age distribution. Most notably, no age modification with an additive (excess absolute rate) model led to the conclusion that risk of menopause increases with radiation exposure at all ages, including ages prior to menarche, which is implausible.

Study Significance

Our study has implications for analyses of RERF data in general, because the onset-age distributions of chronic diseases, such as cancer and cardiovascular disease, in older age adults have similar constraints in that the risk is low or nonexistent in the very young. It is common practice in RERF risk analyses to include interactions with age to assess how risk varies with age as a surrogate for underlying physiological or biological processes that are correlated with age but which are not measured. The implication is that, because interaction with age may be necessary to correctly specify the underlying onset-age distribution and only a single interaction model can be used, researchers should be aware of these competing needs and consider carefully how their fitted models are interpreted in terms of the onset-age distribution, something that is rarely done in risk analyses.

The Radiation Effects Research Foundation has studied A-bomb survivors and their offspring in Hiroshima and Nagasaki for more than 60 years. RERF's research achievements are considered the principal scientific basis for radiation risk assessment by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and for recommendations regarding radiation protection standards by the International Commission on Radiological Protection (ICRP). RERF expresses its profound gratitude to the A-bomb survivors and survivors' offspring for their cooperation in our studies.

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