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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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Abstract

Objective: Statistical interaction between a single, instantaneous exposure and attained age (age during follow-up; attained age = age at exposure + time since exposure) is used in risk analyses to assess potential effect modification by unmeasured factors correlated with age. However, the impact of such interaction on the statistical distribution of age-at-onset of outcome (disease or death) is infrequently assessed. We therefore explored the impact of such interaction on the shape of the onset-age distribution.

Study Design and Setting: We use for illustration age-at-onset of radiation-related early menopause in a cohort of female Japanese Atomic Bomb Survivors. The statistical distribution of age-at-onset was derived from a parametric hazard rate model fit to the data, assuming an underlying Gaussian onset-age distribution among nonexposed women.

Results: Commonly used forms of exposure-by-age (attained age) interaction led to unnatural estimates of the age-specific rate function and unreasonable estimates of the onset-age distribution among exposed women, including positive risk of menopause before menarche.

Conclusion: We recommend that researchers examine the distribution of age-at-onset and exposure-age interaction when conducting risk analyses. To distinguish this from potential etiologic interaction between exposure and unmeasured factors represented by age as a surrogate, richer models or additional data may be required.

Keywords: Cohort study; Effect modification; Excess absolute rate; Menopause; Onset-age distribution; Risk analysis

1. Introduction

Epidemiologic risk assessment focuses on how the occurrence of an outcome, such as disease incidence or mortality, is associated with a particular exposure variable and its possible interaction with other factors (risk modification or effect modification). Additivity is sometimes regarded by epidemiologists as the appropriate scale for assessing biological or mechanistic interaction [1], but the scale on which joint effects of risk factors are analyzed should be chosen according to biological considerations [2,3]. Here, we consider a single, instantaneous exposure, so the relation (attained age) = (age at exposure) + (time since exposure) holds. The term ''age'' refers to ''attained age'' (age at risk during follow-up) throughout this article. Because age is frequently the primary time scale of interest with observational epidemiologic data [4], hazard rate models for outcomes occurring in middle or older age, such as chronic diseases, should generally incorporate some interaction between exposure and age because the excess absolute rate might not be constant in age. Furthermore, examination of interactions between risk factors and age is warranted when comparing multiplicative and additive scales for risk [5].

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What is new?

Key findings

- Statistical interaction between exposure and attained age (age at exposure + time since exposure) has implications for the shape of the distribution of onset age in risk analyses. This seems to be hardly recognized despite the frequent use of such interaction for assessing potential effect modification using age as a surrogate for unmeasured age-related factors.

What this adds to what was known?

- We illustrate how exposure-by-age (attained age) interaction affects the onset-age distribution among exposed persons and show that it can produce unnatural results, including a positive risk of exposure-related outcome when the outcome is physiologically not possible. Such results may go unnoticed in standard analyses.

What is the implication and what should change now?

- Using age as a surrogate to assess interaction between exposure and unmeasured age-related factors requires greater consideration. In particular, an exposure-by-age (attained age) interaction cannot simultaneously capture both the effect of the exposure on the onset-age distribution (statistical interaction) and the risk-modifying effects of unmeasured age-related factors (effect modification), rendering such an interaction term difficult to interpret.

In other words, there may be constraints on the statistical distribution of age-at-onset among exposed persons, but such constraints are not routinely examined in standard epidemiologic risk analyses. A natural way to handle such constraints is via an interaction between exposure and attained age in the statistical model. However, attained age is also frequently considered as a surrogate for unmeasured, underlying biological processes that may interact mechanistically with—or modify the effect of—the exposure, so the question arises whether mechanistic interaction between exposure and age as a surrogate can be distinguished from the need for the rate to depend on age due to constraints on the onset-age distribution. Unfortunately, many studies involving a test of interaction between exposure and age, where the interaction might reflect age-related acceleration of onset in a subset of the exposed individuals, do not mention this distinction [6−12], and we could find few examples of the use of an additive hazard rate model for testing interaction [13,14].

Although the age dependence of the risk can be visualized using a plot of the rate (or hazard function), such a plot typically does not immediately convey features of the onset-age distribution that might require constraints. Because of direct connections between the cumulative incidence proportion (the distribution function, also one minus the survival function), hazard function, and onset-age distribution (the density function), it is relatively straightforward to examine a plot of the onset-age distribution derived from the output of standard survival analyses. Doing so can reveal features of the rate that constrain the statistical interaction between exposure and age. We explore this issue with radiation-related acceleration of age at menopause in the Life Span Study cohort of female Japanese Atomic Bomb Survivors. The results apply also to outcomes such as total mortality or cancer incidence that have restricted ranges of age at occurrence of outcome. The results indicate the need for careful interpretation of what is called ‘‘effect modification’’ by age.

2. Methods

Consider the effect of a single, instantaneous radiation exposure on subsequent female menopause, which in the absence of exposure has an onset-age distribution limited typically to about a decade in middle life (approximately between ages 45−55 years). Radiation exposure to the ovaries can result in loss of fecundity and early menopause due to ovarian failure [15,16], and the LD_{50} of the human oocyte is <2 Gy [17]. Sakata et al. [18] reported that atomic bomb radiation exposure leads to accelerated age at menopause among female survivors. Ignoring the competing risk of artificial menopause, which is related to radiation through uterine myoma and other conditions leading to surgically induced menopause [19], their model for the age-specific incidence of natural menopause included a background rate depending on attained age, city of residence at the time of the bombing, year of birth, parity, smoking behavior, and age at menarche, as well as an excess rate depending on ovarian dose of radiation in weighted Gray (Gy_w, using weight 10 for the neutron component and weight 1 for the gamma component). The excess rate also included a log-linear modification term including age at exposure and a quadratic function of the natural logarithm of attained age (scaled to have value 0 at age 50 years). Cumulative incidence proportions were presented, with estimated median acceleration of age at menopause being 0.5 and 0.8 years for women exposed to 1.0 and 1.5 Gy_w, respectively, compared with women exposed to under 0.4 Gy_w and nonexposed women combined, because a threshold of 0.4 Gy_w was indicated [[18], p. 793]. Their plot is essentially reproduced here (Fig. 1A) based on a normal distribution approximation to the menopause-age distribution among nonexposed women and the model of Sakata et al. [18] for the risk among exposed women (Fig. 1B). The normal approximation was used to facilitate comparisons among the hazard rate model, cumulative incidence proportion, and onset-age density function.