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“Selection of reference groups in the Life Span Study of atomic bomb survivors”

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Study Findings

In an analysis of the Life Span Study (LSS) solid cancer incidence data, different choices for the reference group of unexposed individuals resulted in radiation risk estimates that varied by -7.5% to +9.8%, and reduced evidence for curvature in the radiation dose response.

Explanation

In controlled experiments, random assignment of exposure levels to study participants ensures that the different groups are comparable with respect to the distribution of all factors, other than the exposure, that are related to the outcome. In observational studies, however, due to the absence of randomization, the exposure-outcome association can be distorted if the exposure groups differ with respect to measured and unmeasured factors that are also associated with the outcome. (These factors are referred to as “confounders.”) In observational cohort studies, such as the LSS of atomic bomb survivors, an approach to reduce the potential impact of these confounders is to select an appropriate reference group of unexposed individuals. If exposure levels differ among cohort members, then a group of individuals who were either unexposed or exposed to low levels can be used as an internal reference group. Otherwise, a group of unexposed individuals from outside the study cohort can be used as an external reference group.

1. Study Purpose

Our goal was to illustrate strategies for analyzing cohort studies with multiple reference groups but without adequate data on potential confounding factors, with the LSS as an example. We assessed the sensitivity of radiation risk estimates for solid cancer incidence to the choice of the reference group. We considered zero-dose proximal (within 3km of the hypocenter) and zero-dose distal (beyond 3 km from the hypocenter) survivors, and their combination, as internal reference groups. We considered city residents who were not in either city at the time of the bombings (not-in-city residents) as an external reference group.

2. Study Methods

We reanalyzed the data from the most recent analysis of solid cancer incidence in the LSS (Grant et al., 2017). We used identical analysis methods, but in different analyses used different reference groups. We compared the results to those obtained using a type of standardized incidence ratio in the regression model. We focused on sex-averaged excess relative risks and the shape of the dose-response curve.

3. Study Results

Selection of an internal reference group (zero-dose proximal and/or zero-dose distal survivors) provided radiation risk estimates that were similar to those obtained using internal standardization and provided strong evidence for a curvilinear dose-response among males. In particular, compared to internal standardization, the more-simple model with zero-dose proximal survivors as the reference group provided a better fit to the data. However, models with an external reference group (not-in-city residents) did not fit the data as well, and provided larger radiation risk estimates (+9.8%) and less evidence for a curvilinear dose-response among males.

Study Significance

Based on our analysis, we recommended that analysts consider the following two questions when analyzing the LSS solid cancer incidence data. First, should the reference group include zero-dose proximal and/or zero-dose distal survivors? Our results indicated that a model with zero-dose proximal survivors as the reference group fit the data well and provided inference that was identical to

that obtained from models with internal standardization. Second, should the reference group include not-in-city residents? Our results indicated that inclusion of not-in-city residents in the reference group resulted in either a poorly fitting model or spurious conclusions. Therefore, we recommended that the analysis include all participants (all zero-dose survivors and not-in-city residents) and adjust for city-specific risk differences among distal survivors and not-in-city residents. Including distal survivors and not-in-city residents in this way should provide more information on the effects of age, sex, and time, while minimizing the potential for unmeasured confounding.

The Radiation Effects Research Foundation has studied A-bomb survivors and their offspring in Hiroshima and Nagasaki for around 70 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.

^s*The European Journal of Epidemiology*, published for the first time in 1985, is a peer-reviewed medical journal on the epidemiology of communicable and non-communicable diseases and their control. The results of epidemiologic studies are essential arguments for action in the field of public health policies, and this journal can be used to influence decision makers. (Impact factor in 2016/2017: 7.226)