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Radiosensitivity and the Occurrence of Radiation-related Cataract and Epilation

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Abstract

Our purpose is to ascertain, if possible, whether atomic bomb survivors with cataracts and epilation were more radiosensitive than those survivors with cataracts but without epilation. A major ophthalmologic survey was conducted in Hiroshima and Nagasaki in 1963-64. At that time, 2125 individuals were examined. Among these individuals, estimated eye organ doses, based on the DS86 dosimetry system, and information on the occurrence of epilation within the first 60 days following the bombings are available on 1742. In the analysis of these data we have assumed that each individual represents a sample of one from a binomial distribution, and that the occurrence of cataracts and epilation are independent biological phenomena. We got following results. The threshold for cataract induction and its 95% confidence limits have been estimated from data on the occurrence of cataract and epilation. Among the 1742 study subjects, 40 had both cataracts and severe epilation. The estimated threshold based on these cases is 0.98 sievert(Sv), with 95% lower and upper confidence bounds of 0.72, and 1.32 Sv, respectively, and is highly statistically significant. Among the 27 cases of cataracts where severe epilation was not reported, the estimated threshold is 1.74 Sv with 95% lower and upper confidence bounds of 1.21 Sv, and “not estimable”. The difference between these two estimates is not statistically significant although the effect of dose is highly significant in both instances. The potential importance of biases in the DS86 dose estimates is discussed. The difference between the threshold estimated from cataract cases with epilation and that from cases without epilation is not statistically significant at the 5% or 10% level, and thus affords no support for the notion of increased

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radiosensitivity.

Keywords : Epilation, Mixed model, Profile approach, Radiation cataract, Threshold

1. Introduction

Epidemiological studies commonly generate data in which the variable measured on each individual can take only one of two possible values. Such a variable is called a binary or discrete variable. We have previously examined such data on the atomic bomb survivors in an effort to clarify the relationship of radiation exposure to the occurrence of cataracts, assuming different thresholds for those survivors who epilated("epilators") and those who did not("nonepilators") (Otake et al., 1996). We conjectured that the joint occurrence of cataracts and epilation might suggest an increased radiosensitivity, and sought to determine whether this was or was not true through examination of the threshold associated with cataract induction when epilation occurred and when it did not. We assumed cataract formation and epilation induction to be mutually independent biological processes.

Radiation-induced cataract is, in its early stages at least, usually regarded to be a highly 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 oran ophthalmoscope. In 1990, Otake and Schull estimated the threshold for cataract induction among the atomic bomb survivors to be in the neighborhood of 1.5 sievert(Sv), assuming a constant neutron RBE of 10. However, it was not known then whether, at agiven 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 dose as estimated by the Dosimetry System 1986(DS86) although the dose-response function appears nonlinear. Stram and Mizuno(1989) reported that 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.

As to the issue of radiosensitivity, the data remain ambiguous. Tucker et al. (1992), for example, have reported that they could find no clear evidence of an individual difference inradiosensitivity in the occurrence of acute and late skin reactions in the human. However, recently Stewart and Kneale(2000) have presented data suggesting that cancer mortality among atomic bomb survivors differs between those individuals with bomb-related injuries as contrasted with those without such injuries. Be this as it may, the issue of differences in radiosensitivity remains an interesting one which needs further research.

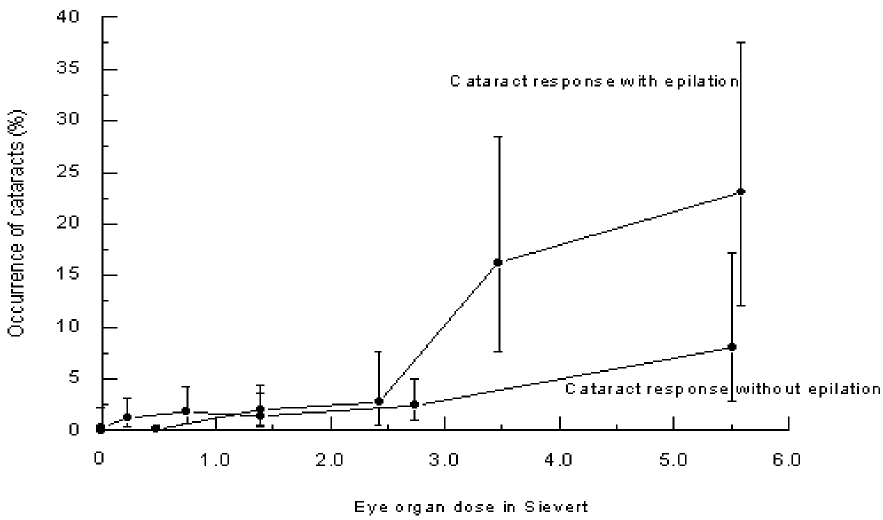
2. Materials and Methods

2.1 Study sample

Miller et al.(1969) conducted a major ophthalmologic survey at the Atomic Bomb Casualty Commission(ABCC) in 1963-64. In 1990, after the DS86 dose estimates (Roesch, 1987) became available, the findings of this survey were reevaluated using the estimated dose to the eye in Hiroshima and Nagasaki(Otake and Schull, 1990). Of the 2125 individuals Miller and his colleagues examined in these two cities, DS86 doses and information on the occurrence of epilation within the first 60 days following the bombings are available on 1742(Table 1). The remaining 383 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).

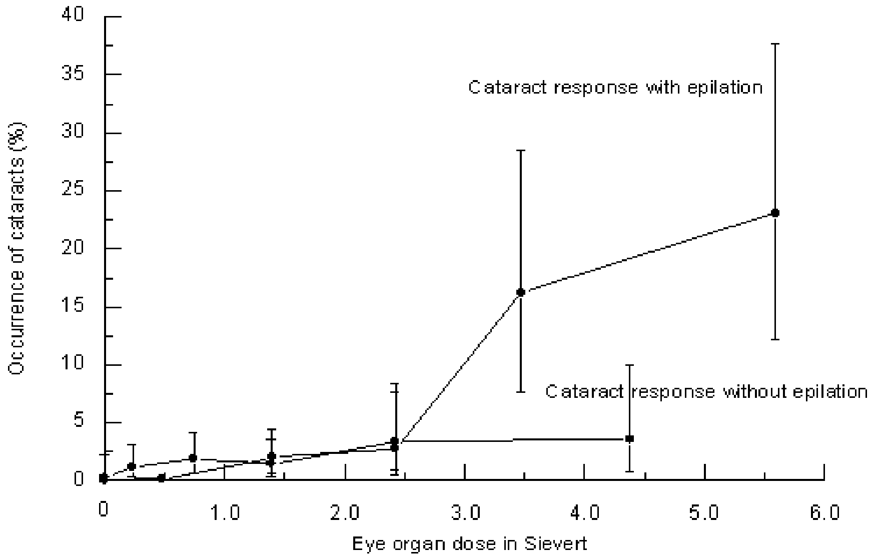
<Table 1> Number of subjects and cataract cases by epilation status

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
Total	1742	67

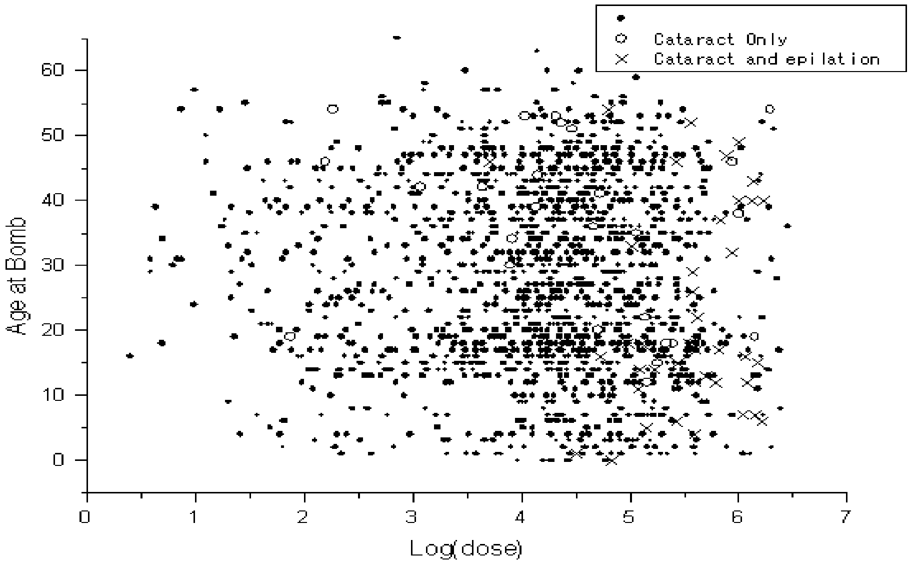


<Figure 1> Occurrence rate of cataracts with 95% confidence limits for epilators and nonepilators

Among the 1742 subjects, 67had radiation cataracts. Based on biomicroscopic classification, about 70% of these cataracts were considered to be small or less than small and only five were classified as large(Miller et al., 1969). Epilation among these 67 individuals was recorded as “absent”, “slight”, “moderate”, or “severe”, as described in Table 1. The relationship between the presence or absence of severe epilation and the occurrence of cataract is plotted by DS86 dose to the eye (Gy) in Figure 1. As is apparent from this figure, at the same dose, cataracts occurred more frequently among individuals with a history of severe epilation than among individuals without such a history. The distribution of individuals with both cataracts and epilation and cataracts alone is indicatedin Table 2 by DS86 dose to the eye (Sv), assuming a neutron RBE of 10. Figure 2 sets forth these data graphically. It will be noted that the occurrence of cataracts seems to be higher among epilators than nonepilators. In Figure 3, we plot by log dose (Sv) the age of the 1742 study subjects at the time of bombings (ATB).



<Figure 2> Occurrence rate of cataracts with 95% confidence limits with and without epilation



<Figure 3> Distribution of cataracts and epilation by age at the time of the bombing and log dose in sievert

<Table 2> Distribution of individuals with cataracts and epilation or with cataracts alone by DS86 eye organ dose in sieverts assuming a neutron RBE of 10

Dose group(Sv)	Average dose(Sv)	Subjecta	Positive opacity	%
Positive response both cataract and epilation				
<0.005	0	292	0	0.0
0.005-0.494	0.227	410	1	0.01
0.495-0.994	0.743	380	0	
0.995-1.994	1.391	371	8	2.2
1.995-2.994	2.424	150	4	2.7
2.995-3.994	3.473	74	12	16.2
>=3.995	5.592	65	15	23.1
Total	-	1742	40	2.3
Positive response of cataract only without epilation				
<0.005	0	292	1	0.3
0.005-0.494	0.227	409	5	1.2
0.495-0.994	0.743	380	7	1.8
0.995-1.994	1.388	363	5	14
1.995-2.994	2.426	146	5	2.4
2.995-3.994	3.468	62	0	
>=3.995	5.514	50	4	8.0
Total	-	1702	27	1.6

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

2.2 DS86 dose estimation

The analysis described here uses the DS86 dose to the eye computed in July 1989 and is thought to provide better estimates of dose than were initially possiblefor 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.

3. Statistical Methods

A task group of the International Commission on Radiological Protection(ICRP) stated in 1969 that the dose-response for cataract induction by ionizing radiation, whether of high or low LET, is highly sigmoid, and assumed the production of cataracts to be a deterministic phenomenon that can be totally avoided with appropriate dose limits. Alternatively stated, the task group assumed that a threshold exists 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 Merriam et al., 1972). Otake et al.(1996) have provided explicit estimates of risk on the basis of a binomial odds or Gompertz regression model, assuming two different thresholds, one for epilators and the other for nonepilators, and including sex and age ATB as discrete and continuous variables, respectively.

In the study cited, Otake et al. applied four statistical procedures and evaluated the goodness of fit of these models based on the numerical deviances, assuming a binomial distribution. They stated that the logistic model gave the poorest fit, when compared to the other three models used, namely, odds regression, Gompertz and simple regressions. The latter three models showed a similar trend in the goodness of fit to the individual data. However, the parameter estimates under the simple regression model were unstable whereas the odds and Gompertz models were stable with fewer iterations required to obtain the estimates of interest than with the simple regression, although the simple regression did converge under proper initial values. These findings prompted us to examine mixed statistical models with a threshold, specifically, an odds regression model and Gompertz regression model. These have been applied to independent binary data on the occurrence of cataracts and epilation. We assume these two events to be mutually independent biological processes and have related them to dose (Sv) based on a constant relative biological effectiveness(RBE) of neutrons of 10.

An estimate of the threshold based on a mixed model with or without both cataract and epilation and the 100(1-a)% confidence limits can be derived using the maximum likelihood approach. The relative risk model can be expressed as Background × RR, where RR includes a threshold. If one supposes that each individual represents a single observation from a binomial distribution, then the likelihood of observing the entire data set becomes

$$L = \prod (P)^{y}(1-P)^{1-y} = f(c, s, \alpha, \beta, T),$$

where y is 1 for an individual with cataracts and epilation, and 0 otherwise, and c, s, α, β and T refer to a constant(the intercept), sex, age ATE, the linear dose-response, and the threshold, respectively. The binomial regression models with one threshold fitted here are given by

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

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 a threshold is given by

$$[1+\beta(D-T)].$$

In this model, $(D-T)$ is zero when $D < T$ and D denotes the DS86 dose to the eye in sievert, based on a neutron RBE of 10 and β is the radiation effect for cataracts and epilation. The odds and Gompertz regression models I and II with a threshold employed here can be expressed as

Model I: Odds ratio regression(model I): $[P/(1-P)] = \text{Background} \times [1+\beta(D-T)]$

Model II: Gompretz regression(model II): $\ln(-\ln(P)) = \text{Background} \times [1+\beta(D-T)]$

Instead of a linear-response function Models I and II become a linear-quadratic response relationship with $[1+\beta(D-T)+\beta_2(D-T)^2]$.

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

$$[\beta_l(r+1)]=[\beta_l(r)]-\left[\frac{\partial^2 \log L}{\partial\beta_l\partial\beta_v}\Bigg|_{(r)}\right]^{-1}\left[\frac{\partial \log L}{\partial\beta_l}\Bigg|_{(r)}\right] \text{for } r=0,1,\cdots,w$$

where $l, v=1,\cdots,\tau$ and $\frac{\partial^2 \log L}{\partial\beta_l^2}\Big|_{(r)}=0$ for $l=v$, and $\frac{\partial^2 \log L}{\partial\beta_l\partial\beta_v}\Big|_{(r)}=0$ for $l\neq v$.

The parameter estimates are calculated using the Newton-Raphson method with step halving with the criterion:

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

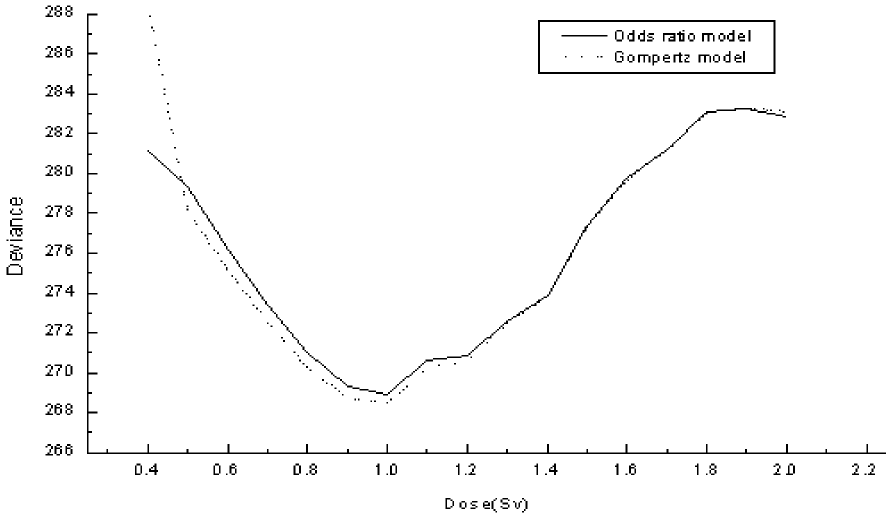
The largest likelihood value was selected from a number of deviances obtained by assigning successive incremental values to T, where T was taken to be 0, 0.05, 0.10,..., 1.5 Sv. The deviance statistic is $\chi^2=-2\log(L_c/L_f)$, where L_c is the likelihood in the current model and L_f is the likelihood 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 EPICURE(Preston et al., 1993). The criterion of 95% confidence limits based on deviance value is used as $\chi^2=3.841$ with one degree of freedom. The $100(1-\alpha)\%$ confidence limits were determined from χ^2 statistic, i.e.

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

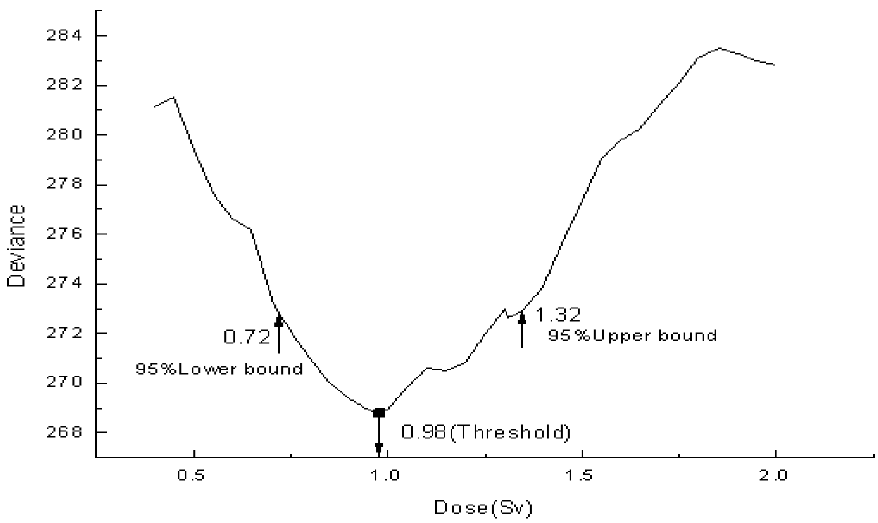
which is known as the log likelihood statistic. Hence, we have

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

where $-2\log L(X\mid T^*)/L_f$ is the deviance at the $100(1-\alpha)\%$ 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 were compared to determine which model was the most appropriate for the estimation of the threshold. The fit of the odds regression model was more stable and convergence occurred more rapidly than in the case of the Gompertz regression model. To examine the goodness of fit, the deviances of the two models I and II were plotted by step threshold in sievert(Figure 4). The Gompertz regression



<Figure 4> Goodness of fits(Deviance) of odds and Gompertz regression models

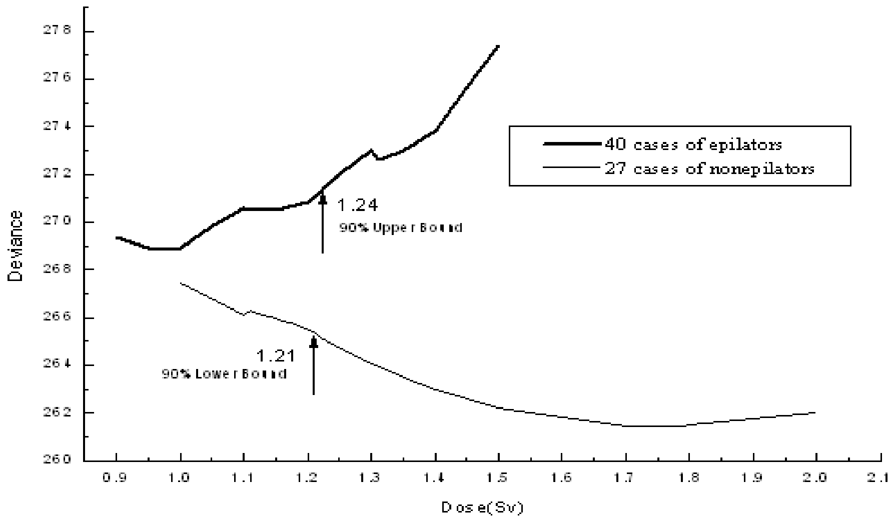


<Figure 5> Determination of a threshold and 95% confidence limits

model fits more poorly than the odds regression model to the data on the 27 cases without epilation, but the Gompertz model is not plotted in this figure. Figure 5 shows how to determine an asymptotic estimate of the threshold and its 95% confidence intervals.

4. Results

Table 2 gives the distribution of prevalences of cataracts with or without accompanying epilation based on the DS86 eye dose assuming a neutron RBE of 10. Analysis of these data indicates a threshold of 0.98 Sv for the 40 cataract cases with epilation. The 95% and 90% upper and lower confidence intervals for this threshold are (0.77, 1.24 Sv) and (0.72, 1.32 Sv), respectively. On the other hand, the threshold estimated for the 27 cataract cases without epilation is 1.74 Sv with 95% and 90% confidence intervals of (1.21 Sv, not estimable) and (1.22 Sv, not estimable), respectively. These two thresholds are both statistically significant, but they do not differ significantly one from the other(Figure 6). 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 for the 40 cases of cataracts with epilation. A highly significant but numerically small effect of age ATB was observed among the 27 cases without epilation(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. The age ATB effect, based on all of the data, is not significant, the deviance values being 567.737 and 567.567.



<Figure 6> Comparison of 90% confidence limits of a mixed positive response in 40 cataract cases with epilation and a positive response in 27 cataract cases without epilation

<Table 3> Parameter estimates for 1742 and 1702 subjects based on a threshold and 95% confidence limits by DS86 equivalent dose(RBE = 10).

Item	Odds regression Model I					
	40 cases of cataract with epilation			27 cases of cataract without epilation		
	Eatimate	Deviance	D.F.	Eatimate	Deviance	D.F.
Constant	0.02350	380.987	1741	0.01612	277.330	1701
Sex	0.009429	379.587	1740	-0.00438	276.865	1700
Age ATB	-0.0003664	377.039	1739	-0.00438**	267.750	1639
	52.72**	269.008	1738	1.999**	261.447	1638
Threshold	0.98	268.008	1737	1.74	261.477	1637
95%T(L, U)	(0.72, 1.32 Sv)	(272.9, 272.8)		(1.21, NE)	(265.32, NE)	

Note. ATB denotes age at the time of the bombings. NE is not estimable. ** is significant at P<0.001.

The ratio of the slope based on the 40 cases of cataracts with epilation to the slope for the 27 cases without epilation is roughly 26(52.7/1.999) under the odds regression model.

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, any dose-response model is conjectural to some extent and the applicability of a given model rests on its accordance with other radiation-related biological events and judgments of apparent “reasonableness”. Here a dose-response model with a threshold 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 gamma-radiation to the appearance of lens opacities in humans varies widely, from six months to 35 years, with an approximate average of 2-3 years(Merriam et al., 1972 and ICRP, 1990). This time of onset was deduced by Merriam et al. in 1972 from the findings from a number of different, and not necessarily equivalent studies. For example, the study of Merriam and Focht(1957) was a retrospective assessment. The average latent period in Hiroshima and Nagasaki cannot be estimated since the first cases were not reported until 1949, about 4 years after the bombing(Cogan et al., 1949). The time of onset of the cataracts seen in the atomic-bomb survivors is unknown in most instances because the data are cross-sectional observations.

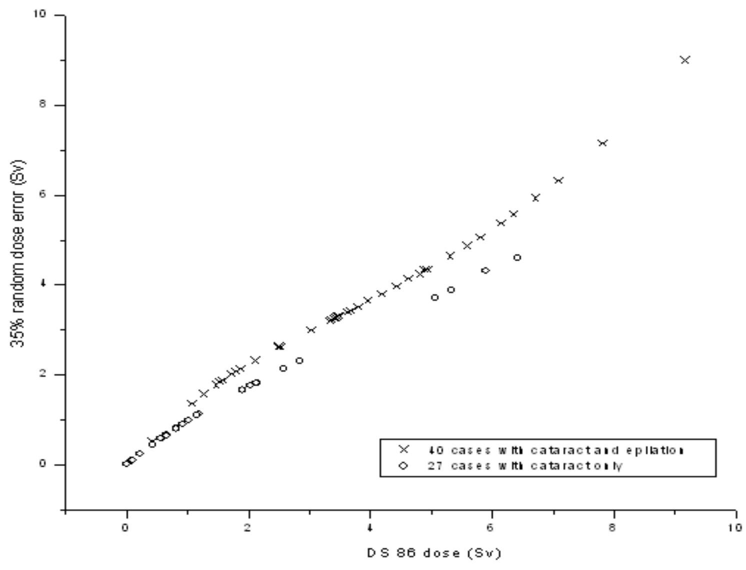
Radiation produces both cataracts and epilation. At issue in this paper is the existence of a difference in individual radiosensitivity. As is evident from Figure 2, it seems there is a difference in the radiosensitivity of cataract cases with and without epilation. However, the mechanism of cataract induction is different from that of epilation. In the former instance, a threshold in the dose-response relationship is easily demonstrable, but this is not so for epilation. Nonetheless, we can assume that the relationship to dose of cataracts, on the one hand, and epilation, on the other, is mutually independent. As previously noted, the ICRP report supported the view that cataracts do not occur as doses less than 2.0 Gy. In our sample among the 324 cases who had epilation, only 40 also had cataracts. The remaining 284 cases did not exhibit such an effect. However, Otake et al.(1996) reported that the issue is not whether radiation has such an effect, but whether there is a difference in radiosensitivity for cataract induction between individuals with epilation and those without. The data suggest the same degree of risk in the low-dose region as in the control when one considers the error variation.

There are many clinical studies of individual variation in 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). In our study, although a threshold is demonstrable for both the 40 cases of cataracts with epilation as well as the 27 cases without, a difference in radiosensitivity between these two groups cannot be demonstrated unequivocally.

Atomic-bomb survivors were simultaneously exposed to gamma and neutron radiation, 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 gamma 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 the safety zone by the following rule: If we assume no interaction and an RBE for neutrons of 12.2, the 0.73 Gy threshold for gamma 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. In the present study, a threshold of 0.98 Sv was estimated for the 40 cases with cataracts and epilation, whereas the threshold for the 27 cases without epilation is 1.74 Sv. No statistically significant difference exists between these two estimates.

Recently Stewart and Kneale(2000) have examined the relationship of cancer mortality in atomic bomb survivors to the presence or absence of bomb-related injuries utilizing a categorical comparison of the two groups with age-stratified adjustment. They purport to show that the two groups differ significantly for specific causes of death. However, their results fail to take into account time effects in the follow-up or the prospective nature of the study. Their analysis also ignores person-years at risk, and merely applies chi-square statistics, assuming a normal distribution, to a subgroup comparison of controls and residue with stratified adjustment for nuisance parameters.

In 1996, Otake et al. evaluated not only the dose-response relationship with two threshold estimates based on the DS86 eye dose estimates, but also analyzed the data assuming a 35% random-dose error. Otake et al. showed that the threshold of occurrence of cataracts for epilators in the higher dose groups tends to be higher(1.21 Sv) when a 35% random error in the dose estimates is assumed. However, the threshold estimate for the nonepilators declined from 1.54 Sv to 1.41 Sv under the same error assumption. In this paper, as earlier noted, we have assumed cataracts and epilation to be mutually independent events and again examined the effect of a 35% random error in the doses on the estimated threshold. The results are similar to those described above. Among the 40 cases of cataract with epilation, the estimated threshold is 1.27 Sv with the 95% and 90% lower and upper confidence intervals, i.e., (1.06, 1.53 Sv) and (1.01, 1.56 Sv). Whereas among the 27 cases of cataract without epilation, the threshold estimate is now zero with an upper confidence interval of 3.5 Sv or more. These two thresholds do not differ significantly. Figure 7 gives the distribution of the cases of cataracts with(40) and without(27) epilation based on the DS86 doses(Sv) and a 35% random-dose error(Sv). From Figure 7, the 35% random-dose error is consistently lower than that of DS86 doses. The study in 1996 involved 27 cases of cataracts among 1419 nonepilators. As previously stated, the threshold value for these cases was 1.41 Sv. However, in the present study, it is zero.



<Figure 7> Distribution of 40 and 27 mixed data of cataracts with or without epilation on DS86 doses (Sv) and 35% random-dose error (Sv)

In 1990 Otake and Schull(1990) fitted simple binomial regression models with and without thresholds for the gamma 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 number 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 regression models required more iterations than the odds regression models. In the present study, we have applied binomial odds or Gompertz regression models with a threshold. The goodness of fit in the odds regression model is more stable for the 27 cases of cataracts without epilation than is the fit from the Gompertz regression model. However, the latter model does converge if the appropriate initial(trial) values are used. We also fitted a linear-quadratic(L-Q) with a threshold to the individual cataract data with and without epilation. We note, first, that the results give not only larger deviances than those of the L-L dose-response model with a threshold, but also the effects associated with the quadratic(Q) term are not significant. Second, the estimated threshold in this study is significantly positive which is consistent with the supposition that cataracts are a deterministic event.

The ICRP(1969, 1990) gives a table of RBE values for the production of opacities of the lens with single exposures to x- or gamma-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 dose based upon an assumed constant neutron RBE of 10 so that we can compare the results between DS86 eye organ dose.

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