Journal of the Korean
Data & Information Science Society
2006, Vol. 17, No. 4, pp. 1349 ~ 1364

Risk Relationship of Cataract and Epilation on Radiation Dose and Smoking Habit

Makoto Tomita[1] · Masanori Otake[2] · Sungho Moon[3]

Abstract

An analytic approach that provides explicit estimates of risk on cataract and epilation data is evaluated by reasonableness of conceivable relative risk models regarding a simple, odds, logistic or Gompertz regression method, assuming a binomial distribution. In these analyses, we apply relative risk models with two thresholds between epilators and nonepilators from a highly characteristic lesion of which radiation cataract does not occur around 2 gray for a single acute exposure. The risk models are fitted to the data assuming 10 as a constant relative biological effectiveness of neutron. The likelihood of observing the entire data set in these models fitted is evaluated by an individual binary-response array. Estimation of a threshold with or without severe epilation and the $100(1-\alpha)\%$ confidence limits are derived from the maximum likelihood approach. The relative risk model with two thresholds can be expressed as a formula with structure of Background × RR, where RR includes threshold models with or without epilation. The radiosensitivity of ionizing radiation to cataracts has been examined for the relationship between epilators and nonepilators.

Keywords : Profile approach, Radiation cataract, Radiosensitivity, Risk model, Threshold model

1) Full-time Lecturer, Department of Information Systems and Mathematical Sciences, Nanzan University, 27 Seirei-cho, Seto, Aichi, 489-0863, Japan, E-mail: tomita@nanzan-u.ac.jp,

2) Professor, Department of environmental and mathematical Sciences, Faculty of Environmental Sciences and Technology, Okayama University, Okayama, 700-8530, Japan

3) Corresponding Author : Professor, Department of Statistics, Pusan University of Foreign Studies, 55-1, Uam-Dong, Nam-Gu, Busan, 608-768, Korea, E-mail: shmoon@pufs.ac.kr

1. Introduction

Epidemiological study generates data in which the response measurement for each individual may take one of only two possible values. Such a response is called a binary or discrete variable. We are to examine a statistical analysis based on binary data which would clarify the relationship of radiation exposure to the occurrence of cataracts with two thresholds of epilators and nonepilators. The effects of ionizing radiation are customarily viewed as either "stochastic" if the probability of their occurrence is a direct function of dose, or "deterministic (nonstochastic)" if it is the severity of the effect which is dose-dependent. It is of great interest to evaluate dose-response models with two thresholds related to epilators and nonepilators. Radiation-induced cataract is, in its early stages at least, usually regarded to be a higltly characteristic lesion(Cogan et al. 1952 and Miller et al. 1969). It is generally defined as a central, posterior subcapsular opacity, easily visible with a slit lamp biomicroscope or an ophthalmoscope. Previous analyses have shown that the frequency of radiation-related opacities among the atomic-bomb survrvors increases linearly with dose above. In 1990 Otake and Schull have indicated a threshold estimate in the neighborhood of 1.5 sievert(Sv), assunung a constant neutron RBE. However, it is not known whether, at a given dose, the frequency of occurrence of this lesion is related to the occurrence of other evidence of early radiation injury, such as epilation. Severe epilation among the survivors is known to increase significantly in frequency with increasing Dosimetry System 1986(DS86) dose although the dose-response function is nonlinear. Stram and Mizuno's evaluation(1989) of the epilation-response function revealed a marked increase in slope at about 0.75 gray(Gy), and then, beginning at about 2.50 Gy, a leveling off, and eventually a decrease in response. Tucker et al. (1992) have reported that they could find no clear evidence of an individual difference in radiosensitivity for the occurrence of acute and late skin reactions in the human. Be this as it may, the issue of differences in radiosensitivity remains an interesting one which needs further research.

The purposes of this study are two-fold, namely, 1) to assess the effect, if any, of the occurrence of severe epilation on the threshold for radiation cataract and 2) to ascertain, if possible, whether epilators may be more radiosensitive than nonepilators and thus more prone to develop cataracts.

2. Study Materials

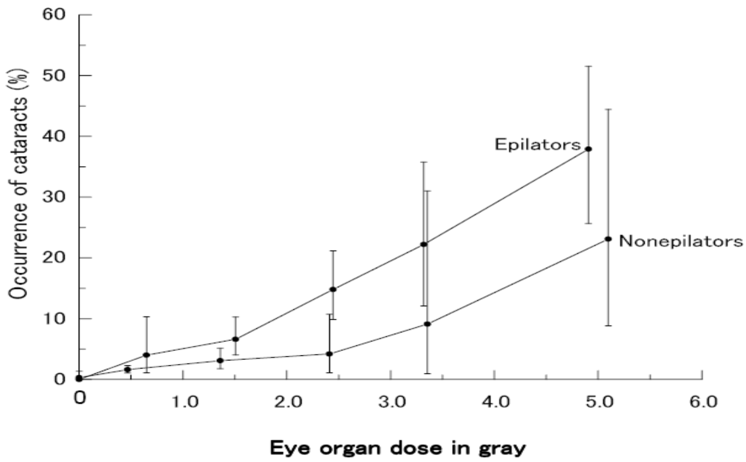
2.1 Applied data

Miller et al.(1969) have conducted a major ophthalmologic survey at the Atomic Bomb Casualty Commission(ABCC) in 1963-64. In 1990, after the DS86 dose estimates(Roesch ed. 1987) became available, the findings of this survey were reevaluated using the eye organ dose estimates in Hiroshima and Nagasaki(Otake an Schull 1990). Of the 2125 individuals examined in Hiroshima and Nagasaki, 1742 have DS86 doses and information on the occurrence of epilation within the first 60 days following the bombings(Table 1).

The remaining subjects were excluded for a variety of reasons -- 108 did not have an estimable dose, 44 had no information on epilation, and 231 were not in the city at the time of the bombing(ATB). Of the 1742 subjects, 67 had radiation cataracts. In most instances, based on biomicroscopic classification, about 70% of the degree of opacification(cataracts) were small or less than small and only five cataracts were classified as large(Miller et al. 1969). The degree of epilation was recorded as “slight”, “moderate”, and “severe”, as described in Table 1. The relationship between the presence and the absence of severe epilation and the occurrence of cataract is plotted in Figure 1 by DS86 eye organ dose.

<Table 1> Number of subjects and cataract cases by epilation status

Item	Number of subjects	Cataract cases
No epilation	1045	12
Slight epilation	147	4
Moderate epilation(less than 2/3 or 1/4 or over)	227	11
Severe epi;ation(2/3 or over)	323	40
Subtotal(study cases)	1742	67
Present, degree of epilation unknown	3	0
Present, in same degree but date of onset unknown	33	1
Occurrence of symptoms questionable	3	0
No information	5	0
Not exposed	231	4
DS86 dose not estimable	108	4
All cases	2125	76



<Figure 1> Occurrence rate of cataracts with 95% confidence limits for epilators and nonepilators

As is apparent from this figure, at the same dose, cataracts have occurred more frequently among individuals with a history of severe epilation than among individuals without such a history.

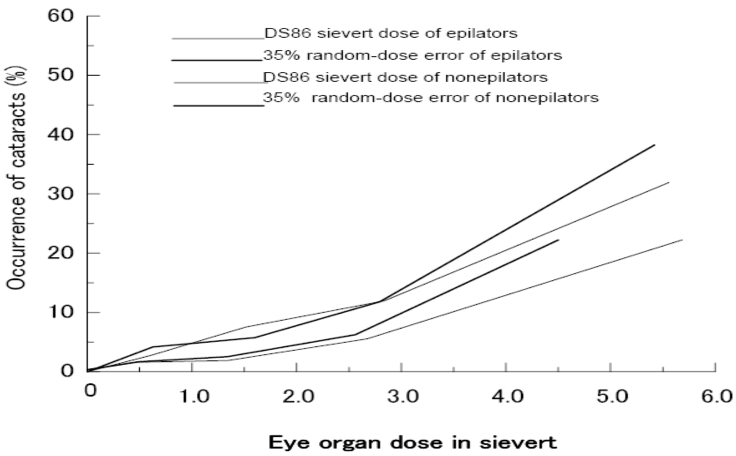
2.2 DS86 dose estimation

An analysis uses the eye organ doses based on DS86 dose, which were computed in July 1989 and are thought to provide better dose estimates than were initially possible with the DS86 dose for distal survivors who were in the open ATB and for survivors who were shielded by terrain or in factories. It should be noted that where detailed shielding histories are available the DS86 dose estimates are derived from a direct evaluation of the effects of body orientation, posture, and dispersion of energy occurring in the tissues or by structures between the burst point and the individual. For those survivors whose shielding histories were incomplete, free-in-air kerma was estimated using regression coefficients, and the estimates were corrected using the mean transmission factors for buildings and the body derived from those individuals with complete histories.

2.3 Estimation of random-dose error

There appears to be a difference between the two groups from Figure 1 and thus there may occur some difference in the dose-response although it should be noted that at all doses the confidence intervals overlap. However, the values exhibited in Figure 1 must be guardedly interpreted for several reasons. First, the variation in time of onset of radiation opacities, if correlated with other radiation damage, could give rise to a spurious association between early acute symptoms and cataract 18-19 years after the atomic bombings. Second, and more important, errors in the DS86 dose estimates exist and complicate the determination of any dose-response relationship. Estimated doses are imperfect reflections of true radiation dose and, as said, are subject to error. Consider, for example, two individuals with approximately the same nominal DS86 dose estimates, one of whom suffered an acute radiation symptom as well as radiation cataract, and the other did not. If substantial random errors exist in estimating the true dose with the DS86 system, it would appear that an individual suffering any radiation symptom other than cataract would most likely have experienced a higher true dose than one reporting no radiation symptom.

Pierce et al.(1990) have pointed out that the risk of cancer mortality among the atomic-bomb survivors in the Life Span Study(LSS) sample is increased 5-15% when random dose errors are taken into account. They gave an approximation function for the joint distribution of true doses, x , and observed doses, z, i,e., $h(x \mid z) \propto f(z \mid x) g(x)$, where $f(z \mid x)$ is the conditional distribution assumed to be lognormal with $\log(z)$ having mean $\log(x)$ and standard deviation equal to either 0.35(the 35 % error model) for the coefficient of variation of $\log(z)$ or 0.50 (the 50% error model), and $g(x)$ is the Weibull distribution with shape parameter
equal to 0.5 and scale parameter equal to 2.84 in Hiroshima and 2.33 in Nagasaki. Neriishi et al.(1991) also evaluate the dose errors with an adjustment or the presence or absence of severe epilation in the LSS sample, i.e., $p(x \mid z, ep=1 \text{ or } 0) \propto k(x \mid ep=1 \text{ or } 0) f(z \mid x) g(x)$, where ep is 1 for severe epilation and 0 for others. We have used the same adjustment model here assuming a 35% random-dose error as a function of true dose with or without the occurrence of severe epilation. The use of the 35% error model is tantamount to assuming a "moderate" amount of error in the dosimetry. The occurrence rates of cataracts for epilators and nonepilators were plotted using the DS86 Sv mean dose and assuming a 35% random error in the mean dose(Figure 2).



<Figure 2> Occurrence rate of cataracts by DS86 mean dose and 35% random-dose error based on an assumed neutron RBE of 10

As is evident from this figure, the rate of occurrence of cataracts among epilators in the higher dose groups tends to be higher when a 35% random-dose error is assumed than for epilators using unadjusted DS86 Sv doses and the same appears to be true for the nonepilators. Otake and Schull(1996) have used the estimated DS86 eye organ dose equivalent based upon an assumed constant neutron RBE of 10 so that we can more easily compare the results between the DS86 eye organ dose and 35% random-dose error estimates. However, Otake and Schull in 1990 has derived a constant RBE for neutrons of 12.2 based on the fact that the 0.73 Gy threshold for gamma ray gives the same safety zone as the 0.06 Gy threshold for neutrons.

3. Statistical Methods

In 1969 Task Group of the International Commission on Radiological Protection (ICRP) has stated that the dose-response for cataract induction by ionizing radiation, whether of high or low LET, seems to be highly sigmoid. The ICRP Task Group assumes the production of cataracts to be a deterministic phenomenon that can be totally avoided with appropriate dose limits; that is to say, the Task Group assumes a threshold below which radiation cataracts do not occur. Based on clinical experience the low-LET threshold dose, for a single acute exposure, has been commonly taken to be around 2 Gy(ICRP 1969 and Merrian et al. 1972). One analytic approach that provides explicit estimates of risk is to fit a binomial odds or Gompertz regression model to the probability(P) of an individual binary response(1 for an individual with cataracts and 0 for others), assuming two different thresholds, one for epilators and the other for nonepilators, and including sex and age ATB as discrete and continuous variables, respectively.

Suppose that each individual has a binomial type distribution. The likelihood of observing the entire data set in models fitted is

$$L=\prod(P)^{y}(1-P)^{1-y}=f(c,s,,\alpha,\beta_e,T_e\cdot\beta_0,T_0)$$

n an individual binary-response array, where y is 1 for an individual with cataracts and 0 for others, and c intercept term, sex, a age ATB, β_e linear dose-response or T_e threshold for epilators, and β_0 linear dose-response or T_0 threshold for nonepilators. The binomial regression type models with two thresholds fitted here are given as

$$[P/(1-P)]=\text{Background}\times\text{RR},$$

where the background includes a constant and terms for sex and age ATB , and the relative risk(RR) is assumed to follow a linear dose-response relationship. The relative risk model assuming a binomial regression procedure with two thresholds is given by

$$1+\beta_e(D_e-T_e)E_e+\beta_0(D_0-T_0)E_0$$

where the RR of radiation cataracts is $[1+\beta_e(D_e-T_e)]$ for the data of epilators when E_e is 1 for epilators and 0 for nonepilators, and other $[1+\beta_0(D_0-T_0)]$ for the data of nonepilators when E_0 is 1 for the data of nonepilators and 0 for epilators. In the RR model, (D_e-T_e) for epilators or (D_0-T_0) for nonepilators is zero when $D_e<T_e$ or $D_0<T_0$, and D_e or D_0 denotes the DS86 eye organ dose equivalent or 35% random-dose error expressed in sieverts, β_e is the radiation effect for epilators and β_0 the radiation effect for nonepilators. The binomial regression models with two thresholds employed here can be expressed as

Odds ratio regression(Model Ⅰ) : $[P/(1-P)]=\text{Background}\times[1+\beta_e(D_e-T_e)E_e+\beta_0(D_0-T_0)E_0]$
Gompertz regression(Model Ⅱ) : $\ln(-\ln(P))=\text{Background}\times[1+\beta_e(D_e-T_e)E_e+\beta_0(D_0-T_0)E_0]$
Logit regression(Model Ⅲ) : $\ln[P/(1-P)]=\text{Background}\times[1+\beta_e(D_e-T_e)E_e+\beta_0(D_0-T_0)E_0]$
Simple regression(Model Ⅳ) : $P=\text{Background}\times[1+\beta_e(D_e-T_e)E_e+\beta_0(D_0-T_0)E_0]$

Instead of a linear-response function Models I to IV become a linear-quadratic response relationship with $[1+\beta_e(D_e-T_e)+\beta_{e^2}(D_e-T_e)^2]$ in the former or $[1+\beta_0(D_0-T_0)+\beta_{0^2}(D_0-T_0)^2]$ in the latter.

The maximum likelihood estimates(MLE) of parameters based on the binomial regression models are readily obtained by the Newton-Raphson iterative method, that is,

$$[\beta_l(r+1)]=[\beta_l(r)]-\left[\frac{\partial^2\log L}{\partial\beta_l\,\partial\beta_\nu}\mid_{(r)}\right]^{-1}\left[\frac{\partial\log L}{\partial\beta_l}\mid_{(r)}\right]\ \text{for}\ r=0,1,\cdots,\omega,$$

where $l,\nu=1,\cdots,\tau$ and $\frac{\partial^2\log L}{\partial\beta_l^2}\mid_{(r)}=0$ for $l=\nu$, and $\frac{\partial^2\log L}{\partial\beta_l\,\partial\beta_\nu}\mid_{(r)}=0$ for $l\neq\nu$.

The iterative procedure is made by the Newton-Raphson method with step halving with a criterion:

$$\mid\text{Deviance}(r+1)-\text{Deviance}(r)\mid<0.0001.$$

The largest likelihood value was selected from a number of deviances obtained by assigning successive incremental values of T_e or T_0, where T_e was taken to be 0, 0.05, 0.10, ... , 1.5 Sv under T_0 = a given value such as 0, 0.5, 1.0, 1.5, etc. The deviance statistic is $\chi^2=-2\log(L_c/L_f)$, where L_c is the likelihood in the current

model and L_f the likelihood in the full model, which does not depend upon the estimates of the parameters considered. The estimates of the risk parameters based on the binomial regression models can be readily obtained using the EPICURE command(Preston et al. 1993). The criterion of 95% confidence limits based on deviance values is used as $\chi^2 = 3.841$ with one degree of freedom. The $100(1-\alpha)\%$ were determined from the χ^2 statistic, i,e,

$$\chi^2 = -2\log\left[\frac{L(X \mid T^*)/L_f}{L(X \mid T)/L_f}\right]$$

which is known as the log likelihood statistic. Hence, we have

$$-2\log L(X \mid T^*)/L_f = -2\log L(X \mid T)/L_f + \chi^2 \quad ,$$

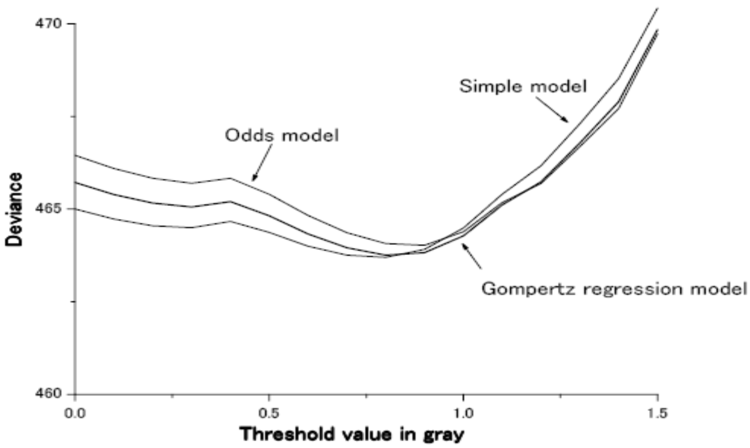
where $-2\log L(X \mid T^*)/L_f$ is a deviance of $100(1-\alpha)\%$ lower or upper bound and $-2\log L(X \mid T)/L_f$ is the smallest deviance. The goodness of fit(deviance) of the different models has been compared to determine which model is most appropriate for the estimation of the threshold. To examine the goodness of fit, the deviances of three models were plotted by step threshold in gray(Figure 3).

The test statistic of no difference between the two dose-response estimates is $\chi^2 = (\hat{\beta}_e - \hat{\beta}_0)^2 / V[\hat{\beta}_e - \hat{\beta}_0]$, which has approximately a χ^2 distribution with one degree of freedom under the null hypothesis, $H_0 : \mid \beta_e - \beta_0 \mid = 0$ where $V[\hat{\beta}_e - \hat{\beta}_0] = [V(\hat{\beta}_e) + V(\hat{\beta}_0) - 2Cov(\hat{\beta}_e, \hat{\beta}_0)]$,$V(\hat{\beta}_e)$ is the asymptotic variance estimate of β_e, $V(\hat{\beta}_0)$ the asymptotic variance estimate of β_0 and $Cov(\hat{\beta}_e, \hat{\beta}_0)$ the asymptotic covariance estimate of β_e and β_0.

4. Results

The fitting results of models described in statistical methods have been contrasted with those obtained using four RR models, namely, an odds, Gompertz, simple, or logistic regresslon procedure, assuming a binomial distribution. The first three models show a similar trend to the goodness of fit to the individual data (Figure 3). However, the logistic results with the poorest fits, compared as those of these three models, were not plotted in the figure 3 because deviances of the logistic model with an increase of assigned threshold values have produced larger values or poorer fits than 475.65 of zero threshold(see Otake et al. 1996). The odds and Gompertz models were more stable with fewer iterations required to obtain estimates of the parameters than the simple regression. Simple model has converged under proper initial values.

As is shown in Figure 3, the three models other than the logistic model give a similar trend and about the same peak estimate, i.e., the smallest deviance, but the deviances of the odds regression model in the low dose area show a slightly higher trend than those of the Gompertz model for determining the $100(1-\alpha)\%$ level, but no statistical significance was observed for the 95% confidence limit of low dose area. Since it is reasonable from a radiobiological standpoint to assume that two thresholds, one for epilators and the other for nonepilators, may exist in the model fitting, estimates of risk parameters can be readily obtained.



<Figure 3> Fitness of models to epilatiors fixed 1.54 threshold Sv for nonepilators

The numbers of cataract cases and subjects with their mean neutron and gamma doses are given in Table 2 by DS86 eye organ dose group.

<Table 2> Occurrence of cataracts by epilation and dose based on DS86 eye organ dose.

Dose group (Gv)	Average dose(Gv)		Subjects	Positive opacity	%
	γ	Neutron			
			Severe epilation		
<0.005	0	0	0	0	-
0.005-0.494	0.269	0.002	12	1	
				}	4.0
0.495-0.994	0.754	0.013	38	1	
0.995-1.994	1.473	0.033	136	9	6.6
1.995-2.994	2.379	0.067	81	12	14.8
2.995-3.994	3.223	0.097	27	6	22.2
>=3.995	4.753	0.153	29	11	37.9
Total	-	-	323	40	12.4
			No severe epilation		
<0.005	0	0	292	1	0.3
0.005-0.494	0.229	0.002	436	5	
				}	1.6
0.495-0.994	0.718	0.011	393	8	
0.995-1.994	1.336	0.024	226	7	3.1
1.995-2.994	2.358	0.052	48	2	4.2
2.995-3.994	3.273	0.082	11	1	9.1
>=3.995	4.979	0.118	13	3	23.1
Total	-	-	1419	27	1.9

Note. The γ and neutron estimates for those survivors who ostensibly had a total dose of more than 6 Gy have been arbitrarily truncated at 6 Gy.

When a binomial odds regression model was fitted to the individual binary data on radiation cataracts, no statistically significant effect of sex or age ATB was observed in the 1963-64 study data(Table 3). This suggests that neither sex nor age ATB is likely to seriously obscure the effect of radiation on the occurrence of cataract in this study. As previously stated, a L-L dose-response model with two thresholds, one for epilators and other for nonepilators, was fitted to the individual data.

<Table 3> Parameter estimates based on two thresholds and 95% confidence limits by DS86 and 35% random-error equivalent dose(RBE = 10).

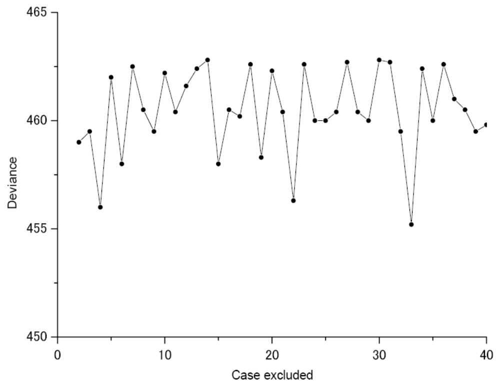
Item	DS86 dose		35% random-dose	
	Odds	Gompertz	Odds	Gompertz
Constant	0.0061	0.0147	0.0062	0.0136
City	0.00815	-0.00727	0.00814	-0.00719
Sex	0.00244	0.00286	0.00239	0.00278
Age ATB	0.000149	0.000146	0.000147	0.000143
$\hat{\beta}_0$(SE)	3.45*(1.76)	3.09*(1.51)	5.14*(2.61)	4.61*(2.26)
$\hat{\tau}_0(L, U)$	1.54(0, 2.07)	1.53(0, 2.09)	1.41(0, 1.78)	1.40(0, 1.80)
$\hat{\beta}_e$(SE)	6.95**(2.33)	6.03**(1.92)	8.33**(2.79)	7.18**(2.29)
$\hat{\tau}_e(L, U)$	0.86(0, 1.41)	0.86(0, 1.39)	1.21*(0.25, 1.76)	1.18*(0.11, 1.73)
Deviance(χ^2)	463.97	463.75	464.68	464.37
Degree of freedom	1734	1734	1734	1734

Note. ATB denotes age at the time of the bombings, SE estimate of the standard error, and RBE is relative biological effectiveness of neutrons. Significance levels are *($P<0.05$) and **($P<0.01$). The lower(L) and upper(U) 95% confidence bounds are given in parentheses beneath each threshold. The covariance estimates are $Cov(\hat{\beta}_0, \hat{\beta}_e)=1.83$ (odds) or 1.35(Gompertz) for the DS86 dose, and $Cov(\hat{\beta}_0, \hat{\beta}_e)=3.25$ (odds) or 2.43(Gompertz) for the 35% random dose error.

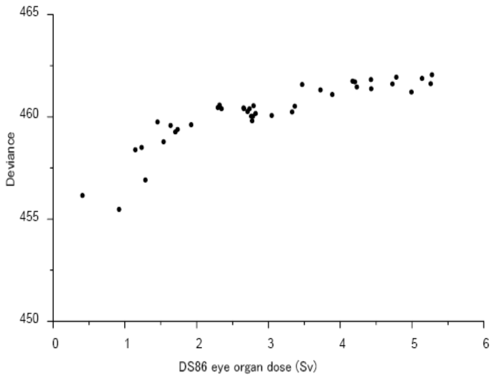
Using the DS86 eye dose equivalent, the slope of the L-L dose-response relationship for cataracts was significantly different from zero for both epilators, 6.95 Sv; $P<0.01$ and 6.03 Sv; $P<0.01$, and nonepilators, 3.45 Sv; $P<0.05$ and 3.09 Sv; $P<0.05$, for odds(I) and Gompertz(II) models, respectively. When the 35% random-dose error estimates were used, the slopes of the L-L dose-response were also statistically significant difference from zero for both groups, epilators: 8.33 Sv; $P<0.01$ or 7.18 Sv; $P<0.01$ and nonepilators: 5.14 Sv; $P<0.05$ or 4.61 Sv; $P<0.05$, for odds(I) and Gompertz(II) models, respectively(Table 3). The ratio between the slope estimates of epilators and nonepilators was reduced from 2 times (6.95/3.45) for odds model and about same 2 times (6.03/3.09) for Gompertz model without allowance for dose errors to 1.6 times (8.33/5.14) for odds model and about same 1.6 times (7.18/4.41) for Gompertz model with such allowance, but no statistical difference between the two dose-response effects for epilators and nonepilators was noted. The slope estimates for epilators were 1.6-2.0 fold larger than those for nonepilators, but there was no statistically significant difference between the two slope estimates for the DS86 Sv dose and 35% random-dose error. In the DS86 Sv dose, the estimated thresholds were the same risk for Gompertz model as well as odds model, i.e., 0.86 Sv(95% CI: 0, 1.41) for epiiators and 1.54 Sv(95% CI: 0, 2.07) for nonepilators, whereas assuming a 35% random-dose error the threshold estimates were 1.21 Sv for epilators and 1.41 Sv for nonepilators, a smaller difference than with the use of the DS86 Sv dose. The threshold value of epilators based on the 35%

random-dose error gets nearer to the threshold estimate of nonepilaors. It seems to be a difference of radiosensitivity between two thresholds of epilators and nonepilators, but no statistical significance was noted for the relationship between 0.86 Sv and 1.54 Sv thresholds. The result was the same as the test statistic of no difference between the two dose-response estimates in odds regression model is $\chi^2 = (\widehat{\beta}_e - \widehat{\beta}_0)^2 / V[\widehat{\beta}_e - \widehat{\beta}_0] = 2.38$ with one degree of freedom.

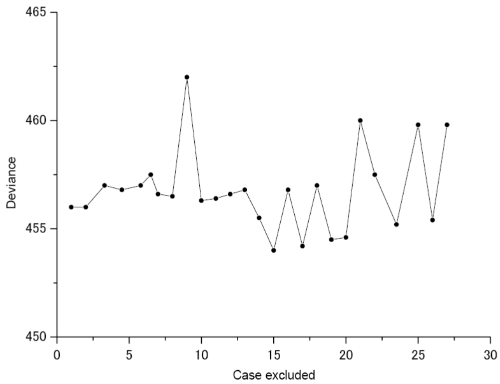
Figure 4a shows a variation of MLEs of individual epilator, using deviance due to goodness of fit when one cataract case was excluded and 1.54 Sv threshold fixed for nonepilators on the basis of odds regression model. Three deviances less than 457 deviance value fairly differ from the remaining ones. The relationship between the corresponding deviances and DS86 dose estimates is given in Figure 4b. However, statistical significance of two parameter estimates gave the same results of 1% level for epilators and 5% level for nonepilators. The MLE variations were indicated in Figures 5a and 5b when 0.86 Sv threshold for epilators on the basis of odds model was fixed. There are slightly changes of around 5% level for significant excess risks for nonepilators. This variation will be due to an decrease from 40 to 27 cataract cases. In particular, nine of 27 cataract cases changed suggestive relation to around 7% level from 5% level for parameter estimate corresponding to nonepilators excluded one cataract case.



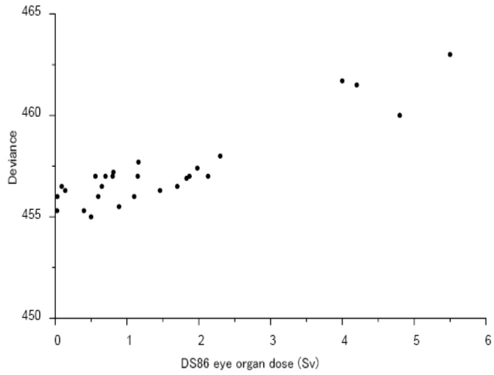
<Figure 4a>



<Figure 4b>



<Figure 5a>



<Figure 5b>

<Figure 4a> Relationship between deviance and individual dose when each epilator was excluded after fixed 1.54 Sv threshold estimate for nonepilators
<Figure 4b> Relationship between deviance and individual dose when each epilator was excluded after fixed 1.54 Sv threshold estimate for nonepilators
<Figure 5a> Relationship between deviance and individual dose when each nonepilator was excluded after fixed 0.86 Sv threshold estimate for epilators
<Figure 5b> Relationship between deviance and individual dose when each nonepilator was excluded after fixed 0.86 Sv threshold estimate for epilators

5. Discussion

The extent of the damage to the lens following exposure is determined primarily by the quantitative and qualitative relationship of dose and its effect. However, given that the cellular events involved in radiation-related cataractogenesis in man are still imperfectly known, all dose-response models are conjectural to some extent and the applicability of a given model rests on its accordance with other radiation-related biological events and judgements of apparent “reasonableness”. Here a dose-response model with two thresholds, one for epilators and the other for nonepilators, has been fitted to the individual binary data based on the assumption that no opacity of the lens occurs if the dose is below a value that can be estimated. The ICRP(1969) has suggested that on the basis of the absence of case reports of cataract following doses of 2 Gy or less, it seems unlikely that the range of sensitivity is wide and that a highly sigmoid dose response exists for high-LET radiation dose. Our analysis supports this conjecture.

Judged by clinical studies, the interval of time from exposure to x- or γ -irradiation to the appearance of lens opacities in humans varies widely, from six months to 35 years, with an approximate average of 2-3 years(Merrian et al. 1972 and ICRP 1990). The time of onset of cataract was reported by Merrian et al. in 1972 as an approximate estimate from these findings based on a number of literatures. The study of Merrian and Focht(1957) was a retrospective assessment. The latent period of their study was due to these results skewed to high dose groups of exposed individuals with cataracts. From these findings, the average latent period would almost certainly have been greater. The latent average in Hiroshima and Nagasaki was not demonstrable but atomic-bomb survivors really have the experience since the first cases were not reported in these cities until 1949, about 4 years after the bombing(Cogan et al. 1949). The time of onset of the radiation cataracts seen in atomic-bomb survivors is unknown in most instances because the data are cross-sectional observations.

Atomic-bomb survivors were simultaneously exposed to γ and neutron doses, and therefore the question arises as to whether an interaction exists in their radiobiological effects. But it is difficult, given the limited data available on the survivors, to determine whether an interaction exists and to estimate its effect. The effect estimated is negative and not statistically different from zero, but the error inherent in the estimate is large. Nevertheless, the individual thresholds for neutron and γ doses may not be comparable with the results from a single x-ray exposure, and it seems prudent to consider both thresholds in defining a safety zone. Otake and Schull(1990), using the Hiroshima and Nagasaki cataract data, estimated a neutron RBE by the following rule: If we assume no interaction and an RBE for neutrons of 12.2, the O.73 Gy threshold for γ rays gives the same safety zone as the 0.06 Gy threshold for neutrons, and their joint effect leads to an estimated minimal dose of 1.46 Sv. The ICRP(1969, 1990) gives a table of RBE values for the production of opacities of the lens with single exposures to x rays or γ rays or to fission neutrons. These values range from 2 to 20, a range within which the value we have used falls. Furthermore, the BEIR report(1980) suggests that the RBE for high-LET radiation for a single cataractogenic exposure may be somewhat lower, in the range of 2-9. However, we have used an estimated DS86 eye organ dose equivalent based upon an assumed constant neutron RBE of 10 so that we can compare the results between DS86 eye organ dose and 35% random-dose error estimates.

In 1990 Otake and Schull(1990) fitted simple binomial regression models with and without thresholds for the γ and neutron doses to grouped as well as individual data from Hiroshima and Nagasaki. The parameters of these models were estimated by the log likelihood method, assuming the observed umber in each cell to be a binomial variate having an expected value based on the model equation. However, the simple binomial regression models generally gave unstable estimates of the parameters of interest, whereas the logistic regression models gave stable estimates, but the deviance values for goodness of fit were poorer with an increase in the threshold as compared to those of the binomial odds and Gompertz models. The logistic model supports a zero threshold, a finding inconsistent with a presumed deterministic phenomenon, and the Gompertz models required more iterations than the odds regression models. In the present study, we have applied binomial odds or Gompertz regression models with two thresholds rather than a simple or logistic regression model. We also fitted a linear-quadratic(L-Q) and (L-Q) dose-response model with two thresholds to the individual data on the epilators and nonepilators. In these dose-response models with two thresholds, we note, first, that the results give not only larger deviances than those of the L-L dose-response model with two thresholds, but also effects of the quadratic(Q) estimates of parameters that are not significant. Second, the estimated threshold is zero which is inconsistent with the supposition that cataracts are a deterministic event.

The best fit among a number of odds and Gompertz regression models with two thresholds for the DS86 Sv dose or the 35% random-dose error yielded slope estimates of 6.95 Sv or 6.03 Sv and 8.33 Sv or 7.18 Sv for epilators, and 3.45 Sv or 3.09 Sv and 5.14 Sv or 4.61 Sv for nonepilators, which are significantly different from zero. No association of radiosensitivities between the slope estimates for epilators and nonepilators was observed for the individual data of the DS86 Sv dose and the 35% random-dose error estimates. This threshold estimate is very similar to the 1.46 Sv(Otake et al. 1990). It was pointed out at that time that the threshold ranged from 1.54 to 1.68 Sv if the estimate was assumed to be 5-15% lower than the unbiased dose estimates derived from DS86(Pierce and Stram 1990). Under the same assumption, the estimated thresholds of 0.86 Sv for the DS86 Sv dose and l.21 Sv for the 35% random-dose error for the epilators would lie in the range of 1.41 to 1.76 Sv for the 95% upper confidence limits. The thresholds estimated for the nonepilators were 1.54 Sv and 1.41 Sv, respectively, and a 95% upper confidence limit of 2.07 Sv for the DS86 Sv dose and 1.78 Sv for the 35% random-dose error. We have failed to detect the radiosensitivity of a difference of two estimated parameters or thresholds to cataracts between epilators and nonepilators among atomic-bomb survivors.

Radiation produces for both cataract and epilation, and also an issue of dose-errors. An issue of this paper is to examine the existence of a difference in individual radiosensitivity. As is evident from Figure 2, it seems there is different in the radiosensitivity between epilator and nonepilator. Data may be the risk of the same degrees of control level in low dose area when we consider error variation of data. The BEIR Committee in 1980 noted that tissues and organs vary considerably in their sensitivity to the induction of cancer by radiation, and that human genotypes are known to confer both increased susceptibility to DNA damage and increased cancer risk after exposure to carcinogenic agents. There are many clinical studies of individual variation in sensitivity of tissue responses to radiotherapy(BEIR report 1980), but these studies do not clearly demonstrate the existence of individual differences in radiosensitivity(Tucker et al. 1992). However, Neriishi et al.(1991) have reported that the linear term in the dose response for leukemia mortality was steeper by a factor of 2.5 among those individuals who had severe epilation within 60 days of the bombing than among those individuals who did not experience severe epilation. In the present study the L dose-response estimate of epilators with or without allowance for dose errors was 1.6-2.0 fold higher than that of nonepilators. Furthermore, there is a variation of deviance values of individual epilator due to goodness of fit when one epilator was excluded and 1.54 Sv threshold fixed for nonepilator on the basis of odds regression model. Three deviances less than 457 deviance value fairly differ from the remaining ones. It is obvious that these different values are strongly related to lower values than others of DS86 doses. The fact may be estimated as a wrong value by DS86 calculation factors and individual information related to shielding histories obtained from individual interviews. However, statistical significance of two parameter estimates gave the same results of I % level for epilators and 5% level for nonepilators when one cataract case of epilator was excluded. On the other hand, MLE variations have been examined when 0.86 Sv threshold for epilators on the basis of odds model was fixed. There are slightly changes of around 5% level for significant excess risks for nonepilators. This variation will be due to an decrease from 40 to 27 cataract cases. In particular, nine of 27 cataract cases changed suggestive relation to 7% level or less from 5% level for parameter estimate corresponding to nonepilators when a threshold of 0.86 Sv for epilators was fixed. Four cases of them were prodigiously exposed to high doses from 3.96 to 5.45 Sv for nonepilators.

Acknowledgment

This report makes use of data obtained from the Radiation Effects Research Foundation(RERF), Hiroshima and Nagasaki, Japan. RERF is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare(MHLW) and the U.S. Department of Energy(DOE), the latter through the National Academy of Sciences. The conclusions in this report are those of the authors and do not necessarily reflect the scientific judgment of RERF or its funding agencies. “The authors want to express their thanks for use of data with regard to clinical study information of atomic bomb survivors on RERF Adult Health Study Population”.

References

1. BEIR report (1980). *National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation*, Effects on Populations of Exposure to Low Levels of Ionizing Radiation (BEIR-III), 1980, National Academic Press, Washington DC.

2. Cogan, D. G., Martin, S. F. and Kimura, S. J. (1949). Atomic bomb cataracts, *Science,* 110, 654-655.
3. Cogan. D. G., Donaldson, D. D. and Reese, A. B. (1952). Clinical and pathological characteristics of radiation cataract, *Archives of Ophthalmology*, 47, 55-70.
4. ICRP (1969). *Radiosensitivty and Spatial Distribution of Dose,* Appendix I, Radiation cataract in man. Publication 14. International Commission on Radiological Protection, Pergamon Press, Oxford.
5. ICRP (1990). *Recommendations of the International Commission on Radiological Protection,* Publication 60. Annex B, Biological effects of ionizing radiations, International Commission on Radiological Protection. Pergamon Press, Oxford.
6. Merriam, G. R. Jr, and Focht, E. F. (1957). A clinical study of radiation cataracts and the relationship to dose, *American Journal of Roentgenology*, 77, 759-85.
7. Merriam, G. R. Jr, Szechter, A. and Focht, E. F. (1972). The effects of ionizing radiations on the eye. *Frontiers Radiation of Therapy and Oncology*, 6, 346-385.
8. Miller, R. J., Fujino, T. and Nefzger M. D. (1969). Eye findings in atomic bomb survivors, Hiroshima-Nagasaki, 1963-64, *American Journal of Epidemiology*, 89, 129-138.
9. Neriishi, K., Stram, D. O., Vaeth, M., Mizuno, S. and Akiba, S. (1991). The observed relationship between the occurrence of acute radiation sickness and subsequent cancer mortality among A-bomb survivors in Hiroshima and Nagasaki, *Radiation Research*, 125, 206-213.
10 Otake, M. and Schull, W. J. (1990), Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system, *Radiation Research*, 121, 3-13.
11. Otake, M., Neriishi, K. and Schull, W. J. (1996). Cataract in atomic bomb survivors based on a threshold model and the occurrence of severe epilation, *Radiation Research*, 146, 339-348.
12. Pierce, D. A, Stram, D. O. and Vaeth, M. (1990). Allowing for random errors in radiation exposure estimates for atomic bomb survivors data, *Radiation Research*, 123, 275-284.
13. Roesch, W. C. (ed) (1987). US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Final Report, Vols. I and 2. *Radiation Effects Research Foundation*, Hiroshima.
14. Preston, D. L., Lubin, J. H. and Pierce, D. A. (1993). EPICURE Command Summary, *HiroSoft International Corporation,* Suite 103, 1463 E. Republican, Seattle. WA 98112, USA.
15. Stram, D. O. and Mizuno, S. (1989). Analysis of DS86 atomic bomb radiation dosimetry methods using data on severe epilation, *Radiation Research*, 117, 93-ll3.
16. Tucker, S. L., Turesson, I. and Thames, H. D. (1992). Evidence for individual differences in the radiosensitivity of human skin, *European Journal of Cancer*, 28A, 1783-1791.

[received date : Sep. 2006, accepted date : Nov. 2006]