Reported Occurrence of Severe Epilation vs. Location and Dose Estimates among the Life Span Study Cohort of Atomic-Bomb Survivors

CULLINGS Harry[1]

[1] *Radiation Effects Research Foundation* hcull@rerf.or.jp

Abstract

There has long been a concern that clinical symptoms of acute radiation injury, reported by survivors in the questionnaires used by the Atomic Bomb Casualty Commission (ABCC) in the 1950s to gather information for creation of the Life Span Study cohort, were reported at low but non-zero proportions in relatively distal survivors. Because the data were self-reported, there were various potential sources of error that could have resulted in false-positive data. In the most definitive RERF studies, severe epilation (of scalp hair) has been considered to be the most specific and reliable of the reported symptoms potentially related to acute radiation injury. The data on severe epilation: 1,288 cases in Hiroshima and 384 in Nagasaki, have been subjected to a new, exploratory spatial analysis, to see if there are any patterns that might plausibly be associated with exposure to residual radiation. A method used by RERF investigators in 1983 to check for circular asymmetry about the hypocenters, by comparing compass octants in various directions, was repeated with DS02 dose estimates, and a parametric model for dose response including octant indicators was also fitted. In addition, the cities were divided into 200-yard-square geospatial cells and spatial plots were made of the proportions in the cells to allow visualization of any patterns that might exist. A result was that all of the cells with more than a few cases of severe epilation were within about 1.6 km of the hypocenters, consistent with the epilation expected for the corresponding DS02 doses. Among the more distal cells were a number of cells with one or two cases per cell, which are increasingly sparse at longer distances and otherwise appear to be randomly distributed in location – no pattern potentially associated with fallout is obvious on visual inspection. In the future these data may be further analyzed with spatial methods appropriate for binomial random variables with possible spatial autocorrelation, which must also correct for expected proportions due to DS02 dose.

Introduction

Several of the main forms used to collect data on atomic-bomb survivors in the early days of ABCC, such as the Radiation Questionnaire, Migration Questionnaire, and Master Sample Questionnaire(1), were designed to record information on symptoms known at the time to be associated with acute exposure to relatively large doses of ionizing radiation. Individual data on three of those symptoms: epilation (loss of scalp hair), purpura (bleeding under the skin), and oropharyngeal lesions (sores of the mouth and throat) are coded in a database at RERF that dates from the time of dosimetry system T65D(2), and were available for this work. These data were studied in various early reports, such as an early report on the Life-Span Study (LSS) cohort of atomic-bomb survivors studied by ABCC and RERF(3). It was noted that very small but non-zero proportions of survivors reported symptoms at distances where the estimated doses received directly from the bombs were far smaller than the estimated threshold dose for occurrence of the symptoms[3]. In 1983, Gilbert and Ohara studied severe epilation and purpura in a report motivated by issues that had been raised about T65D, using dose estimates made with early prototypes of Dosimetry System DS86[4]. They studied the dose response in different shielding categories and performed a partial spatial analysis in which they looked at compass direction from the bomb hypocenters by dividing the data into compass octants according to survivors' locations at the times of the bombings and making comparisons among octants. In 1988 Stram and Mizuno analyzed the data on severe epilation to compare results of dose-response analyses performed with DS86 doses to those performed with T65D doses[5].

The investigations reported in 1983 and 1988 were aimed at resolving issues about the direct doses calculated by the dosimetry systems, and not residual radiation sources. Among other considerations, estimated maximal doses from residual sources, which were analyzed in detail in Chapter 6 of the DS86 Final Report, were far too low to produce such symptoms. However, in recent years, there have continued to be questions raised about the possibility of fallout associated with "black rain" that may have occurred in areas not well documented by the field surveys of gamma-ray exposure rates performed by U.S. and Japanese teams in 1945 and 1946[6], particularly in Hiroshima. In addition, Endo and colleagues have suggested that previously unaccounted beta dose may have increased the total skin dose associated with exposure to local fallout and made it more plausible that some cases of epilation could have been caused by fallout[7]. For these reasons it may be of interest to know whether there are apparent spatial patterns in the occurrence of the symptoms after adjusting for the effect of direct doses calculated by the newest dosimetry system, DS02.

Choice of Outcome Measure for Analysis

Table 1 presents a complete cross-tabulation of members of the LSS with data on acute symptoms, including the vast majority with no symptoms, showing all possible combinations of symptoms. There are 25,930 members, virtually all in the "not in city" control group, who lack data on symptoms; only 440 survivors with known DS02 doses and located at distances < 2,000 m in either city have missing data.

The proportions reporting the various symptoms are plotted in Figure 1 with linear segments connecting them; the category boundaries are at 0.1, 0.5, 1, 2, 3, 4, and 5 Gy, and the proportion for each category is plotted at the category midpoint; the value for the final category – all survivors with dose estimates exceeding 5 Gy – is plotted at 5.5 Gy, although a few survivors in this category have dose estimates much greater than 6 Gy. Severe epilation exhibits a typical sinusoidal (S-shaped) response, which can be fitted with a standard function used in plotting the probability of binary responses vs. dose, such as a logit or probit. Purpura, although it attains a maximum response almost equal to that of severe epilation, exhibits an oddly convex shape over the entire dose range above 0.5 Gy, and would require further study to determine whether a plausible dose-response function could be fitted, perhaps with some re-scaling of the dose metric. Oropharyngeal lesions exhibit an odd pattern similar to purpura, but with a maximum response about 70% of severe epilation. Mild and moderate grades of epilation show almost no dose response.

Table 1 Cross-tabulation of three symptoms of acute radiation exposure in RERF database.

			Hiroshima		Nagasaki	
Purpura	Oropharyngeal lesions	Severe Epilation	N	%	N	%
-	-	-	58,258	92.7	30,022	93.6
+	-	-	1,705	2.7	667	2.1
-	+	-	732	1.2	491	1.5
-	-	+	381	0.6	141	0.4
+	+	-	858	1.4	527	1.6
+	-	+	349	0.6	60	0.2
-	+	+	78	0.1	30	0.1
+	+	+	479	0.8	153	0.5
		Total	62,840		32,091	

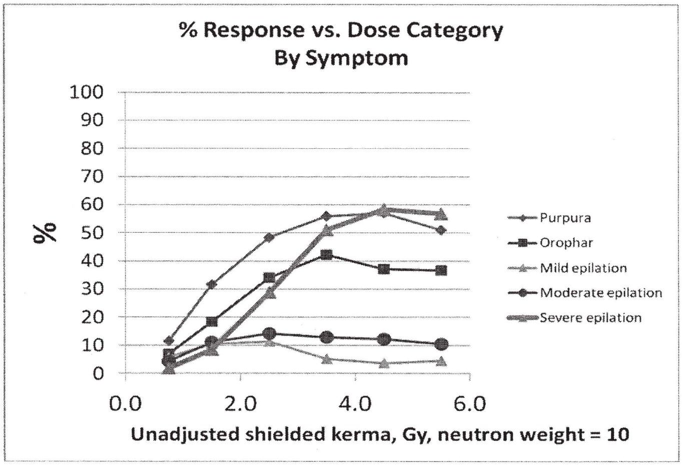


Figure 1 Crude dose-response of available symptoms.

Severe epilation is thought to be the most specific symptom for acute exposure to ionizing radiation, and has been the main symptom of choice in previous studies(3,4,5). The combination of all three symptoms (severe epilation, purpura, and oropharyngeal lesions) is expected to be even more specific to ionizing radiation than severe epilation alone, and indeed the survivors reporting all three symptoms have a substantially smaller proportion at distances > 1.6 km than the totality of those reporting all combinations including severe epilation; however, the total numbers are much smaller, as shown in Table 1. Based on these considerations, all of the analyses reported here were done with severe epilation alone as the outcome. Some analyses were repeated with the simultaneous occurrence of all three symptoms as an outcome, but patterns were similar to severe epilation alone.

Re-analysis of Compass Octants Using the Non-parametric Methods of Gilbert and Ohara with DS02 Doses

Gilbert and Ohara used a special method to correct for the effect of several covariates (age, sex, direct radiation dose estimate) on severe epilation, without assuming a parametric model for the risk as a function of the covariates(4). They divided the data into many strata based on cross-classification by ordered categorical values of the covariates, and then they used the Mantel-Haenszel formulation to sum the results of the 2x2 tables, one table per stratum, that compare each compass octant to all of the other octants. For example, males who were in their 30s at the time of the bombings and had neutron and gamma doses in particular ranges might define one stratum, and one would make a 2x2 table for that stratum comparing the proportion with severe epilation in Octant 1 vs. the total proportion with severe epilation in Octants 2 through 8. Gilbert and Ohara used prototype pre-DS86 doses that were available at the time from the Lawrence Livermore National Laboratories (LLNL) in the U.S., with a correction for house shielding developed by Marcum of Oak Ridge National Laboratories(4). Their analysis was repeated for the present work using DS02 doses, but two shielding categories that were calculated by LLNL are not available in DS02: survivors in concrete buildings, and those in miscellaneous shielding not modeled by DS86 or DS02, such as streetcars, other vehicles, etc.(2). Therefore these shielding categories were analyzed as a separate dose category with unknown dose for this work. Proximal and distal survivors were analyzed separately, as by Gilbert and Ohara, using 1.6 km in Hiroshima and 2 km in Nagasaki to distinguish proximal from distal.

Table 2 Results of Nonparametric Analysis Using Compass Octants: All Proximal Survivors

		ENE	NNE	NNW	WNW	WSW	SSW	SSE	ESE
Gilbert, Hiroshima	OR	1.18	1.64	1.82	0.81	0.69	0.90	1.16	0.87
	p-val	0.26	0.025	<0.001	0.08	0.005	0.43	0.24	0.18
This work, Hiroshima	OR	1.10	1.19	1.51	0.75	0.88	1.07	1.14	0.88
	p-val	>0.5	0.49	0.002	0.023	0.34	>0.5	0.32	0.23
Gilbert, Nagasaki	OR	1.04	1.14	0.63	1.05	1.97	1.03	0.86	0.91
	p-val	0.50	0.46	0.14	>0.5	0.043	>0.5	0.38	>0.5
This work, Nagasaki	OR	0.66	1.03	0.86	0.77	1.05	1.22	1.10	1.03
	p-val	0.31	>0.5	>0.5	0.37	>0.5	0.32	>0.5	>0.5

Results for all proximal survivors combined, from the present work, are compared to those of Gilbert and Ohara in Table 2, and results from this work for the more detailed classifications of Gilbert and Ohara, based on dose and distance, are shown in Table 3. In Table 3, to save space, only the odds ratios with p-values < 0.05 are shown. Note that the p-values have not been corrected for the multiple comparisons involved. In considering only the eight octants for proximal survivors in two cities in Table 2, a conservative Bonferroni correction would

Table 3 Results of Nonparametric Analysis Using Compass Octants: Odds Ratios for Detailed Categories: Octants with p-values < 0.05.

Hiroshima				Nagasaki			
Category	Octant	OR	p-value	Category	Octant	OR	p-value
Proximal, 0 to 500 mGy	SSE	1.99	0.014	Proximal, 0 to 500 mGy	SSW	2.71	0.007
Proximal, 500 to 2000 mGy	NNW	1.94	<0.001	DS02 dose unknown	WNW	2.51	0.004
DS02 dose unknown	SSW	0.29	0.003	DS02 dose unknown	WSW	4.96	<0.001
DS02 dose unknown	SSE	1.70	0.003	DS02 dose unknown	SSW	0.46	0.01
Distal	NNW	0.50	0.028	Distal	NNE	3.75	0.022

suggest that an experiment-wise p-value of 0.05 requires an individual comparison to have p < 0.05/16 = 0.0032, by which only the high odds ratio for the north-northwest quadrant, found in both the analyses of Gilbert and Ohara and in this work, is significant. The detailed categories, which involve five times more comparisons, for three proximal dose categories plus a distal category and a category for unknown DS02 dose, require a correspondingly smaller p, and perhaps the only significant results are the high odds ratios for the middle proximal dose category in the NNW octant in Hiroshima, and the unknown dose category in the WSW octant in Nagasaki. Less conservative methods than Bonferroni are available for adjusting the p-values for multiple comparisons, but the emphasis here will be placed on the parametric models and spatial plots to be described next, rather than debating the statistical significance of the odds ratios in Table 3. The three dose categories of Gilbert and Ohara have unclear spatial boundaries due to variable shielding among individual survivors, and the detailed octant comparisons are not as useful as some of the other spatial methods described below and being investigated for future work.

Analysis by Parametric Models

Proportions with severe epilation vs. dose category are shown separately for the main DS02 shielding categories[2] in Figure 2. One clear feature is that the response for Nagasaki factories is distinctly lower than the other shielding categories. Another is a pronounced downturn at high doses for the "average house" category. This is a category for survivors who had some indication from one of the questionnaires that they were in a light wooden building, but did not have a shielding history collected. The downturn at high doses is consistent with the idea that, in the "average house" category even more than the other shielding categories, a large proportion of the dose estimates > 4 Gy are erroneous, because they are inconsistent with the estimated median lethal dose (LD_{50}) for humans. The human LD_{50} is typically considered to be in the range from 3 to 4 Gy[8], although it may be less than this for the atomic-bomb survivors, particularly in that many survivors suffered combined injury involving blast trauma or thermal injury, many other stresses and lack of medical care. Questionably high doses were avoided in the model fitting for this work by using only survivors whose estimated weighted shielded kerma, with a neutron weight of ten, was less than 4 Gy. In addition, the doses used were adjusted for the effect of dose error by applying factors derived by Pierce, Stram and Vaeth[9], and model fitting was restricted to proximal survivors, i.e., < 1.6 km in Hiroshima or 2 km in Nagasaki. The shape of the dose response for severe epilation in the corresponding dose range suggested that the observed response was due completely or preponderantly to direct DS02 dose, and that fitting a model using DS02 dose estimates and other covariates would allow the proportion of epilation due to direct dose to be subtracted out so that any excesses due to other causes in geographically limited parts of the proximal areas would be more apparent.

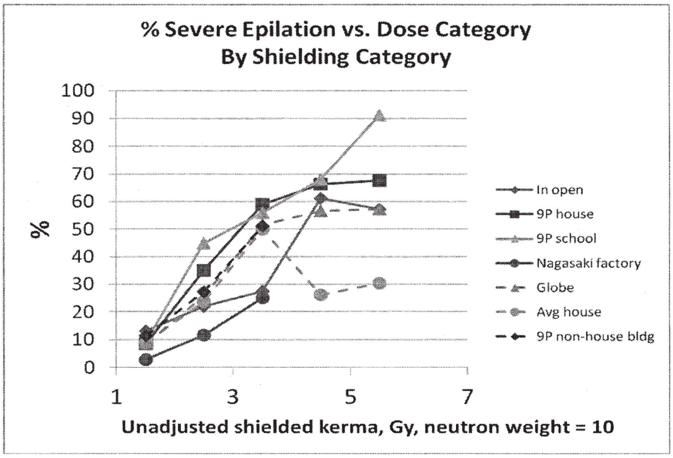


Figure 2 Crude dose response of severe epilation in different shielding categories.

If the aforementioned restrictions are used, the proportions with severe epilation can be fitted well with a logistic regression using only DS02 dose as the independent variable, as shown in Figure 3, which compares the proportions for individual dose categories to the fitted curve. A neutron weight of ten gives an estimated median dose of about 3 Gy, which is more consistent with accepted values for epilation than the median dose ~2 Gy suggested by a neutron weight of one. For example, the ICRP suggests a threshold of 3 Gy for temporary epilation[10], and it is well established that *tinea capitis* (ringworm) was routinely treated by using a dose of 3.3 to 3.5 Gy to the scalp to induce temporary complete epilation[11]. A neutron weight of ten is also consistent with the findings of Stram and Mizuno[5]. The fitted logistic function for a neutron weight of ten in Figure 3 suggests that fallout deposition would have to be quite large to substantially affect the probability of epilation. For example, a dose ~1.8 Gy would be necessary to cause ~10% epilation in the absence of any appreciable direct dose. Even using the integrated first-month beta dose per unit ^{137}Cs deposition of 500 mGy kBq^{-1} m^2 ^{137}Cs calculated by Endo *et al.*[7], which is at least 17 times larger than corresponding integral of gamma dose calculated by Imanaka[12], this would require fallout deposition corresponding to at least 1800 mGy/500 mGy kBq^{-1} m^2 ^{137}Cs = 3.6 kBq m^{-2} ^{137}Cs, a larger deposition than any known for the Hiroshima bomb, and on the order of the Nishiyama fallout in Nagasaki. For example, deposition in a sample near the known Koi-Takasu fallout area of Hiroshima was estimated at about 0.36 kBq m^{-2} ^{137}Cs by Shizuma *et al.*, based on analysis of the Nishina soil samples[13].

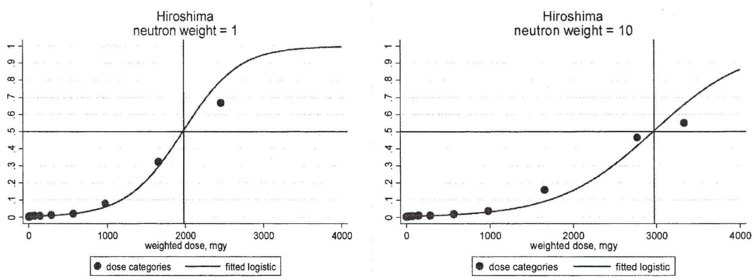


Figure 3 Fitted logistic regression models using only DS02 adjusted shielded kerma.

A complete model-selection procedure was performed separately for each city to find the best model for severe epilation using the same inclusion criteria, with indicators for combinations of age and sex, for shielding categories, and for compass octants. The only octant indicator that was retained in the final model for either city was that for a high OR in the NNW octant in Hiroshima, consistent with the results of the nonparametric analysis. Based on the results for the two cities, a combined model was developed. No octant indicators were used in the combined model, because the intent was to correct for direct dose and other covariates and then use spatial methods other than compass octants to look for remaining patterns. Terms for city and interaction of city with direct dose (i.e., a different dose response in each city) were also tested and rejected in developing the model. The final model, shown in Table 4, has interesting implications.

In the table we report the estimated coefficients rather than the associated odds ratios, i.e., we report the estimated β_i s in the equation $\Pr(severe\ epilation) = \frac{e^{\beta_0+\beta_1 I_1+...+\beta_{k-1}I_{k-1}+\beta_k SK}}{1+e^{\beta_0+\beta_1 I_1+...+\beta_{k-1}I_{k-1}+\beta_k SK}}$, where I_i is the indicator for the i^{th} category of shielding or age and sex, SK is shielded kerma, and the reference category is males aged 21 to 30 at the time of bombing, shielded by wooden houses with full coded "9-parameter" data. The estimated coefficient for wooden schools suggests that the probability of epilation is slightly higher than in wooden houses at the same dose, indicating that possibly the model for wooden schools produces slightly low dose estimates: the point estimate being about 28% low, but the 95% confidence interval is from about

0.3% low to 48% low. The coefficient for Nagasaki factories suggests that the dose estimates are quite a bit too high, consistent with Figure 2. The coefficient for "average house" suggests that the doses are too high, but this effect may be partly or completely due to random errors in survivor's location data for this shielding category's being larger than the errors for categories with full coded shielding data, as suggested above in relation to Figure 2. The next entry is for survivors in wooden buildings other than houses or schools, that have the full coded "9-parameter" shielding data, and suggests that the use of the "9-parameter house model" for these buildings may result in doses that are too low. The entries for sex and age categories suggest that survivors who were girls or boys at the time of the bombings reported less epilation than young men, and the same for middle-aged and older men, with a very pronounced under-reporting for men over 60. On the other hand, women in their 30s and 40s reported more epilation than young men. Many of these results have logical interpretations or similarities to other findings in RERF studies, but a full discussion would be too long for this report.

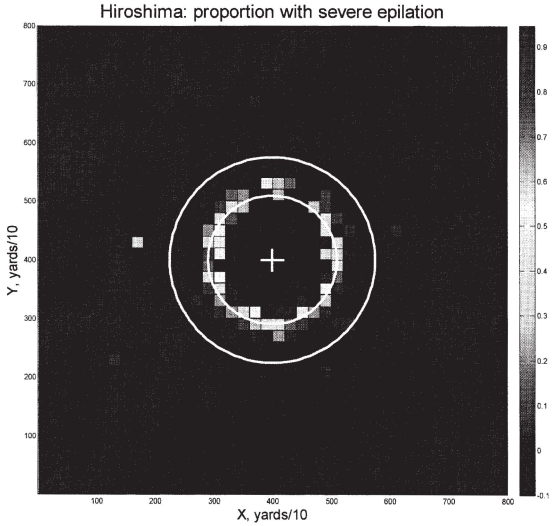
Table 4 Combined Logistic Regression Model for Severe Epilation in Hiroshima and Nagasaki

covariate	**coefficient**	**p-value**	**covariate**	**coefficient**	**p-value**
Wooden school	0.34	0.041	Male, ages >60	-2.35	<0.001
Nagasaki factory	-1.13	<0.001	Female, ages 0-10	-0.41	0.009
Average house	-0.51	<0.001	Female, ages 30-40	0.36	0.004
Non-house wooden building	0.57	0.051	Female, ages 40-50	0.35	0.005
Male, ages 0-10	-0.44	0.006	Shielded kerma, mGy	0.0015	<0.001
Male, ages 40-50	-0.45	0.007	Constant	-4.54	<0.001
Male, ages 50-60	-1.25	<0.001			

Spatial Plots

The proportions reporting severe epilation among survivors with known DS02 doses are plotted in Figure 4 for 200x200-yard square spatial cells. It is clear that the vast preponderance of epilation occurs at proximal distances, inside the outer white circles, which are at the previously stated boundaries of 1.6 km in Hiroshima and 2 km in Nagasaki. (The inner white circles are 1 km in radius.) In both plots, the darkest blue cells are those with no data, shown at a value of -0.1 on the color scale, and the cells with data are covered by the values between 0 and 1 on the remainder of the color scale.

In Figure 5, the expected proportions for Hiroshima in each cell from the combined logistic-regression model have been subtracted from the observed proportions and the resulting excess proportions are shown using a different color scale. The scale now uses -0.6 for cells with no data, and a range from -0.5 to 0.5 for the cells with data. It should be noted that this plot can be misleading, because under the null hypothesis that the true proportion in each cell is equal to that predicted by the regression model, i.e., that the true excess proportion is zero in all cells, the distribution of *observed* proportions becomes



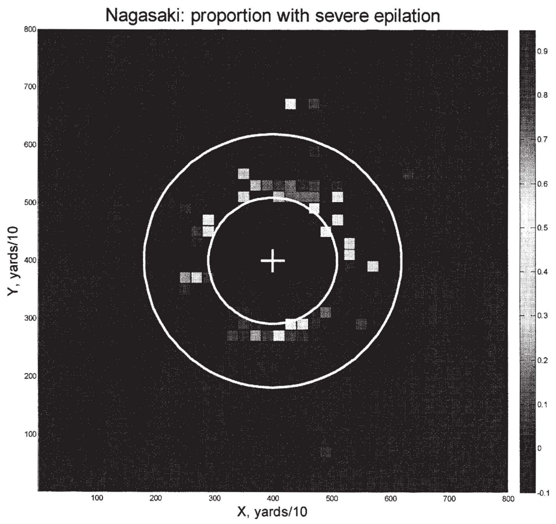


Figure 4 Observed proportions with epilation in spatial cells, Hiroshima and Nagasaki.

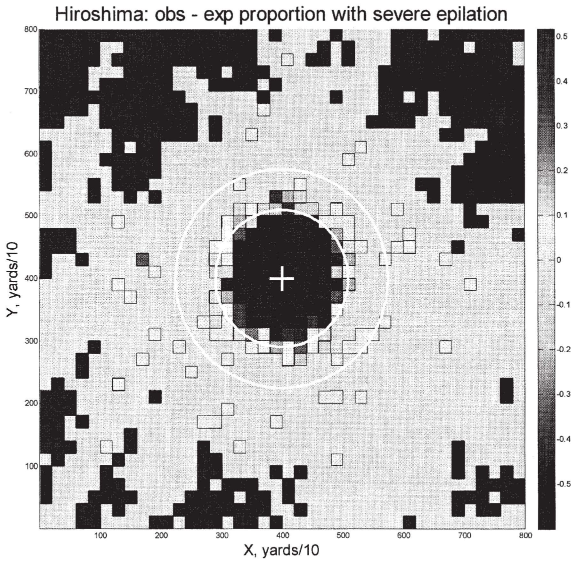


Figure 5 Observed – expected proportions with severe epilation in spatial cells, Hiroshima.

increasingly skewed for small numbers of expected cases in a cell. At the limit, for cells with a few survivors and a small probability of epilation, say 1/100, we expect to see a vast preponderance of cells with no cases, hence a proportion of zero, and a few cells with one case of epilation, hence an excess proportion of 1/N – 1/100, which is a large fraction for N = 1, 2, 3, etc. Unfortunately there is no simple way to correct the plot for this situation in which we expect to see rare occurrences of high-appearing values due to small discrete numbers of events in cells with only a few survivors.

Figure 5 shows small numbers of cells with positive excess proportions due to small numbers of events, which become increasingly sparse at longer distances and appear to be fairly random in spatial distribution. There is one cell with a high-appearing value, about 2100 m west of the hypocenter, which has 2 cases of severe epilation among 6 survivors in the cell. To determine whether there are any statistically significant patterns, i.e., localized areas with proportions in excess of those predicted by the covariates, it will be necessary to carefully choose a spatial statistical method for binomial data that can handle the necessary covariate adjustment and the range from sizeable numbers of expected events in proximal cells to very rare events in distal cells, or restrict the analysis to distal areas where the expected proportion epilating due to direct dose is very small. Methods for further analysis are being investigated.

Conclusions

Previously observed anomalies in the direct (i.e., DS02) dose dependence of severe epilation at high doses may be explainable by errors in self-diagnosis or self-reported location and shielding by some individual survivors, along with the mortality at high doses in the range above about 3 Gy that is expected from estimates of the human LD_{50} for ionizing radiation. For severe epilation, a standard logistic regression model can be fitted on a suitable range of the data, with interesting results. The scattered cases at longer distances that cannot be explained by direct dose under the resulting model lack an apparent spatial pattern, and may be due to misclassification arising because the data were taken from self-diagnosis a number of years after the bombings. Although there may be some subtle spatial patterns in proportions with severe epilation after correction for proportions expected from direct dose, such patterns are not obvious, other than perhaps a low area in the distal part of the NNW octant of Hiroshima. Features of the data make spatial statistical analysis difficult, but methods are being investigated.

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