Supplementary Material 1. Epidemiological methods for evaluating risks from radiotherapy.

Most information on long-term risks from radiotherapy derives from epidemiological studies of cancer survivors. Because many health effects of interest do not occur until many years after the first cancer diagnosis, long-term follow-up is essential. Thus, study results cannot directly reflect the effects of the most recent treatment regimens, although extrapolation may sometimes be possible using dose–response relationships.

In a cohort study, a defined population is followed forward in time to evaluate the occurrence of specified diseases. Disease rates are usually compared with those of the underlying general population by estimating standard incidence ratios (SIRs), obtained as the ratio of the observed number of cancers (O) to the expected number of cancers (E). The excess absolute risk (EAR) is often estimated as the difference in rates, which can be calculated by subtracting the expected number of cancers in the cohort from the observed number, dividing the difference by the person-years of follow-up, and multiplying this value by 1000. In case–control studies, subjects with and without a specified disease (case subjects and control subjects, respectively) are compared with respect to the exposures of interest. The much smaller number of subjects needed for case–control studies often makes it feasible to obtain the detailed data on radiotherapy needed to estimate radiation doses to organs of interest for individual patients. Analyses focus on evaluating the dose–response relationship by estimating relative risks (RRs) by level of radiation dose (with minimally exposed subjects serving as the referent group), and by expressing the excess relative risk (ERR = RR – 1) as a continuous function of radiation dose. A linear model is often used for this latter purpose, and departures from linearity are investigated.