

## **Investigation on circular asymmetry of geographical distribution of mortality risk in Hiroshima atomic bomb survivors**

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### **ABSTRACT**

While there are a considerable number of studies on the relationship between the risk of disease or death and direct exposure from the atomic bomb in Hiroshima, the risk for indirect exposure caused by residual radioactivity has not yet been fully evaluated. One of the reasons is that risk assessments have utilized estimated radiation doses, but that it is difficult to estimate indirect exposure. To evaluate risks for other causes, including indirect radiation exposure, as well as direct exposure, a statistical method is described here that evaluates risk with respect to individual location at the time of atomic bomb exposure instead of radiation dose. The proposed method is applied to a cohort study of Hiroshima atomic bomb survivors. The resultant contour map suggests that the region north-west to the hypocenter has a higher risk compared to other areas. This in turn suggests that there exists an impact on risk that cannot be explained by direct exposure.

### **INTRODUCTION**

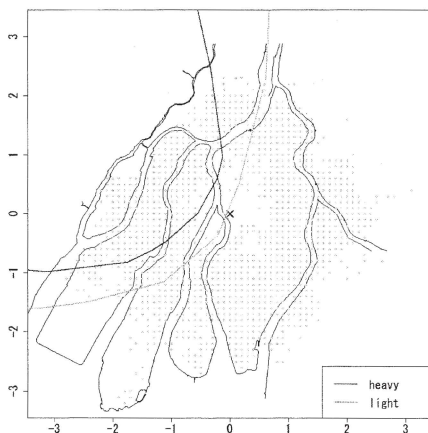
The risk of disease or death caused by exposure to atomic bomb radiation has been evaluated using estimated radiation doses based on information concerning age, shielding conditions and distance from the hypocenter under the assumption that the radiation dose decreases with increasing distance from the hypocenter (see, e.g., Preston et al 2007; Matsuura et al. 1997). For details of the dosimetry system used, see e.g. DS02 system (Cullings et al. 2006; Young and Kerr 2005). The corresponding risk analyses focused solely on the risk from direct exposure to the atomic bomb, while the risk from indirect exposure due to residual radioactivity has been not evaluated in previous analyses. This means that the geographical distribution of risk has been structurally restricted to concentric circles under the assumption that the influence of direct exposure essentially depends on the distance from the hypocenter. For example, Peterson et al. (1983) have fitted Cox's proportional hazard models to cancer mortality rates, to investigate circular asymmetry around the hypocenter in Hiroshima and Nagasaki. Gilbert and Ohara (1983) have analyzed data on acute symptoms. They divided the survivors in the Life Span Study (LSS) cohort, registered at the Radiation Effect Research Foundation (RERF), into eight groups according to the survivors' location at the time of atomic bomb exposure relative to the hypocenter and evaluated the relative risk of each octant compared with that for survivors in the octant of east-north-east direction. However, we consider their approach to be not enough to investigate circular asymmetry around the hypocenter, because they evaluated only relative risks for each octant with respect to the location at exposure relative to the hypocenter and did not consider heterogeneity of risk in each octant.

Recently, survivors suspected of having suffered from indirect exposure were reported by Kamada et al. (2006), Kamada and Kawakami (2008), and Tonda et al. (2008) through biological studies and statistical analyses of the incidence of leukemia among the survivors who entered Hiroshima City on August 6, 1945, after the explosion of the atomic bomb. Furthermore, several questionnaire surveys (Uda et al. 1953; Masuda 1989) showed that so-called "Black Rain", which might have included radioactivity, fell around the western part of Hiroshima City and the northwest suburbs for several hours just after the explosion. Ohtaki (2011) demonstrated spatial-time distributions of Black Rain using a nonparametric smoothing method applied to data from a questionnaire survey conducted by Hiroshima City in 2008, of about 37,000 inhabitants of Hiroshima and its suburbs who might have experienced Black Rain.

In the present paper, a statistical method is applied to evaluate the risk with respect to individual location at exposure rather than dose, and construct a "risk map", i.e. a map based on the risk evaluated by location, to visually grasp the geographical distribution of risk without structural restrictions. The risk map allows discussing possible effects of indirect exposure due to "Black Rain" and other radioactivity on risk of mortality.

## DATA

The database of Atomic Bomb Survivors (ABS), registered at the Research Institute for Radiation and Medicine (RIRBM) at Hiroshima University, was used in the present study. The ABS differs from the LSS of the RERF, because the ABS cohort includes examined survivors residing in Hiroshima Prefecture, and data on health status for survivors also have been cumulatively compiled in the database. The extent of overlap between survivors in the ABS and the LSS was examined by Hayakawa et al. (1994) and Hoshi et



**FIGURE 1.** Plot of location at exposure on the map of Hiroshima City, where the vertical and horizontal scales are the coordinates in units of kilometers with the origin being the hypocenter (red cross); Gray points represent locations of survivors at the time of exposure; Red and green lines represent the boundary of heavy and light rainfall area of "Black Rain" based on Uda's questionnaire survey.

al. (1996). Hayakawa et al. (1994) showed that the dose estimates of the ABS were close to those of the LSS among the overlapped subjects. However, it has not been tested how they agree to DS02.

From the ABS, we chose 37,382 subjects for analysis who satisfied the following conditions: (i) being alive and recognized as an atomic bomb survivor as of January 1, 1970 and (ii) having coordinate information on location at the time of atomic bomb exposure (abbreviated in the following as “location at exposure”). These subjects were followed until December 31, 2009. The endpoint is death from all causes (number of deaths: 19,119). Subjects were treated alive at the end of follow-up, in case migration and loss to follow-up for other reasons as censoring (number of subjects: 18,263). Mesh coordinates of 100 m in width were used to define location at exposure (Hoshi et al. 1996). Sex, age at atomic bomb exposure (abbreviated in the following as “age at exposure”) and shielding condition were used as covariates. Figure 1 is the scatter plot of location at exposure with the hypocenter as the origin (cross). Gray lines represent the map of Hiroshima city according to the town planning map made between 1925 and 1928. The vertical and horizontal scales are the coordinates in units of kilometers with the origin being the hypocenter. The red and green lines are boundary of heavy and light rainfall area of “Black Rain” based on Uda’s questionnaire survey (Uda, et al. 1953). Note that upper left region of boundary is rainfall area.

## STATISTICAL METHOD

Data containing information on location are called “spatial data”. Several methods for analyzing spatial data have been proposed, depending on the type of outcome. Geographically weighted regression (GWR), proposed by Fotheringham et al. (2002), corresponds to multiple linear regression analysis of spatial data. GWR is essentially repeated local multiple linear regressions applied to data in the neighborhood of a given location. The GWR approach can be extended to logistic regression for spatial binary data and Poisson regression for spatial count data, but the methodology for spatial survival data, such as those in the study of atomic bomb survivors, still remains to be developed. Recently, Tonda and coworkers (Tonda et al. 2010) proposed a statistical method for spatial data by extending a method proposed for longitudinal data (Satoh and Yanagihara 2010; and Satoh et al. 2009). Their approach is applicable not only to spatial continuous and discrete data but also to spatial survival data. In the present paper a method is developed for estimating the geographical distribution of mortality risk for atomic bomb exposure by extending Cox’s proportional hazards model for spatial survival data (Tonda et al. 2010); the resulting method is applied to a cohort study of Hiroshima atomic bomb survivors.

Consider the proportional hazards model with spatially varying coefficients, which allows the effect of covariates to vary with location. Let  $(u, v)$ ,  $r$ ,  $t$ ,  $sex$  and  $atb$  denote location at exposure, registered age, attained age, gender ( $sex = 1$  if male,  $sex = 0$  if female), and age at exposure. The proportional hazards function with spatially varying coefficient is then given by

$$h(t | u, v, t > r) = h_0(t | shielding) \exp(\beta_l(u, v) + \beta_s \times sex + \beta_a \times atb) \quad (1)$$

where  $h_0(t | shielding)$  is the baseline hazard function dependent on the shielding condition, and  $\beta_l(u, v)$  is the spatially varying coefficient, and  $\beta_s$  and  $\beta_a$  are ordinary regression coefficients that

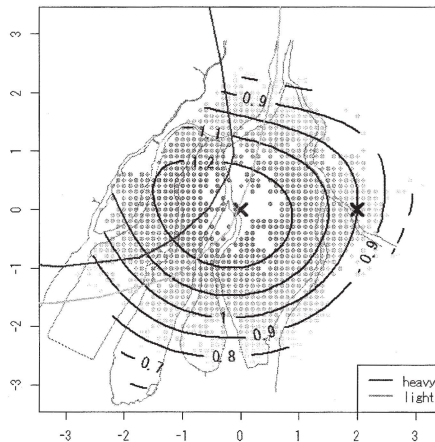
are constant with regard to location at exposure. Note that Eq. 1 represents an ordinary Cox model if the spatially varying coefficients are replaced by constant coefficients. Therefore, Eq. 1 represents an extension of a Cox model, and the interpretation of coefficients in Eq. 1 is similar to that with a Cox model. In particular,  $\exp(\beta_j(u, v))$  denotes the hazard ratio compared with the location as the reference.

It is assumed that the shape of  $\beta_j(u, v)$  is in a class described by linear combinations of unknown parameters  $\theta$  and known basis functions  $x(u, v)$ . We use a polynomial surface basis, which is commonly used in the field of spatial interpolation (Ripley 1981; Venables and Ripley 2002). For example, a quadratic polynomial surface basis is given by  $x(u, v) = (1, u, v, u^2, v^2, uv, u^2v, uv^2, u^2v^2)'$ . To obtain a smoother shape for the spatially varying coefficient, one can use, for example, a B-spline or a Gaussian basis. Details are given in Satoh et al. (2003), Ruppert et al. (2003), and Konishi and Kitagawa (2010).

For spatial survival data,  $\{(u_i, v_i), \delta_i, t_i, sex_i, atb_i; i = 1, \dots, n\}$ , where  $\delta_i$  denotes the indicator variable specifying whether subject  $i$  is censored or not at time  $t_i$ , with 1 denoting a failure and 0 denoting censored, the unknown parameters  $\theta$ ,  $\beta_s$  and  $\beta_a$  can be estimated by maximizing the partial likelihood (Cox 1972; 1975). Let  $\hat{\theta}$  denote the estimator of  $\theta$ ; the estimator of  $\beta_j(u, v)$  is expressed by  $\hat{\beta}_j(u, v) = \hat{\theta}'x(u, v)$ . Theoretical properties of  $\hat{\beta}_j(u, v)$  are given in Tonda et al. (2010). Any further discussion of the methodology for confidence regions and tests for  $\beta_j(u, v)$  are beyond the scope of this paper; for additional information, see Tonda et al. (2010).

## RESULTS

The proposed method was applied to data from a cohort study of Hiroshima atomic bomb survivors. The method is easy to implement using statistical packages that execute Cox model, such as SAS, SPSS,



**FIGURE 2.** Estimated risk map of mortality based on the quadratic polynomial model. Values on the contours are hazard ratios compared with the reference location (blue cross) that is 2 km from the hypocenter to the east. The red and green lines represent the boundary of heavy and light rainfall area of "Black Rain" based on Uda's questionnaire survey.

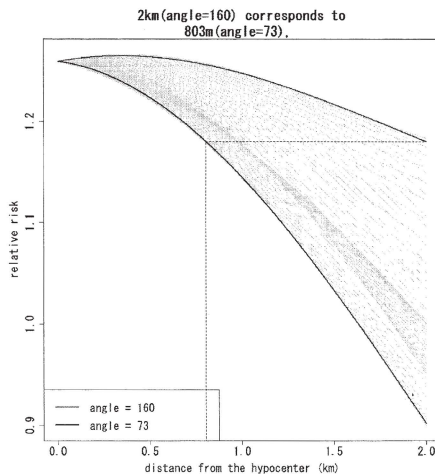
STATA and R. We here used the “survival” package version 2.36-10 in R version 2.14.1 (R Development Core Team 2010).

**TABLE 1.** Estimated coefficients for the quadratic polynomial model.

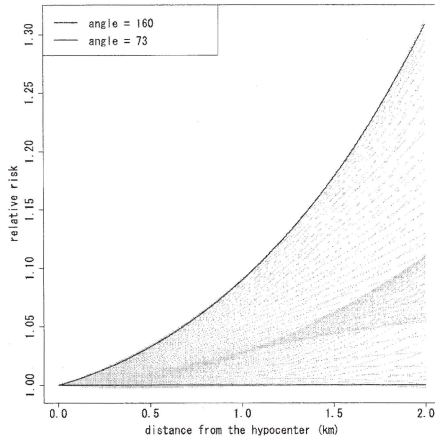
Parameter	Estimates	Standard Error	z-value	p-value
$\beta_s$	0.569	0.0149	38.296	< 0.001
$\beta_a$	0.007	0.0006	12.388	< 0.001

Figure 2 shows the estimated risk map of mortality risk based on the quadratic polynomial model, while Table 1 shows the estimated coefficients of  $\beta_s$  and  $\beta_a$ . In Figure 2, the contours on the map represent the hazard ratio,  $\exp(\beta_j(u, v))$ , for each location compared with the reference location, marked as the blue cross, that is 2 km from the hypocenter towards the east. From Figure 2 it can be seen that the mortality risk decreases with increasing distance from the hypocenter, but the geographical distribution of the risk map is not concentric: The north-west area appears to have a higher risk compared with other areas.

In Figure 3, the decreasing trend of risk with distance from the hypocenter by direction of location at exposure defined by angle from the hypocenter is compared. Angles  $160^\circ$  (about west-direction) and  $73^\circ$  (about north-north-east direction) had highest and lowest relative risks, respectively. Figure 3 also suggests that the risk at 2 km from the hypocenter at angle  $160^\circ$  corresponds to the risk at 803 m at angle  $73^\circ$ . Figure 4 shows the differences of relative risks by angle from the hypocenter compared with those of angle  $73^\circ$  (about north-north-east direction). Figure 4 suggests that the differences of relative risks become



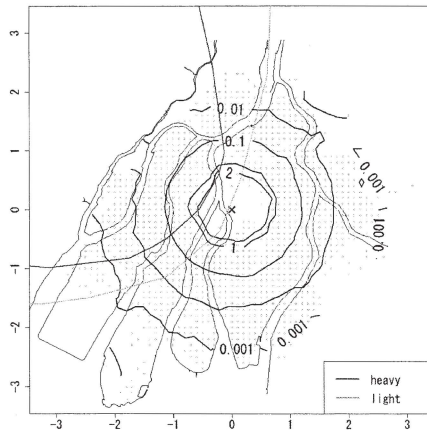
**FIGURE 3.** Comparison of decreasing trend of relative risks with distance from the hypocenter by angles of location at exposure. The red and blue curves denote the highest and lowest trend, whose angles are  $160^\circ$  (about west-direction) and  $73^\circ$  (about north-north-east direction).



**FIGURE 4.** Comparison of increasing trend of relative risks, relative to those at angle 73° (about north-north-east direction), with distance from the hypocenter by angles of location at exposure.. large with distance from the hypocenter.

**DISCUSSIONS**

Figure 5 presents the contour map based on estimated direct radiation dose (Hoshi et al. 1996; Matsuura et al. 1997) averaged by location at exposure, where the red and green lines are boundary of heavy and light rainfall area of "Black Rain" based on Uda's questionnaire survey. From Figure 5 it can be seen that



**FIGURE 5.** Geographical distribution of location-averaged radiation dose. Values on the contours represent the average of radiation dose (Gy) by location at exposure. The red and green lines represent the boundary of heavy and light rainfall area of "Black Rain" based on Uda's questionnaire survey.

the geographical distribution of direct radiation dose is close to concentric circles. This means that if the risk due to causes other than the direct exposure was negligible compared with that of direct exposure, then the contours in the risk map should be well approximated by concentric circles. If not, however, the risk contours should be far from concentric and circular. According to Figures 2 to 4, the resultant risk map for a cohort of Hiroshima atomic bomb survivors (Figure 2) suggests that the quadratic polynomial contours are suitable indeed, but not concentric circles. This suggests that there existed risk factors other than direct radiation exposure.

As was mentioned in the introduction, several questionnaire surveys showed that Black Rain, which might have included radioactivity, fell around the western part of Hiroshima city and north-west suburbs for several hours just after the explosion. According to the latest results on the geographical distribution of Black Rain (Ohtaki 2011) and Uda's rainfall area described in Figure 2, the area of rainfall appears roughly similar to the region of high risk in Figure 2. This similarity suggests that Black Rain might be a possible risk factor accounting for the geographical distribution of cancer mortality in Figure 2. It should be noted, however, that there might be other risk factors affecting mortality such as socioeconomic status, life style and environmental factors which are probably unrelated to radiation exposure due to the atomic bomb. These factors might correlate through association with particular regions, but this will be difficult check.

Note that Peterson et al. (1983) have also studied the circular asymmetry around the hypocenter in Hiroshima and Nagasaki for the LSS cohort of RERF. They divided the survivors into eight groups by the octants according the survivors' location at exposure and fitted a Cox's proportional hazard model. According to their results, the survivors in the west-north-west octant had the highest risk and the relative risk of survivors in the west-north-west compared with those in the east-north-east was about 1.24. As was mentioned in the introduction, their approach suffered from a lack of continuity of risks within groups and between groups. Therefore, they could not grasp any regional spatial trend of risk within and between octants. On the other hand, our results for the ABS cohort of RIRBM can be used to understand the spatial trend visually. Our result in Figure 3 is roughly consistent with the areas with higher risks in Peterson et al (1983). In addition, Figure 4 shows that the differences in the relative risk among angles of location at exposure become larger with increasing distance from the hypocenter, while Peterson e al. (1983) could only evaluate the relative risks by octants. In this sense, our results are somewhat more valuable than those of Peterson et al (1983).

In this paper, we focused on death from all causes and evaluate its risks with respect to individual location at the time of atomic bomb exposure instead of radiation dose. Tonda et al. (2012) have analyzed data on solid cancers and evaluated risks of cancer mortality by applying the similar approach. In addition, they also considered to split the risks into separate risks due to direct exposure and other causes using a mathematical model of carcinogenesis (Ohtaki et al. 1985; Pierce and Mendelsohn 1999; Ohtaki and Niwa 2001; Pierce and Vaeth 2003).

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