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CARDIOVASCULAR DISEASE MORTALITY OF A-BOMB SURVIVORS AND THE HEALTHY SURVIVOR SELECTION EFFECT

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The latest A-bomb survivor data for cardiovascular diseases are analysed to investigate whether in the first years after the bombings the baseline rates of proximal survivors were markedly different compared with those of the distal survivors. This phenomenon relates to a healthy survivor selection effect. This question is important for the decision whether to include or exclude the early years of follow-up when analysing the biological effects from acute low and high dose exposures following the nuclear weapons explosions in Hiroshima and Nagasaki. The present study shows that for cerebrovascular diseases and heart diseases the baseline rates are not significantly different in the first two decades of follow-up. Thus, for these two detrimental health outcomes, there is no need to exclude distal survivors and the first decades of follow-up time when investigating the shapes of the related dose–responses.

INTRODUCTION

The Life Span Study (LSS) cohort of A-bomb survivors has been analysed extensively for long-term effects from low, medium and higher doses of ionising radiation under acute exposure conditions. Detrimental health outcomes that have been investigated include various cancer- and non-cancer-related diseases, e.g. mortalities from various cardiovascular diseases including cerebrovascular diseases (ICD-9 codes 430–438) and cardiovascular diseases excluding cerebrovascular diseases (ICD-9 390–429, 440–459; here, referred to as heart diseases)[1]. Recently, an extensive reanalysis of the LSS Report 13 data from Ref.[1] has been performed by Schöllnberger *et al.*[2] for cerebrovascular diseases and heart diseases using a larger series of dose–response models including various step and hormesis-like models in addition to the linear-no-threshold (LNT) model, quadratic, linear-quadratic and linear-threshold models that had already been tested[1]. Following the approach of Preston *et al.*[1], in their reanalysis Schöllnberger *et al.*[2] used exactly the same subset of data, i.e. follow-up starting in 1968 and restricting the analyses to proximal survivors (i.e. survivors who were within 3 km of the hypocentre at the time of the bombing). As will be further detailed below, the reason for this restriction had been the finding of a so-called healthy survivor selection effect for the biological endpoint of all non-cancer diseases that leads to spurious curvature of the dose–response[1]. Related to this reanalysis valuable comments had been presented by Little *et al.*[3] who criticised the restrictions in follow-up time and with respect to proximal survivors. The present study was triggered by this letter of comment. Here, it is shown that there is indeed no healthy survivor effect within the latest LSS mortality data[4, 5] for cerebrovascular diseases and heart diseases.

HEALTHY SURVIVOR SELECTION EFFECT

In the context of characterising the shape of the dose–responses for various non-cancer diseases, Preston *et al.*[1] state that this characterisation is complicated by a 'healthy survivor' selection effect: 'For a few years after the bombings, baseline (zero dose) non-cancer disease death rates for proximal survivors were markedly lower than those for distal survivors. The difference diminished steadily over the first two decades of follow-up, by which time it had largely vanished. This statistically significant pattern, which has the nature of the classical "healthy worker" effect often seen in occupational studies, suggests that proximal survivors included in the LSS were initially healthier than the general population for reasons related to their selection by having survived the bombings. In particular, analyses of the LSS non-cancer mortality data indicate that in 1950 baseline death rates for proximal survivors were 15 % lower than those for distal survivors. The difference decreased to about 2 % in the late 1960s'. A substantial healthy survivor selection leads to spurious curvature in the dose–response (illustrated in Fig. 9 of Ref.[1]). Preston *et al.* had found a substantial healthy survivor effect for all non-cancer diseases (ICD-9

codes 0–139, 240–279, 290–799). Given this finding they restricted all of their analyses of non-cancer diseases (including cerebrovascular diseases and heart diseases) to the sub-datasets of proximal survivors with follow-up starting in 1968[1].

METHODS

For the present study, the latest publicly available LSS data for cerebrovascular diseases and heart diseases were used. Details about these grouped data have been provided[4, 5]. The data were analysed with the MECAN software package that facilitates the application of risk models to radio-epidemiological datasets[6]. MECAN allows the fitting of model parameters, an analysis of the observed versus the expected cancer or non-cancer risk and the estimation of confidence intervals (CI) for risk variables. It uses Poisson regression to estimate the values of the adjustable model parameters by fitting the model to the data. For the minimisation of the Poisson likelihood MECAN applies Minuit2[7].

For plots of the crude rates the data were stratified by sex, ground distance (<3 km, 3–10 km), age at exposure, age attained and weighted colon dose. Then, for each of the resulting categories the crude rates were calculated as the number of death cases divided by the number of person-years within each category. The crude rates were then plotted versus the mean age in the specific category.

An LNT model, implemented as an excess relative risk (ERR) model, was fitted to the full datasets for cerebrovascular diseases and heart diseases. The general form of an ERR model is as follows: $h = h_0 \times (1 + ERR(D))$, where h is the total hazard function, h_0 is the baseline model and the function $ERR(D)$ describes the change of the hazard function with weighted colon dose D. No dose effect modifiers were applied. Therefore, the model had the following form: $h = h_0 \times (1 + err \times D)$, where err is the slope of the LNT model (free parameter) and h_0 a parametric baseline model (for the mathematical form of this modified exponential function confer Eq. (A1) in the Supplementary material of Ref.[2]; this form of baseline model had also been used by Preston *et al.*[1]). The parametric baseline functions of the ERR-LNT models were plotted using the maximum likelihood estimates of the baseline parameters. Due to the acuteness of exposure, there is a one-to-one relationship between age at exposure and birth cohort. The figures were produced for an age at exposure of 50 y, which corresponds to birth cohort 1895.

RESULTS

The main results are shown in Figures 1 and 2. Here, the baseline death rates (i.e. number of deaths from the lowest dose category (0–5 mGy) per 10^4 person-years of follow-up) are plotted versus calendar year for birth cohort 1895. Clearly, for both detrimental health outcomes, the baseline rates for proximal male survivors are not significantly different compared with those of distal male survivors (for cerebrovascular diseases, for example, the crude rates of male distal and male proximal survivors at an attained age of 75 y are 190 and 212 per 10^4 person-years, respectively. The difference of 22 per 10^4 person-years is well within the size of the 95 % CI, cf. Figure 1). The same is true for females. Other birth cohorts yield similar results (not shown). The parametric baseline functions (dashed lines) show consistency with the crude rates.

DISCUSSION AND CONCLUSIONS

In their letter of comment Little *et al.*[3] state that Schöllnberger *et al.*[2] restricted their attention to deaths in proximal survivors from 1968 onwards, due to possible 'healthy survivor' selection effects. In their commentary[3] they specify that '...the evidence for these selection effects (absence of, or negative, dose–response in the pre-1968 data) is only manifest in relation to certain categories of non-cancer disease apart from circulatory disease, so that there is little justification for applying such restrictions for circulatory disease (or cancer)'. Indeed, the results of the present study clearly showed the absence of a healthy survivor selection effect for cerebrovascular diseases and heart diseases in the latest LSS data on atomic bomb survivors. Consequently, when analysing the shape of the related dose–responses there is no need to exclude distal survivors and the first decades of follow-up time to prevent spurious curvature. This finding is in line with the study of Shimizu *et al.*[4] and was not yet reflected in the reply by Schöllnberger *et al.*[8] to the comment by Little *et al.*[3]

For all circulatory diseases (ICD-9 codes 390–459) of LSS Report 14, Ozasa *et al.*[9] found that the difference between the dose–response curves for the early period of follow-up (1950–65) and the late period (1966–2003) was not significant. Using the LSS Report 13 data, Nonaka *et al.*[10] used a change point model for the background death rate, i.e. they allowed the background model to change at a certain point in time (free parameter). They also allowed different mathematical functions for the proximal–distal baseline rate difference over time. With this approach Nonaka *et al.*[10] allowed to distinguish between two different contributions to differences in the baseline mortality rates of proximal and distal survivors: one contribution from a constant baseline-rate difference that reflects demographic effects (for example, differences from urban and rural lifestyles) and another one that reflects possible time-dependent changes in the baseline-rate difference between proximal and distal survivors. The latter relates to the healthy

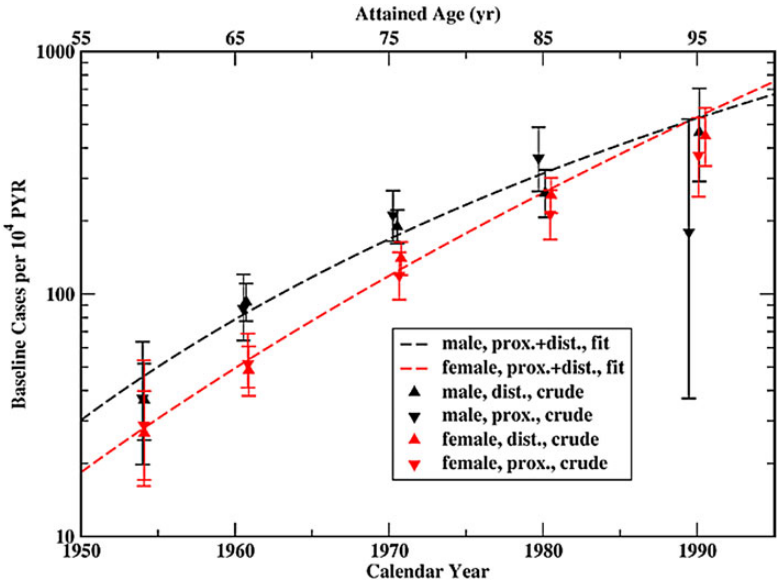

Figure 1. Baseline rates for mortality from cerebrovascular diseases versus calendar year for birth cohort 1895. For the lowest dose category (0–5 mGy) the crude rates (i.e. number of cases divided by number of person-years within each category) are provided on the *y*-axis. Error bars represent the 95 % CI. Dashed lines: plot of the parametric baseline functions using the maximum likelihood estimates from two fits of ERR-LNT models to the full datasets of males and females. Symbols and lines in black refer to males; symbols and lines in red (in online version) refer to females.

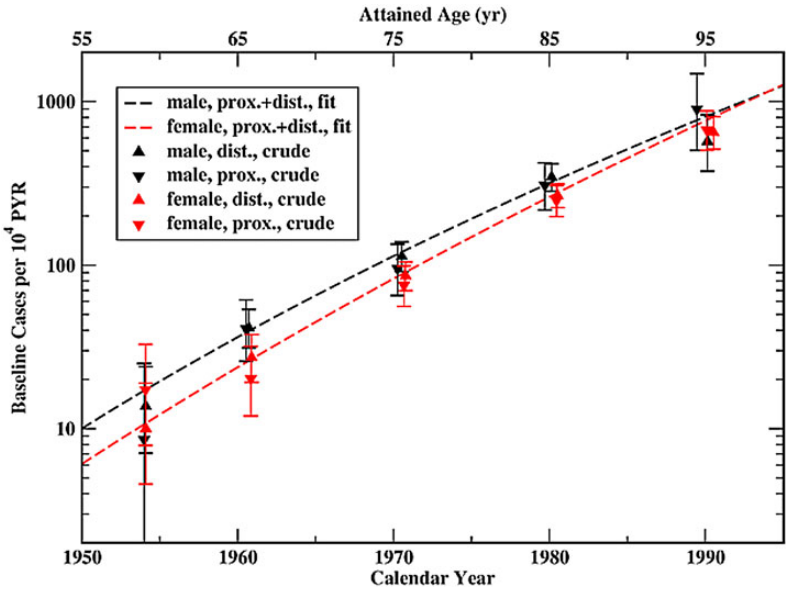

Figure 2. Baseline rates for mortality from heart diseases versus calendar year for birth cohort 1895. For the lowest dose category (0–5 mGy) the crude rates (i.e. number of cases divided by number of person-years within each category) are provided on the *y*-axis. Error bars represent the 95 % CI. Dashed lines: plot of the parametric baseline functions using the maximum likelihood estimates from two fits of ERR-LNT models to the full datasets of males and females. Symbols and lines in black refer to males; symbols and lines in red (in online version) refer to females.

survivor selection effect. For all cardiovascular diseases (i.e. sum of cerebrovascular diseases and heart diseases) their preferred model contains two different background death rates with a change point at 1968 and a constant 3 % difference of baseline rates between proximal and distal survivors (Model C in Table 2 of Ref.[10]). The difference of 3 % was not statistically significant, i.e. there was no healthy survivor effect for cardiovascular diseases. This result lends support to the findings of the present study.

Extensive analyses of the latest publicly available full datasets for cerebrovascular diseases and heart diseases using a larger number of different dose–response models for the excess risk from radiation together with the statistical technique of multi-model inference are ongoing at the Institute of Radiation Protection (ISS), Helmholtz Zentrum München.

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