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Technical Report Series

Radiation-related Posterior Lenticular Opacities in Hiroshima and Nagasaki Atomic Bomb Survivors Based on T65DR and DS86 Dosimetry Systems

Masanori Otake, Ph.D.; William J. Schull, Ph.D.

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1989年から，放射線影響研究所の業績報告書は，従来の日英両文を併記した方式では発行しない．主要な報告書については，今後も日英両文で印刷するが，それぞれ別に発行する．内容が高度に専門的であり，一般の関心が少ないと思われる報告書については英文のみとし，日本文の要約を添付する．

これにより，広島・長崎の原爆電離放射線被曝の人体に及ぼす晩発性生物学的影響に関する最近の知見を今までよりも速やかにお知らせできることと思う．

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業　績　報　告　書

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広島・長崎原爆被爆者の水晶体後嚢下混濁と放射線との関係—T65DR及びDS86線量推定方式に基づく検討§

Radiation-related Posterior Lenticular Opacities in Hiroshima and Nagasaki Atomic Bomb Survivors Based on T65DR and DS86 Dosimetry Systems

大竹正徳[1]，William J. Schull[2]

[1]統計部及び[2]元常務理事

要　約

電離放射線被曝によって水晶体に傷害が起こることが証明されており，以前の調査で広島・長崎の原爆被爆者に水晶体後嚢下混濁の発生が認められている．原爆被曝線量の再評価の結果，DS86と呼ばれる新しい線量推定方式が決定された．本報では，広島・長崎の原爆被爆者における水晶体後嚢下混濁の発現率と電離放射線との定量的関係を，この新しいDS86線量推定方式に基づいて再検討し，水晶体後嚢下混濁発生とガンマ線及び中性子との関係を評価し，更に以前のT65DR線量推定方式に基づくリスク推定との比較を行った．

前回の1982年調査の解析対象であった原爆被爆者2,124名のうち1,983名（93.4%）に対してDS86線量が利用可能である．広島原爆被爆者の場合，以前のT65DRに比べてDS86に基づくカーマ中性子成分は極めて少ない．しかし，広島におけるDS86カーマ中性子成分（総線量6 Gyで0.38 Gy）は，長崎の中性子成分（総線量6 Gyで0.09 Gy）の割合よりも依然として4.2倍も大きい．したがって，もし眼が中性子に対して特別に感受性が高いとすれば，特に広島において中性子の影響について何か有用な知見が得られるかもしれない．

線量反応関係は，推定されたガンマ線及び中性子線量別の関数として検討した．二つの閾値を仮定した場合と仮定しない場合に基づいて幾つかの線量反応関係モデルを考察し，モデル適合度における最小のχ^2値，又は最大の対数尤度値によって最適モデルを選んだ．最もよい

§本報告にはこの要約以外に訳文はない．

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適合度を示したのは，ガンマ線について線形，中性子についても線形で，放射線に対して異なる二つの閾値を仮定した線量反応関係モデルである．

本報では，眼に到達したエネルギーをDS86方式に基づいて推定した眼の臓器線量とした．これに対して適合度が最もよいモデルにおいて，ガンマ線及び中性子線の回帰係数はともに正であり，極めて有意であると認められた．

個人データのDS86カーマ線量について見れば，DS86ガンマ線の回帰係数とT65DRガンマ線の回帰係数の比は1.1倍（95%信頼限界：0.5～2.3）であり，両者はほとんど同程度である．次に眼のDS86臓器線量とDS86カーマ線量との間のリスクを比べると，その比は1.3倍（0.6～2.8）である．しかし，中性子について見れば，DS86カーマの場合のリスク推定は，T65DRカーマの場合に比べて6.4倍（2.2～19.2）も高くなり，眼のDS86臓器線量ではDS86カーマの場合よりもリスクは1.6倍（0.5～5.2）高い．

眼のDS86臓器線量に基づいて求めた個人のガンマ線及び中性子線の各成分から得た相対的生物効果比（RBE）の推定値は$32.4+0.73/(D_\nu-0.06)>0$，その95%信頼限界は11.8から$88.8+1.39/(D_\nu-0.06)>0$の範囲である．この場合，D_νはGy単位で示した中性子線量である．中性子線についてこのような閾値を使用した場合のRBE推定値は，D_νが0.07 Gyのときに総線量0.01 Gyで105，D_νが0.16 Gyのときに0.10 Gyで40，D_νが0.26 Gyのときに0.20 Gyで36，D_νが0.36 Gyのときに0.30 Gyで35などである．このRBEの95%下限推定値から12という定数が示唆される．なお，$(D_\nu-0.06)>0$の制限から，D_νが0.06より小さい場合又は等しい場合にRBEを推定できないことに注意すべきである．

いずれにしても，眼に対する中性子成分の重要性は，人体の他の部位の場合よりも一層顕著であることがこれらの値から強く示唆される．中性子閾値の95%下限推定値につき，ゼロの場合を含めて考慮すると，RBEは11.8から$88.8+1.39/D_\nu$の範囲内で$32.4+0.73/D_\nu$として推定される．

最後に，適合度がやや劣るが，ガンマ線について線形・2次関数関係，中性子線について線形関係を仮定した線量反応関係モデルを用い，二つの閾値を仮定したRBEの推定値が，ガンマ線について線形関係，中性子線についても線形関係を仮定した線量反応関係モデルに基づく推定値に極めて類似していることは興味深い．ただし，このモデルでは，ガンマ線の2次関数関係の回帰係数は線量と有意な関係を示さない．

Technical Report Series

Radiation-related Posterior Lenticular Opacities in Hiroshima and Nagasaki Atomic Bomb Survivors Based on T65DR and DS86 Dosimetry Systems§

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Summary

This paper investigates the quantitative relationship of ionizing radiation to the occurrence of posterior lenticular opacities among the survivors of the atomic bombings of Hiroshima and Nagasaki, as suggested by the DS86 dosimetry system. DS86 doses are available for 1,983 (93.4%) of the 2,124 A-bomb survivors analyzed in 1982. The DS86 kerma neutron component for Hiroshima survivors is much less than its comparable T65DR component, but is still 4.2-fold higher (0.38 Gy at 6 Gy) than that in Nagasaki (0.09 Gy at 6 Gy). Thus, if the eye is especially sensitive to neutrons, some useful information on neutron effects may yet be discernible, particularly in Hiroshima. The dose-response relationship has been evaluated as a function of the separately estimated gamma-ray and neutron doses. Among several different dose-response models with and without two thresholds, we have selected the the one with the smallest χ^2 or the largest log likelihood value associated with the goodness of fit. The best fit is a linear gamma-linear neutron relationship which assumes different thresholds for the two types of radiation.

In the DS86 system, both gamma-ray and neutron regression coefficients for the best-fitting model are positive and highly significant for the estimated energy deposited in the eye, here termed the eye organ dose. The DS86 gamma regression coefficient is almost the same as that associated with the T65DR gamma kerma, the ratio of the two coefficients being 1.1 (95% confidence limits: 0.5–2.3) for DS86 kerma in the individual data. If the risks based on the DS86 eye organ dose and DS86 kerma are compared, the ratio is 1.3 (0.6–2.8). However, the risk estimates associated with neutron exposure are 6.4-fold (2.2–19.2) higher for the DS86 kerma than for the T65DR kerma and 1.6-fold (0.5–5.2) higher for the DS86 eye organ dose than for the DS86 kerma.

§**The complete text of this report will not be available in Japanese.**

A paper based on this report has been accepted for publication in Radiation Research.

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The relative biological effectiveness (RBE) values based on the individual gamma and neutron components of the DS86 eye organ dose are estimated to be 32.4 + $0.73/(D_\nu - 0.06) > 0$ with the 95% confidence limits ranging from 11.8 to 88.8 + $1.39/(D_\nu - 0.06) > 0$, where D_ν is the neutron dose in gray. When such a threshold for the neutron dose is used, the RBE estimates are 105 at 0.01 Gy when D_ν is 0.07 Gy, 40 at 0.10 Gy when D_ν is 0.16 Gy, 36 at 0.20 Gy when D_ν is 0.26 Gy, 35 at 0.30 Gy when D_ν is 0.36 Gy and so on. The RBE value with the 95% lower bound suggests the constant to be 12. It should be noted that we cannot estimate the RBE when D_ν is less than or equal to 0.06 Gy based on the restriction of $(D_\nu - 0.06) > 0$.

In any case, these values strongly suggest that the neutron component could be more important for the eyes than for other sites of the body. If we take into consideration the 95% lower bound of the neutron threshold including zero, we estimate the RBE values as 32.4 + $0.73/D_\nu$ with a range from 11.8 to 88.8 + $1.39/D_\nu$. Finally, it is interesting to observe that a linear-quadratic gamma and linear neutron model with two thresholds, which fits the data less well, produces very similar estimates of the two thresholds as the linear gamma-linear neutron-response model. In this model, however, the regression coefficient is not significantly associated with the quadratic gamma response.

Introduction

Damage to the lens is a well-recognized sequela of exposure of the eye to ionizing radiation.[1] Cataracts have been observed experimentally in several species of laboratory animals[2–5] after X-ray or neutron exposure and they have also been seen clinically in man[6] following similar exposures. Radiation cataracts have also been observed in cyclotron workers[7] and in A-bomb survivors in Hiroshima and Nagasaki. Since the original description of radiation-related cataracts among A-bomb survivors by Cogan et al[8] in 1949, many ophthalmologic reports of a clinical, histopathological, or statistical nature have been published.[9–18] It is apparent from these studies as well as others that radiation-induced cataract is, in its early stages, at least, a highly characteristic lesion. It is generally defined as a central, posterior subcapsular opacity, easily visible with a slit lamp biomicroscope or an ophthalmoscope.

In 1982, a reexamination of these earlier findings on posterior lenticular opacities among A-bomb survivors in Hiroshima and Nagasaki was initiated by Otake and Schull.[19] They examined the dose-response relationship of lenticular opacities to gamma and neutron exposures based on three different dosimetry systems, i.e., the tentative 1965 dose estimates revised (T65DR),[20,21] the Oak Ridge National Laboratory estimates (ORNL),[22] and the Lawrence Livermore National Laboratory estimates (LLNL).[23] These latter two reassessments were tentative, since their estimates of individual exposure used were based on the T65DR dosimetry system and the average attenuation factors which were then under extensive review.

In March 1986, as a result of a comprehensive reevaluation of the exposures of the A-bomb survivors of Hiroshima and Nagasaki, a new method for estimating individual doses was introduced, termed the Dosimetry System 1986 (DS86).[24] There are important differences between this system and its predecessor. The T65DR kerma estimates are merely the estimates of free-in-air kerma multiplied by average correction factors for structural materials. The organ or tissue doses based on the T65DR system are also estimated using fixed coefficients to describe the attenuation of radiation in tissue.[25] On the other hand, the new DS86 kerma estimates are individually computed without use of explicit average building transmission factors. Estimates of the energy deposited in the eye, based on the T65DR dosimetry, are not available, but such estimates do exist for the DS86 dosimetry. We shall hereafter refer to the latter as the DS86 eye organ dose.

In the present study, we will evaluate the relationship of gamma rays and neutrons to the occurrence of posterior lenticular opacities among A-bomb survivors using the newer DS86 dose estimates, and we will briefly compare these risk estimates with those derived from the earlier T65DR dosimetry.

Materials and Methods

Miller et al[14] reviewed the major ophthalmologic surveys conducted at ABCC in 1949–62 and undertook a large investigation in 1963–64[15] to evaluate the effects of ionizing radiation on the lens of the eye. The appendix of their report lists 84 persons (56 in Hiroshima and 28 in Nagasaki) with ostensible posterior opacification of the lens observed with an ophthalmoscope and later examined with a slit lamp. In 1982, we reviewed all of their medical records.[19] As a result, five cases in Hiroshima and two in Nagasaki were excluded, for either there was no recorded slit lamp confirmation or the slit lamp revealed a cortical (including anterior subcapsular) or a nuclear opacity but no posterior subcapsular defect. We considered a) the slit lamp more reliable and accurate than the ophthalmoscope in the localization of a lenticular lesion and b) evidence of a posterior subcapsular defect to be the sine qua non of a radiation-induced lesion. Interestingly, three of the five cases exhibited only nuclear opacities which were interpreted in two instances as congenital by the ophthalmologist, and one case, exhibiting only an anterior subcapsular defect, was not in the city at the time of the bombing (ATB). Finally, the children exposed in utero have also been excluded; only one of the 309 prenatally exposed survivors examined was observed to have any degree of lens opacification. Thus, our analysis rests on 76 of the 84 cases in the Adult Health Study (AHS) population[26] reported by Miller et al.[15] Detailed information on these cases will be found in Appendix 1 compiled by Otake and Schull.[19]

Dosimetry

For comparative purposes, the results of three analyses will be presented, one based on the estimates of kerma using the T65DR, the second based on the DS86 kerma, and the last based on the DS86 eye organ dose. As previously stated, estimates of the energy deposited in the eye, based on the T65DR dosimetry, were not included among the 18 organs studied by Kerr.[25] In the

DS86 system, individual doses are computed in one or the other of two ways.[24] When detail shielding histories exist for survivors within 1,600 m of hypocenter in Hiroshima (within 2,000 m in Nagasaki), dose estimates are obtained by modeling directly the circumstances attending an individual's exposure including posture and orientation toward the burst point; fixed transmission coefficients are not used. These estimates are termed direct. At distances beyond 1,600 m (or 2,000 m), individual doses are assigned in most instances by regression methods which employ average transmission factors computed from the experiences of individuals exposed between 1,000 and 1,600 m in Hiroshima (or between 1,000 and 2,000 m in Nagasaki). Such estimates are said to be indirect. However, it should be noted that whenever a detailed shielding history was available, even if exposure occurred beyond 1,600 m (or 2,000 m), the direct method of computation was used. Appendix 1 gives the number of individuals within the ophthalmologic study population whose doses were directly and indirectly estimated by dose groups.

To examine briefly the comparative risks between the DS86 dose estimates and those derived from the T65DR dosimetry, individuals have been classified on the basis of their estimated combined gamma and neutron exposures into the same dose intervals for the T65DR kerma, DS86 kerma, and DS86 eye organ dose. If the total (gamma + neutron) kerma or organ dose exceeded 6 Gy, it was truncated to 6 Gy. Table 1 shows the correspondence in estimated kerma between the two systems. The DS86 sample used here consists of 1,983 (93.4%) of 2,124 subjects, 1,325 (95.1%) of 1,393 in Hiroshima and 658 (90.0%) of 731 in Nagasaki. Of these 76 individuals who exhibited lenticular opacities, 71 (93.4%) are included in the DS86 sample (Table 2 and Appendix 2). Figure 1 shows their distribution by the gamma and neutron components of the DS86 eye organ dose and by city.

It should be noted that in Table 2 the mean gamma and neutron doses for the 6+ Gy group differ from those given in the previous paper[19] in 1982. At that time, individuals ostensibly exposed to more than 10 Gy were given the same mean gamma and neutron doses observed in the 6.00–9.99 Gy group in their respective cities. As is evident from Table 1, the principal difference between the T65DR and DS86 samples is a shift from high estimates with the T65DR dosimetry to lower estimates with the DS86.

Statistical Considerations and Methods

The extent of the biological effects on the eye resulting from exposure to ionizing radiation was determined primarily by the quantitative and qualitative relationship of dose and its effect. A number of different relationships can be envisaged: These include situations in which the effects increase linearly, quadratically, exponentially or logistically with dose. However, given that the cellular events involved in radiation-related cataractogenesis in man are imperfectly known, all dose-response models are conjectural to some extent. Their applicability can be evaluated only by an appeal to experimental findings on infrahuman species, to models fitted to other radiation-related biological events,

Table 1. A comparison of the individual T65DR and DS86 dose estimates in the study sample by city

T65DR kerma dose in gray	DS86 kerma in gray											
	<0.01	0.01–0.49	0.50–0.99	1.00–1.99	2.00–2.99	3.00–3.99	4.00–4.99	5.00–5.99	6.00+	Subsample dose	Unknown	Total
Hiroshima												
<0.01	300									300	0	300
0.01–0.49		169	19							188	19	207
0.50–0.99		54	143	6						203	8	211
1.00–1.99			145	158	3					306	13	319
2.00–2.99				111	28					139	8	147
3.00–3.99				14	53	13				80	5	85
4.00–4.99				2	35	14	3			54	2	56
5.00–5.99					5	12	2	1		20	7	27
6.00+					2	5	9	13	6	35	6	41
Total	300	223	307	291	126	44	14	14	6	1325	68	1393
Nagasaki												
<0.01	227									227	0	277
0.01–0.49	3	101								104	22	126
0.50–0.99		53	11							64	19	83
1.00–1.99		9	57	17						83	15	98
2.00–2.99			30	51	1					82	4	86
3.00–3.99			1	33	10	1				45	5	50
4.00–4.99				6	16	3				25	1	26
5.00–5.99				3	6					9	2	11
6.00+					2	1	6	4	6	19	5	24
Total	230	163	99	110	35	5	6	4	6	658	73	731

Table 2. Occurrence of lens opacification by city and dose based on T65DR kerma, DS86 kerma, and DS86 eye organ dose*

Dose group in gray	Hiroshima							Nagasaki						
	Total	Gamma	Neutron	Examined	Mean age ATB	Positive	%	Total	Gamma	Neutron	Examined	Mean age ATB	Positive	%
						T65DR kerma								
<0.01	0.00	0.00	0.00	300	29.5	3	1.0	0.00	0.00	0.00	227	21.0	2	0.9
0.01–0.99	0.49	0.39	0.10	418	30.5	3	0.7	0.43	0.43	0.00	209	25.8	5	2.4
1.00–1.99	1.43	1.12	0.31	319	30.3	5	1.6	1.49	1.47	0.02	98	24.0	1	1.0
2.00–3.99	2.83	2.14	0.69	232	26.0	17	7.3	2.85	2.81	0.04	136	25.8	8	5.9
4.00–5.99	4.74	3.55	1.19	83	26.6	9	10.8	4.68	4.60	0.08	37	23.1	4	10.8
6.00+	6.00	4.19	1.81	41	26.3	14	34.1	6.00	5.83	0.17	24	24.0	5	20.8
Total	-	-	-	1393	29.1	51	3.7	-	-	-	731	23.9	25	3.4
						DS86 kerma								
<0.01	0.00	0.00	0.00	300	29.5	3	1.0	0.00	0.00	0.00	230	21.2	2	0.9
0.01–0.99	0.54	0.53	0.01	530	30.6	6	1.1	0.40	0.40	0.00	262	25.3	7	2.7
1.00–1.99	1.40	1.35	0.05	291	29.0	5	1.7	1.38	1.37	0.01	110	24.9	7	6.4
2.00–3.99	2.65	2.53	0.12	170	25.7	20	11.8	2.53	2.50	0.03	40	21.9	4	10.0
4.00–5.99	4.98	4.67	0.31	28	26.8	11	39.3	4.87	4.79	0.08	10	17.0	2	20.0
6.00+	6.00	5.62	0.38	6	27.0	3	50.0	6.00	5.91	0.09	6	19.3	1	16.7
Total	-	-	-	1325	29.3	48	3.6	-	-	-	658	23.4	23	3.5
						DS86 eye organ dose								
<0.01	0.00	0.00	0.00	300	29.5	3	1.0	0.00	0.00	0.00	230	21.2	2	0.9
0.01–0.99	0.54	0.53	0.01	587	30.6	7	1.2	0.40	0.40	0.00	248	24.9	8	2.8
1.00–1.99	1.43	1.40	0.03	269	28.3	9	3.3	1.38	1.37	0.01	101	26.0	8	7.9
2.00–3.99	2.64	2.56	0.08	143	25.5	18	12.6	2.56	2.54	0.02	30	21.3	3	10.0
4.00–5.99	4.87	4.67	0.20	26	28.0	11	42.3	4.90	4.85	0.05	12	14.8	2	15.4
6.00+	-	-	-	0	-	0	-	6.00	5.92	0.08	1		0	
Total	-	-	-	1325	29.3	48	3.6	-	-	-	658	23.4	23	3.5

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

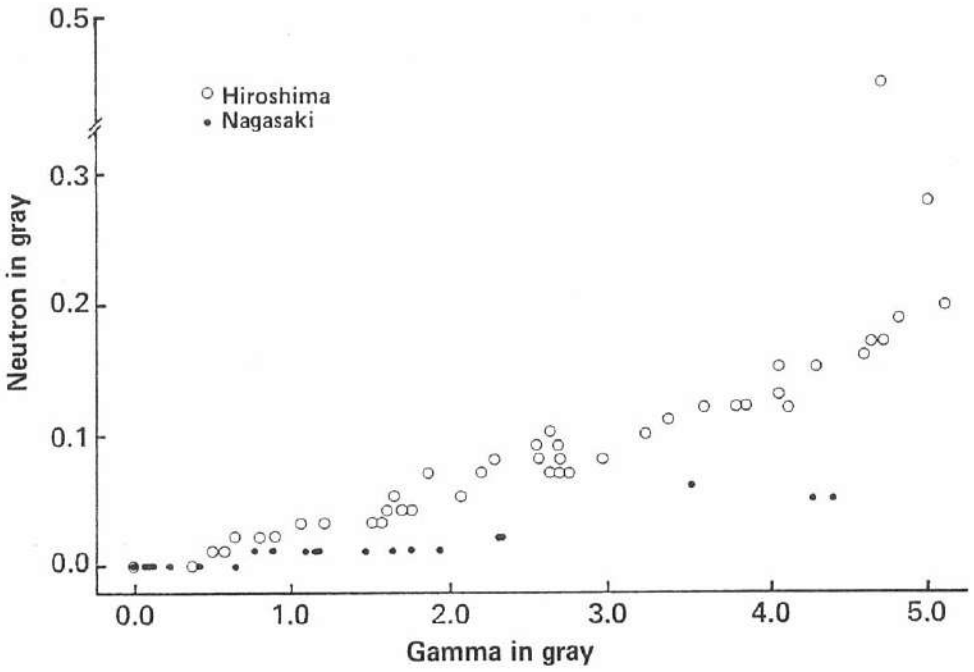

Figure 1. *The distribution by city of the 71 cases with lenticular opacities based on the estimated DS86 absorbed doses to the eye of gamma rays and neutron*
Note that the neutron dose in one instance in Hiroshima (MF# [redacted] *) is much higher than the dose in any other case.*

to statistical judgments of "goodness of fit," or to apparent "reasonableness." A 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."[27] A second Task Group of Committee I of ICRP has reiterated this position. Both the commission and the task group assume the production of cataracts to be a nonstochastic phenomenon, one which can be totally avoided with appropriate dose limits; i.e., both assume a threshold below which radiation cataracts do not occur. The latter, for a single exposure, has been commonly taken to be around 2 Gy.

Suppose, now, that P is the probability that an individual who has received doses, D_γ and D_ν, of gamma and neutron radiation, respectively, will develop a posterior subcapsular opacity. Assume further that n_{ij} is the number of independent individuals examined in the ij^{th} dose group of whom a_{ij} are affected (i = gamma dose category; j = neutron dose category). If the a_{ij} are binomially distributed, then the likelihood of observing the entire data set or binary array is

$$L_{ij} = \prod_{ij} \binom{n_{ij}}{a_{ij}} (P_{ij})^{a_{ij}} (1 - P_{ij})^{n_{ij} - a_{ij}} \quad \text{or} \quad L = \prod P^y (1 - P)^{1-y} \quad ,$$

where y is 1 for an individual with lenticular opacities and 0 for others.

As simple approximations, we have fitted two models, but present only the formulas for the case of the individual binary data. One assumes the dose response to be linear for both gamma rays and neutrons, i.e.,

$$P_k = \alpha_k + \beta_\gamma D_{\gamma k} + \beta_\nu D_{\nu k} \quad . \qquad \text{(A)}$$

The other assumes a linear-quadratic response to gamma irradiation, but a linear one to neutrons, i.e.,

$$P_k = \alpha_k + \beta_\gamma D_{\gamma k} + \beta_{\gamma^2} D_{\gamma k}^2 + \beta_\nu D_{\nu k} \quad . \qquad \text{(B)}$$

The variations which arise from the assumption of a threshold (or thresholds) of damage in the occurrence of radiation-dependent lenticular opacities have been fitted to the following models:

$$P_k = \alpha_k + \beta_\gamma (D_{\gamma k} - T_\gamma) + \beta_\nu (D_{\nu k} - T_\nu) \qquad \text{(C)}$$

and

$$P_k = \alpha_k + \beta_\gamma (D_{\gamma k} - T_\gamma) + \beta_{\gamma^2} (D_{\gamma k} - T_\gamma)^2 + \beta_\nu (D_{\nu k} - T_\nu) \quad , \qquad \text{(D)}$$

where (C) and (D) hold only if $(D_{\gamma k} - T_\gamma) \geq 0$ and $(D_{\nu k} - T_\nu) \geq 0$, T_γ and T_ν are thresholds of gamma and neutron doses, respectively, and $k = 1$ or 2 (Hiroshima or Nagasaki, respectively), etc. In the frequency data, we have used mean doses in the various dose categories, and in the binary response data, we have used the individual dose estimates.

The parameters of these models were estimated by the method of maximum likelihood (ML), assuming the observed number in each cell to be a binomial variate having an expected value based on the model equation. The data used to assess the dose-response relationship are given by city and six total dose categories in Table 2. The smallest χ^2 or largest log likelihood value was selected from a number of χ^2 or log likelihood values obtained through assigning successive incremental values to T_γ, the gamma-ray threshold for a given T_ν (the neutron threshold), where T_ν was taken to be 0, 0.05, 0.10,..., Gy. The 95% confidence limits were determined from the same likelihood ratio χ^2 statistic, namely,

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

where $T^* = L$ (a 95% lower bound) or U (a 95% upper bound) and T is the ML estimate of the threshold.[28]

Results

The number of cases of lenticular opacities and subjects with their mean ages ATB, mean gamma and mean neutron doses corresponding to each dose group are given by T65DR kerma, DS86 kerma, and DS86 eye organ dose in Table 2. As

can be seen, by applying the DS86 dose estimates in Hiroshima and Nagasaki, a large number of subjects shift from higher to lower dose groups as compared to their T65DR exposures. In particular, the number of individuals exposed to 6 Gy or more decreases from 41 (T65DR kerma) to 6 (DS86 kerma) to 0 (DS86 eye organ dose) in Hiroshima and from 24 to 6 to 1 in Nagasaki. The contribution of neutrons to the total mean DS86 kerma is only 0.38 Gy (6.3%) at 6 Gy total kerma in Hiroshima and 0.09 Gy (1.5%) in Nagasaki, as contrasted with 1.81 Gy (30.2%) in Hiroshima and 0.17 Gy (2.8%) in Nagasaki using the T65DR dosimetry. The observed risk rates based on the DS86 dose estimates are higher than those seen with the T65DR doses. This trend is stronger in Hiroshima than in Nagasaki (Figure 2).

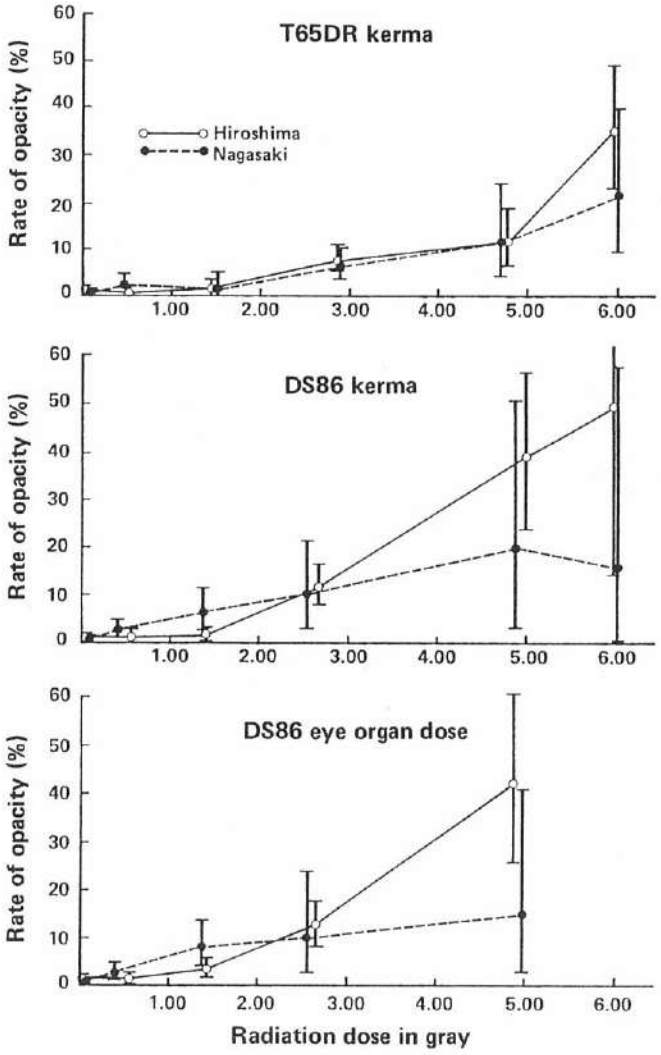

Figure 2. Occurrence rate of lenticular opacities and 95% confidence intervals by type of dosimetry and city

Age at exposure could be a determinant in the occurrence of a lenticular opacity and ages ATB may be unequally distributed among the exposed and the nonexposed. The mean age of the city-specific data changed from 29.3 years ATB in Hiroshima to 23.4 years ATB in Nagasaki for the DS86 subsample. This difference between the cities in mean age at exposure is highly significant in both samples, but in neither city does age increase systematically with dose. A test of the homogeneity of the mean ages within the six dose categories by city reveals significant heterogeneity for the DS86 dosimetry system as well as the T65DR. Significance appears to be ascribable largely to a difference in mean ages between the lower and higher dose groups. The mean age in the higher dose group is significantly less than that in the lower dose group in both cities, which suggests that age ATB could contribute spuriously to the effect of radiation.

To examine this matter further, three different regression analyses of the individual binary response data (1 or 0) were made, each of which includes age and city as well as gamma and neutron doses among the independent variables (Appendix 3). With all three models indicated in Appendix 3, the regression coefficient associated with the neutron dose is more strongly positive than the coefficient associated with the gamma-ray dose. A highly significant difference was also observed for the regression coefficients associated with city and age for the three different estimates of dose using Model I. Based on the log likelihood value, Model II, which includes city-specific age effects, gives almost the same fit as Model I. No significant difference between cities is noted with Model II. Model III, which takes into account city-specific background effects, gives not only a good or reasonable fit but also a stable positive estimate for all the expectations. Therefore, the differences in age at exposure did not have a strong effect on the occurrence of opacities of the lens. Accordingly, we will focus on the four models with and without thresholds described in Statistical Considerations and Methods.

Dose-Response Relationship and Thresholds

The parameter estimates and the goodness of fit for the models with and without thresholds for the grouped data are shown in Table 3. As is evident from the results given in this table, a linear-linear (L-L) regression model without a threshold does not fit either the T65DR kerma data ($P < 0.01$), the DS86 kerma data ($P = 0.02$), or the DS86 eye organ dose data ($P = 0.03$), but it does fit a linear-quadratic-linear (LQ-L) model without a threshold. In the latter instance, although the regression coefficients associated with the square of the gamma-ray dose and the neutron dose are significant for all three sets of dose estimates, the linear gamma coefficient is not. However, since it is reasonable from a radiobiological standpoint to assume that two different thresholds may exist, one associated with gamma and the other with neutron exposure, thresholds were included in the model fitting. Their inclusion improves the fit of both the L-L model and the LQ-L model, and statistically significantly so in most instances. As is evident from the results in Table 3, both regression coefficients in the L-L model with two thresholds are significantly different from zero, whereas in the LQ-L model with two thresholds only two of the three regression coefficients are.

Table 3. The relationship of the occurrence of lenticular opacities to exposure based on using the grouped T65DR, DS86 kerma, and DS86 eye organ gamma and neutron doses

Dosimetry	Maximum likelihood estimates of regression coefficients							χ^2	df	Prob.
	$\hat{\alpha}_H$	$\hat{\alpha}_N$	$\hat{\beta}_\gamma 10^{-2}$(Gy)	$\hat{\beta}_{\gamma^2} 10^{-4}$(Gy)	$\hat{\beta}_\nu$(Gy)	$\hat{T}_\gamma$(Gy)	$\hat{T}_\nu$(Gy)			
Model A: Linear-linear model without threshold										
T65DR	0.44	1.10	1.54**		0.05*	-	-	22.87	8	<0.01
	(0.24)	(0.59)	(0.52)		(0.02)					
DS86	0.47	1.99	0.98		0.67*	-	-	18.07	8	0.02
	(0.26)	(0.85)	(1.00)		(0.26)					
Eye organ	0.47	2.05	1.05		1.10*	-	-	13.98	6	0.03
	(0.26)	(0.88)	(1.24)		(0.49)					
Model B: Linear-quadratic and linear model without threshold										
T65DR	0.70	2.08	–1.90	0.96**	0.08**	-	-	9.39	7	0.23
	(0.35)	(0.75)	(1.08)	(0.28)	(0.03)					
DS86	0.75	1.97	–0.26	1.24**	0.16	-	-	10.22	7	0.18
	(0.39)	(0.80)	(1.15)	(0.45)	(0.34)					
Eye organ	0.67	2.00	0.13	1.18*	0.38	-	-	8.18	5	0.15
	(0.37)	(0.87)	(1.41)	(0.53)	(0.67)					

Note: $\hat{\alpha}_H$, $\hat{\alpha}_N$, $\hat{\beta}_\gamma$, $\hat{\beta}_{\gamma^2}$, and $\hat{\beta}_\nu$ are the estimates of city-specific intercepts per 100 individuals (H=Hiroshima, N=Nagasaki) and the regression coefficients associated with gamma dose, gamma dose squared and neutron dose, expressed in kerma and organ, respectively. $\hat{T}_\gamma$ and $\hat{T}_\nu$ are the thresholds estimated for gamma and neutron exposures and χ^2 is a measure of the "goodness of fit" of the stated mode. Standard errors for the various estimates are given in parentheses beneath each individual estimate. Under the threshold estimates are given the upper (U) and lower (L) 95% confidence bounds. The estimate, 1.54, of $\hat{\beta}_\gamma 10^{-2}$(Gy) for T65DR in a linear-linear model without threshold means 0.0154 Gy. Significance levels: $^{Sug}p < 0.10$, $^{*}p < 0.05$, and $^{**}p < 0.01$

(Continued on the next page)

Table 3. Continued

Dosimetry	Maximum likelihood estimates of regression coefficients							χ^2	df	Prob.
	$\hat{\alpha}_H$	$\hat{\alpha}_N$	$\hat{\beta}_\gamma 10^{-2}$(Gy)	$\hat{\beta}_{\gamma^2} 10^{-4}$(Gy)	$\hat{\beta}_\nu$(Gy)	$\hat{T}_\gamma$(Gy)	$\hat{T}_\nu$(Gy)			
Model C: Linear-linear model with two thresholds										
T65DR	0.84	1.51	3.70**		0.10**	1.67*	0.24	6.30	6	0.39
	(0.31)	(0.52)	(1.04)		(0.03)	(L=0.73, U=2.67)	(L=0, U=0.59)			
DS86	0.98	2.19	4.35**		0.98*	1.00	0.08*	5.31	6	0.50
	(0.31)	(0.66)	(1.41)		(0.42)	(L=0, U=1.37)	(L=0.02, U=0.31)			
Eye organ	0.75	2.07	3.10**		1.81**	0.35	0.05*	4.28	4	0.37
	(0.34)	(0.66)	(0.87)		(0.64)	(L=0, U=1.15)	(L=0.01, U≥0.20)			
Model D: Linear-quadratic and linear model with two thresholds										
T65DR	0.85	1.55	2.05	0.47	0.10**	1.47	0.25	5.89	5	0.32
	(0.31)	(0.54)	(2.00)	(0.67)	(0.03)	(L=0, L=2.64)	(L=0, U=0.64)			
DS86	0.98	2.16	7.16**	−0.78	1.11*	1.14	0.10*	5.03	5	0.41
	(0.32)	(0.64)	(2.25)	(0.83)	(0.51)	(L=0, U=2.04)	(L=0.01, U≥0.38)			
Eye organ	0.75	2.07	3.10*	<0.01	1.81*	0.35	0.05*	4.28	3	0.23
	(0.35)	(0.66)	(1.41)	(0.67)	(0.79)	(L=0, U=1.22)	(L=0.01, U≥0.20)			

The regression coefficient for the gamma dose squared is not significant for either the T65DR kerma, the DS86 kerma or the DS86 eye organ doses. The critical χ^2 values for the goodness of fit to the L-L model with two thresholds are smaller than those associated with the LQ-L model, with and without two thresholds, irrespective of the dose estimates used.

To explore the dose-response relationship further, the L-L model with two thresholds was fitted to the individual binary response data. Analytic approaches based on individual dose estimates are more powerful in the statistical sense than regression analyses from mean dose estimates of grouped data. The results of such fitting to the individual binary data based on the T65DR kerma, DS86 kerma, and DS86 eye organ dose are shown in Table 4. It should be noted that the regression coefficients that emerge from fitting to the individual doses do not differ markedly from those found with the grouped data, but the estimates of the two thresholds, based on the T65DR kerma, change somewhat, decreasing from 1.67 Gy to 1.35 Gy for gamma rays and increasing from 0.24 Gy to 0.56 Gy for neutrons. When the DS86 kerma and eye organ doses are used, the estimate of the gamma threshold decreases slightly from 1.00 Gy to 0.86 Gy with the former doses and increases from 0.35 Gy to 0.73 Gy with the latter doses, but the estimates of the neutron threshold are almost the same, being 0.05 Gy and 0.06 Gy. The 95% upper bound for the gamma threshold is 1.41 Gy for the DS86 kerma and 1.39 Gy for the eye organ dose. The 95% upper estimates for the gamma threshold are obviously very close, a reasonable finding from a radiobiological standpoint. The regression coefficients for gamma rays and neutrons in the L-L model with two thresholds are highly significant ($P < 0.01$) for all three different sets of doses, i.e., T65DR kerma, DS86 kerma, and DS86 eye organ dose.

The gamma regression coefficient, based on the L-L model with two thresholds, is almost the same as that for the T65DR kerma, the ratio of the coefficients being 1.1-fold with 95% confidence limits of 0.5 and 2.3 for the individual DS86 kerma data. When we compare the DS86 gamma kerma risk with that for the DS86 eye organ dose, the changes are slightly greater, being 1.3-fold with 95% bounds of 0.6 and 2.8; whereas the ratios for the neutron regression coefficients are 6.4-fold higher with 95% bounds of 2.2 and 19.2 for DS86 kerma, and the risks for eye organ dose are 1.6-fold higher than those for DS86 kerma with 95% bounds of 0.5 and 2.3 (Tables 3 and 4).

Estimation of RBE

The estimates of RBE based on the L-L model with two thresholds are given in Table 5 with their 95% confidence bounds for the grouped as well as the individual dose data. The method of estimation of the RBE and its 95% lower and upper bounds is described in Appendix 4. The RBE in the individual lenticular opacity data gives a comparatively conservative estimate for eye organ dose. Table 5 shows the changes in the RBE and their 95% lower and upper bounds from individual doses on the basis of T65DR kerma, DS86 kerma, and DS86 eye organ

Table 4. The relationship of the occurrence of lenticular opacities to exposure based on using the individual T65DR, DS86 kerma, and DS86 eye organ gamma and neutron doses

Dosimetry	Maximum likelihood estimates of regression coefficients							Log likelihood value
	$\hat{\alpha}_H$	$\hat{\alpha}_N$	$\hat{\beta}_\gamma 10^{-2}$(Gy)	$\hat{\beta}_{\gamma^2} 10^{-4}$(Gy)	$\hat{\beta}_\nu$(Gy)	$\hat{T}_\gamma$(Gy)	$\hat{T}_\nu$(Gy)	
			Model A: Linear-linear model without threshold					
T65DR	0.40	1.32	1.27**		0.06**	-	-	–278.5
	(0.22)	(0.60)	(0.44)		(0.02)			
DS86	0.44	2.13	0.56		0.74**	-	-	–258.7
	(0.24)	(0.08)	(0.91)		(0.24)			
Eye organ	0.46	2.03	0.87		1.18**	-	-	–261.4
	(0.25)	(0.78)	(1.21)		(0.46)			
			Model B: Linear-quadratic and linear model without threshold					
T65DR	0.61	2.06	–1.79*	0.89**	0.08**	-	-	–271.6
	(0.32)	(0.71)	(0.88)	(0.25)	(0.02)			
DS86	0.62	2.23	–0.76	0.93*	0.47[Sug]	-	-	–255.5
	(0.34)	(0.78)	(1.06)	(0.39)	(0.28)			
Eye organ	0.63	2.07	–0.17	1.06*	0.56	-	-	–258.7
	(0.34)	(0.76)	(1.21)	(0.46)	(0.54)			

See the description in Table 3.

(Continued)

Table 4. Continued

Dosimetry	Maximum likelihood estimates of regression coefficients							Log likelihood value
	$\hat{\alpha}_H$	$\hat{\alpha}_N$	$\hat{\beta}_\gamma 10^{-2}$(Gy)	$\hat{\beta}_{\gamma^2} 10^{-4}$(Gy)	$\hat{\beta}_\nu$(Gy)	$\hat{T}_\gamma$(Gy)	$\hat{T}_\nu$(Gy)	
Model C: Linear-linear model with two thresholds								
T65DR	0.97 (0.31)	1.42 (0.51)	3.39** (0.78)		0.14** (0.03)	1.35* (L=0.53, U=2.01)	0.56* (L=0.32, U=1.29)	–268.1
DS86	0.96 (0.31)	2.18 (0.66)	3.62** (1.18)		0.90** (0.34)	0.86 (L=0, U=1.41)	0.07* (L=0.02, U=0.23)	–253.3
Eye organ	0.98 (0.32)	2.13 (0.64)	4.57** (1.11)		1.48* (0.67)	0.73 (L=0, U=1.39)	0.06 (L=0, U=0.16)	–257.4
Model D: Linear-quadratic and linear model with two thresholds								
T65DR	0.95 (0.30)	1.44 (0.52)	3.20[Sug] (1.71)	0.05 (0.56)	0.12** (0.03)	1.38 (L=0, U=2.10)	0.46* (L=0.20, U=1.36)	–268.2
DS86	1.01 (0.31)	2.27 (0.64)	7.61** (2.31)	–1.07 (0.75)	0.99* (0.41)	1.20 (L=0, U=1.59)	0.09* (L=0.03, U≥0.27)	–252.7
Eye organ	1.05 (0.32)	2.27 (0.65)	7.61** (2.37)	–0.01 (0.01)	1.69* (0.85)	0.96 (L=0, U=1.53)	0.06 (L=0, U=0.16)	–257.0

Table 5. RBE and 95% confidence limits based on a L-L model with two thresholds

Dosimetry	RBE	95% Confidence limits	
		Lower	Upper
	Grouped data		
T65DR	$2.6 + \frac{1.67}{(D_\nu - 0.24)>0}$	$1.2 + \frac{0.73}{(D_\nu - 0.24)>0}$	$5.9 + \frac{2.67}{(D_\nu - 0.24)>0}$
DS86	$22.6 + \frac{1.00}{(D_\nu - 0.08)>0}$	$7.8 + 0^\dagger$	$64.8 + \frac{1.37}{(D_\nu - 0.08)>0}$
Eye organ	$58.3 + \frac{0.35}{(D_\nu - 0.05)>0}$	$24.0 + 0^\dagger$	$141.8 + \frac{1.15}{(D_\nu - 0.05)>0}$
	Individual data		
T65DR	$4.1 + \frac{1.35}{(D_\nu - 0.56)>0}$	$2.1 + \frac{0.53}{(D_\nu - 0.56)>0}$	$8.0 + \frac{2.01}{(D_\nu - 0.56)>0}$
DS86	$24.8 + \frac{0.86}{(D_\nu - 0.07)>0}$	$9.3 + 0^\dagger$	$66.3 + \frac{1.41}{(D_\nu - 0.07)>0}$
Eye organ	$32.4 + \frac{0.73}{(D_\nu - 0.06)>0}$	$11.8 + 0^\dagger$	$88.8 + \frac{1.39}{(D_\nu - 0.06)>0}$

†Denotes that the calculation of estimates close to a 0 Gy gamma dose, which are dependent upon the lower bound, $\hat{T}_{\gamma L}$, is not possible with the DS86 kerma or eye organ doses. D_ν in the expression $(D_\nu - \hat{T}_\nu)>0$ is the neutron dose in gray, and T_ν is either the estimate of the neutron threshold or its upper or lower 95% bound. The maximum likelihood (ML) estimates of the variance and the standard deviation are given in Tables 3 and 4. The MLsof covariance, Cov $(\hat{\beta}_\gamma, \hat{\beta}_\nu)$, are -0.151×10^{-5}(Gy) for T65DR, -0.417×10^{-4}(Gy) for DS86 kerma, and -0.306×10^{-4}(Gy) for eye organ dose in the grouped data of Table 3, and -0.112×10^{-5}(Gy) for T65DR, -0.271×10^{-4}(Gy) for DS86 and -0.429×10^{-4}(Gy) for eye organ dose in the individuals of Table 4.

dose. The RBE values associated with lenticular opacities in the individual data are found to be 111 (95% CI: 9 to 207) at 0.08 Gy of neutrons when we consider a neutron threshold of 0.07 Gy, 53 (9 to 113) at 0.10 Gy, 27 (9 to 70) at 0.5 Gy, 26 (9 to 68) at 1 Gy for DS86 kerma, and 105 (12 to 228) at 0.07 Gy with a neutron threshold of 0.06 Gy, 51 (12 to 124) at 0.1 Gy, 34 (12 to 92) at 0.5 Gy, 33 (12 to 90) at 1 Gy for eye organ dose. On the other hand, the RBE with a neutron threshold of 0.56 Gy derived from the T65DR kerma in the individual data gives 38 (15 to 58) at 0.6 Gy and 7 (3 to 13) at 1 Gy, and in the grouped data, the RBE for the T65DR kerma with a 0.24 Gy neutron threshold yields 170 (74 to 273) at 0.25 Gy, 9 (4 to 15) at 0.50 Gy and 5 (2 to 10) at 1 Gy. The RBE values for the grouped and individual dose data are 3.7- to 4.8-fold higher for the DS86 kerma than for the T65DR kerma, and 1.3- to 2.5-fold higher for the DS86 eye organ dose than for the DS86 kerma.

Discussion

The eye is generally considered to be an organ sensitive to radiation. Damage to any part of the eye may occur, but for long-term effects the most sensitive structure is thought to be the lens. The characteristic feature of radiation cataract is the initial axial opacity which ophthalmoscopically appears as a dot usually situated at the posterior pole, and as this enlarges, small granules and vacuoles appear around it. With continued enlargement, the opacity develops a relatively clear center, giving it a doughnut-shaped appearance. At this stage, it is 3–4 mm in diameter.[15] Unfortunately, the word "cataract" connotes to many a defect which impairs vision, although it is also commonly used to describe any detectable change in translucency in the lens. To avoid confusion we have adopted the ICRP[27] convention and used synonymously the phrases "lenticular opacities," "opacity of the lens" or "lens opacification," since our data are not restricted to those radiation-induced changes which impair vision measurably.

A causal involvement of radiation-induced damage to the epithelial cells in the germinative zone of the lens in radiation cataractogenesis has not yet been proved. However, the BEIR III report[29] notes that evidence from animal studies strongly suggests this mechanism, on the basis of the differentiation of the affected cells into abnormal lens fibers and the time coincidence between the appearance of lens opacification and the rate of migration of lens epithelial cells into the posterior lens cortex. Furthermore, the report points out that there is no direct evidence that lens opacification depends on the killing of epithelial cells in the germinative zone. The sigmoid cataract dose-response curves and the protective effect of partial lens shielding provide evidence that other factors are involved in radiation cataractogenesis in addition to cell-killing.

Our analysis also supports a sigmoid dose-response relationship with a threshold (or thresholds) for lens opacification. In this study, however, the extent of the opacification of the lens in either or both eyes has been classified biomicroscopically as equivocal, minimal, small, moderate, or large. In most instances, the degree of opacification was small or less (about 70%) and only five opacities were classified as large. Dodo[18] observed that in the majority of affected survivors the degree of opacification is minimal to moderate, and unchanging. It should be emphasized that bilateral involvement is much more common (67 cases out of 76) than unilateral, and the correlation between the degree of opacification in the left and right eyes is high (0.81, based upon the assignment of the numeric values 1, 2, ..., 5 to the successive degrees of opacification). This suggests, in turn, a high correlation in the exposure received by the left and right eyes of a given individual and militates against an analysis which treats a subject's two eyes independently.

As is evident from Appendix 2 and Figure 2, lenticular opacification does not always appear consistent with estimated dose. However, opacification may depend on individual sensitivity and the angular distribution of the radiation upon the lens. The DS86 eye organ dose estimates are based on 12 mean angles to the burst point, but the opacification in A-bomb survivors is not entirely consistent with the angular distribution of the flash. Of 1,453 ophthalmologic cases exposed to 0.01 Gy or more, almost 100% have directly estimated doses (see Appendix 1). From Appendix 2, we see that the 68 individuals with opacities for whom the angles are known (after the exclusion of 8 cases belonging to the "not-in-city" or "distal group" for which no angular distribution information exists) are randomly distributed with respect to the 12 directions from the burst point. Estimates of eye organ dose also vary from low to high even for those survivors who have a small opacity. This suggests, if the eye dose estimate is correct, that the lens may have been exposed to substantial radiation, presumably from scatter, even when the burst point was behind the individual. This seems counter to intuition, and certainly, experimental evidence suggests that shielding of a major portion, albeit not all of the lens, can protect against cataract formation. Patently, it is difficult to ascertain in any given case whether all or only a part of the germinative epithelium of the lens of an eye of a survivor was exposed. It should be noted, however, that the experimental evidence is based on shielding of the lens which approximates the contact with the cornea experienced with contact lenses; a similar shielding in the context of the bombing seems unlikely.

Characterizing the shape of the dose-response relationship for radiation-induced lenticular opacities among A-bomb survivors is an essential prerequisite in predicting and quantifying the effect of radiation exposure. An apparent difference in the dose response between the two cities, based on the DS86 dosimetry system, is also important from the radiobiological standpoint, specifically with regard to the RBE. The neutron component of the radiation emitted by the Hiroshima bomb, based on the new doses, is much less than that computed with the T65DR dosimetry. The neutron dose in Hiroshima was 10.6-fold higher at 6 Gy than that in Nagasaki using the T65DR dosimetry, but is still 4.2-fold higher in the DS86 dose, although the DS86 kerma neutron component in Hiroshima is only 0.38 Gy at 6 Gy and in Nagasaki 0.09 Gy. However, if the eye is especially sensitive to neutrons, this difference could still produce a difference in risk between the cities, and the observed risks of lenticular opacities are strikingly different (higher in Hiroshima than in Nagasaki), particularly in the DS86 high-dose region. Couched in terms of dose equivalent, in Hiroshima, a neutron eye organ dose of roughly 0.28 Gy (at a total eye organ dose of 6 Gy), given an RBE of 36 (95% CI: 12 to 95), would be the equivalent of 10.1 Sv (= 36 $\times$ 0.28) with a range from 3.4 to 26.6 Sv based on a restriction of the neutron threshold, i.e., $(D_\nu - 0.06) > 0$; whereas a neutron dose of 0.08 Gy in Nagasaki with an RBE of 69 (95% CI: 12 to 158) is only 5.5 Sv (= 69 $\times$ 0.08) with a range from 1.0 to 12.6 Sv. This fact suggests that the neutron component could be more important for the eyes than for other sites in the body, reflecting either the relatively greater contribution of neutrons to the total absorbed dose to the eye

than to the total absorbed dose for deep organs, or an intrinsically higher RBE for cataracts than other endpoints, or both. When we evaluated the interactive effect between gamma and neutron components in the L-L model with two thresholds, both neutron and interactive effects showed no significant difference other than a significant elevation of gamma rays.

Shimizu et al[30] argue that a meaningful estimate of the neutron RBE with regard to cancer mortality data is difficult, but that neutrons cannot be totally neglected in Hiroshima, even though the neutron dose is substantially less under the DS86 dosimetry system than the T65DR. They augmented the models they fitted to the cancer mortality data to include the individual contributions of gamma rays and neutrons, but it was impossible to assert that one of the models is better than any other. Consequently, they estimated the risk coefficients per sievert assuming an arbitrary but constant RBE of 1, 10, and 20. Using the cancer mortality data for leukemia and all cancers other than leukemia, Preston and Pierce[31] also determined a dose-response relationship assuming a constant RBE. They show that the goodness of fit varies almost negligibly with RBE values in the range of 1 to 50 for the DS86 dosimetry system. They concluded that the city difference in the excess risk of cancer is not statistically significant even at an RBE of 1, and does not diminish rapidly as the RBE is increased.

It is well known that the RBE generally increases with decreasing dose. The difference in dose response for lenticular opacities between the two cities strongly suggests not only the possibility of estimating an RBE but also seems to provide information that the RBE is higher for survivors who were exposed at low dose. The estimated parameters are significantly positive for gamma and neutron doses under the most suitable L-L model with two thresholds. The T65DR, DS86 kerma, and eye organ dose all suggest the existence of two thresholds, probably in the range from 0.30 to 1.70 Gy for gamma rays and from 0.05 to about 0.60 Gy for neutrons. Note that these estimates of the gamma threshold are lower than those commonly inferred from clinical exposures. The estimate of the threshold for neutrons, based on the dose grouped data or the individual dose data, is 0.24 or 0.56 Gy for T65DR kerma, 0.07 or 0.08 Gy for DS86 kerma, and 0.05 to 0.06 Gy for the DS86 eye organ dose. It should be noted that the LQ-L model with two thresholds which fits the A-bomb survivor data less well, but not significantly so, yields very similar estimates of the two thresholds as the L-L model. Finally, the Q-L model with two thresholds, not presented in the Statistical Considerations and Methods, was evaluated from a radiobiological standpoint. This model fitted the survivor data more poorly than the LQ-L model with two thresholds in the dose grouped data or the individual dose data. The best fit in the Q-L model with two thresholds showed 0 Gy for the gamma threshold and 0.04 or 0.05 Gy for neutron threshold, respectively, and demonstrated a highly significant effect of gamma rays only but not of neutrons.

Only the T65 dosimetry gives an appreciably different estimate of the neutron threshold for the grouped and individual data. If we use a conservative threshold for neutrons and calculate the RBE corresponding to neutron doses of 0.08, 0.25, 0.50, and 1.00 Gy, the values are (105 at 0.07 Gy) 69, 36, 34, and 33 for the DS86 eye organ dose and a 0.06 Gy neutron threshold; 111, 30, 27, and 25 for the DS86 kerma with a 0.07 Gy neutron threshold; and not estimated, 170, 9, and 5 for the T65DR kerma with a 0.24 Gy neutron threshold, respectively. The RBE values for opacification of the lens derived from the newer DS86 kerma and eye organ dose are higher than previously published results. If we take into account the 95% lower bound of the neutron threshold including zero for the DS86 eye organ dose, the RBE values are estimated to be $32.4 + 0.73/D_\nu$ with the 95% confidence limits ranging from 11.8 to $88.3 + 1.39/D_\nu$, where D_ν is the neutron dose in gray. Rossi[32] and Bateman et al,[33] comparing a number of neutron energies against X rays, reported that the RBE for opacification of the murine lens was $0.44/D_\nu$. The ICRP[27] gives a table of RBE values for production of opacities of the lens with single exposures to X rays or gamma rays or to fission neutrons. These values range from 2 to 20. The BEIR III report[29] suggests that the RBE for high LET radiation for a single cataractogenic exposure is in the range of 2–9. A recent NCRP report[34] summarizes the general findings on cataractogenesis in many experimental animals and human beings and on the existence of time thresholds for lens opacity in rabbits from acute exposure, but does not review the RBE of neutrons.

In any event, estimating the RBE of neutrons at doses less than 0.50 Gy remains an interesting and important radiobiological issue.

APPENDIX

Appendix 1. The distribution of DS86 eye organ dose estimates by dose groups and the method of dose estimation

Method of estimation	DS86 dose category (Gy)							
	<0.01	0.01–0.99	1.00–1.99	2.00–2.99	3.00–3.99	4.00–4.99	5.00–5.99	6.00+
Direct		861	369	135	38	22	14	1
Indirect	267	10	1				2	
Total	267	871	370	135	38	22	16	1

Note that 263 cases (Hiroshima = 152 and Nagasaki = 111) in the not-in-city group are not included in the group that received less than 0.01 Gy.

Appendix 2. List of cases with lenticular opacities by city and type of dosimetries

Master file no.	Sex	Age ATE*	T65DR			DS86			Eye organ			DS86 codes**	Mean angle to burst point
			Total	Gamma	Neutron	Total	Gamma	Neutron	Total	Gamma	Neutron		
						Hiroshima							
[redacted]	2	32	4.69	2.67	2.02	4.13	3.90	0.23	3.89	3.78	0.12	01	270°
	2	22	2.96	2.45	0.51	2.37	2.27	0.10	1.74	1.70	0.04	05	150°
	1	06	6.00	4.19	1.81	6.00	5.62	0.38	5.26	4.98	0.28	07	240°
	1	07	6.00	4.19	1.81	5.84	5.17	0.67	5.14	4.69	0.45	07	240°
	2	54	2.07	1.57	0.50	1.45	1.40	0.05	1.23	1.21	0.03	03	120°
	1	18	3.91	3.05	0.86	2.79	2.66	0.13	2.79	2.70	0.09	03	0°
	2	12	3.38	1.97	1.41	3.19	3.04	0.15	3.33	3.24	0.10	01	330°
	1	53	1.22	0.97	0.25	0.62	0.61	0.01	0.58	0.57	0.01	05	60°
	2	30	0.57	0.41	0.16	0.57	0.55	0.02	0.50	0.50	0.01	07	270°
	1	16	6.00	4.19	1.81	6.00	5.62	0.38	4.43	4.28	0.15	07	150°
	2	35	3.00	2.39	0.61	2.09	2.02	0.07	1.60	1.57	0.03	05	150°
	1	11	2.43	1.95	0.48	1.78	1.72	0.06	1.64	1.60	0.04	03	Unk
	2	33	1.77	1.08	0.69	2.07	1.99	0.08	1.54	1.51	0.03	01	180°
	1	12	3.61	2.49	1.12	2.46	2.36	0.10	1.79	1.75	0.04	03	240°
	2	47	6.00	4.19	1.81	4.00	3.79	0.21	3.72	3.60	0.12	03	270°
	2	26	3.49	2.18	1.31	2.75	2.59	0.16	2.74	2.63	0.10	07	330°
	2	50	5.65	3.21	2.44	Unk	Unk	Unk	Unk	Unk	Unk	13	180°
	2	00	3.51	2.79	0.72	1.46	1.41	0.05	1.09	1.06	0.03	03	180°
	2	40	6.00	4.19	1.81	6.00	5.62	0.38	4.73	4.57	0.16	07	240°
	2	17	5.34	4.15	1.19	3.52	3.35	0.17	2.78	2.71	0.08	05	180°
	2	13	6.00	4.19	1.81	2.93	2.78	0.15	3.05	2.96	0.08	05	0°
	2	52	3.67	2.96	0.71	2.84	2.71	0.13	2.66	2.58	0.08	05	60°
	1	40	6.00	4.19	1.81	4.60	4.26	0.34	4.21	4.05	0.15	07	120°
	2	46	4.90	3.92	0.98	2.86	2.72	0.14	2.35	2.27	0.08	05	150°
	2	22	4.82	3.79	1.03	2.79	2.67	0.11	2.82	2.75	0.07	03	0°
	1	15	6.00	4.19	1.81	Unk	Unk	Unk	Unk	Unk	Unk	02	270°
	2	42	0.47	0.37	0.10	0.40	0.40	0.01	0.39	0.38	0	03	300°
	1	40	6.00	4.19	1.81	5.90	5.51	0.39	5.28	5.08	0.20	01	270°
	1	43	6.00	4.19	1.81	4.49	4.11	0.38	4.78	4.61	0.17	07	330°
	1	18	2.95	2.32	0.63	1.79	1.70	0.09	1.70	1.66	0.05	03	270°
	1	01	1.18	0.94	0.24	0.94	0.91	0.02	0.92	0.90	0.02	03	60°
	2	43	0	0	0	0	0	0	0	0	0	16	
	1	46	6.00	4.19	1.81	5.29	4.96	0.33	3.96	3.84	0.12	01	180°
	1	18	3.93	3.04	0.89	2.27	2.16	0.11	2.26	2.19	0.07	03	300°
	2	15	6.00	4.19	1.81	4.88	4.62	0.26	4.99	4.80	0.19	03	270°
	1	04	4.37	3.54	0.83	2.60	2.49	0.11	2.76	2.69	0.07	03	300°

*Age ATE: Age at examination

**The codes of the DS86 method are as follows; 01 = in the open, unshielded with flash burns; 02 = in the open, unshielded without flash burns; 03 = in a Japanese house, 9-parameter $\leq$2,500m; 05 = in a tenement, 9-parameter $\leq$2,500m; 07 = Globe application (ref. 24), house shielding $\leq$2,500m; 10 = Globe application, terrain shielding $\geq$2,500m; 13 = other proximal survivors with shielding history; 16 = DS86 free-in-air kerma <5 mGy; and 21 = not-in-city late entrants or entrants unknown.

(Continued)

Appendix Table 2. Continued

Master file no.	Sex	Age ATE*	T65DR Total	T65DR Gamma	T65DR Neutron	DS86 Total	DS86 Gamma	DS86 Neutron	Eye organ Total	Eye organ Gamma	Eye organ Neutron	DS86 codes**	Mean angle to burst point
						Hiroshima							
	1	49	6.00	4.19	1.81	4.39	4.18	0.22	4.17	4.05	0.13	03	30°
	2	17	5.80	4.65	1.15	3.78	3.59	0.19	3.47	3.36	0.11	03	90°
	2	39	5.09	3.05	2.04	Unk	Unk	Unk	Unk	Unk	Unk	13	180°
	1	52	1.91	1.56	0.35	1.06	1.02	0.05	0.82	0.80	0.02	05	150°
	2	29	3.99	2.30	1.69	3.63	3.45	0.19	2.71	2.64	0.07	01	180°
	1	14	3.71	2.66	1.05	2.07	1.94	0.13	1.92	1.86	0.07	07	300°
	2	12	6.00	4.19	1.81	3.29	3.13	0.16	2.77	2.70	0.07	01	120°
	1	18	3.75	2.99	0.76	2.61	2.49	0.12	2.65	2.57	0.09	03	180°
	1	38	5.96	4.54	1.42	4.39	4.16	0.23	4.21	4.09	0.12	03	330°
	2	18	2.52	2.11	0.41	2.06	1.98	0.08	2.12	2.07	0.05	03	330°
	2	46										21	
	2	44	1.09	0.91	0.18	0.65	0.63	0.02	0.66	0.64	0.02	05	120°
	2	34	0.77	0.64	0.13	0.67	0.65	0.02	0.51	0.51	0.01	03	210°
	2	19	6.00	4.19	1.81	5.29	4.98	0.31	4.86	4.69	0.17	03	90°
	2	38										21	
						Nagasaki							
	2	19										21	
	2	18	2.56	2.54	0.02	1.43	1.42	0.01	1.47	1.46	0.01	03	0°
	2	20	2.86	2.82	0.04	1.04	1.02	0.01	1.13	1.12	0.01	03	0°
	2	19	0.10	0.10		0.07	0.07	0	0.7	0.07	0	07	Unk
	1	41	2.25	2.21	0.04	1.65	1.64	0.02	1.14	1.14	0.01	07	180°
	2	19	6.00	5.83	0.17	Unk	Unk	Unk	Unk	Unk	Unk	13	270°
	2	46	0.20	0.20		0.10	0.10	0	0.09	0.09	0	03	30°
	2	54	0.18	0.18		0.11	0.11	0	0.10	0.10	0	03	30°
	2	15	4.17	4.12	0.05	2.06	2.03	0.02	1.94	1.93	0.01	03	270°
	2	51	2.98	2.95	0.03	1.19	1.18	0.01	0.89	0.88	0.01	03	180°
	2	05	3.73	3.69	0.04	1.88	1.86	0.02	1.75	1.74	0.01	03	90°
	2	42	0.69	0.69		0.21	0.21	0	0.22	0.22	0	03	60°
	2	46	0.74	0.73	0.01	0.42	0.42	0	0.41	0.41	0	05	60°
	1	54	6.00	5.83	0.17	Unk	Unk	Unk	Unk	Unk	Unk	10	90°
	2	37	6.00	5.83	0.17	5.09	4.98	0.11	3.56	3.51	0.06	05	180°
	1	16	4.09	4.03	0.06	1.39	1.36	0.03	1.16	1.14	0.01	03	270°
	2	36	2.99	2.95	0.04	1.50	1.49	0.02	1.08	1.08	0.01	03	180°
	1	12	6.00	5.83	0.17	6.00	5.91	0.09	4.43	4.38	0.05	03	210°
	1	15	4.44	4.35	0.09	2.43	2.40	0.02	2.34	2.32	0.02	03	0°
	2	39	1.70	1.68	0.02	0.70	0.69	0.01	0.63	0.63	0	05	60°
	1	14	2.86	2.80	0.06	2.23	2.21	0.02	1.65	1.64	0.01	01	180°
	2	07	6.00	5.83	0.17	4.68	4.62	0.06	4.31	4.26	0.05	03	Unk
	2	23										21	
	1	06	5.21	5.12	0.09	2.70	2.67	0.03	2.32	2.30	0.02	03	Unk
	2	53	2.39	2.36	0.03	0.84	0.83	0.01	0.77	0.76	0.01	05	270°

Appendix 3. The effects of age at the time of the bombing and city on the linear regression coefficients derived from the individual binary response data

Maximum likelihood estimate of regression coefficients	Dosimetry System		
	T65DR	DS86	Eye organ
Number of subjects used	2124	1983	1983
Model I: $P = \alpha_o + \alpha_c City + \alpha_a Age + \beta_\gamma D_\gamma + \beta_\nu D_\nu$			
$\hat{\alpha}_o$	−5.14 (0.95)	−4.71 (0.98)	−5.81 (1.08)
$\hat{\alpha}_c$	2.08** (0.54)	2.11** (0.60)	2.43** (0.61)
$\hat{\alpha}_a$	0.09** (0.02)	0.08** (0.02)	0.24** (0.02)
$\hat{\beta}_\gamma 10^{-2}$(Gy)	1.41** (0.44)	1.76^{Sug} (0.96)	1.84^{Sug} (1.12)
$\hat{\beta}_\nu$(Gy)	0.08** (0.02)	0.64** (0.24)	1.22** (0.47)
Log likelihood value	−273.5	−254.4	−256.9
Model II: $P = \alpha_o + \alpha_c City + \alpha_{aH} AgeH + \alpha_{aN} AgeN + \beta_\gamma D_\gamma + \beta_\nu D_\nu$			
$\hat{\alpha}_o$	−4.13 (1.86)	−2.92 (1.85)	−4.27 (2.02)
$\hat{\alpha}_c$	1.16^{NS} (1.53)	0.46^{NS} (1.56)	1.05^{NS} (1.64)
$\hat{\alpha}_{aH}$	0.86** (0.17)	0.73** (0.18)	0.93** (0.20)
$\hat{\alpha}_{aN}$	0.13^{Sug} (0.07)	0.15* (0.07)	0.16* (0.07)
$\hat{\beta}_\gamma 10^{-2}$(Gy)	1.39** (1.42)	1.67^{Sug} (0.89)	1.81^{Sug} (1.06)
$\hat{\beta}_\nu$(Gy)	0.08** (0.02)	0.65** (0.30)	1.19** (0.45)
Log likelihood value	−273.8	−254.5	−256.9
Model III: $P = \alpha_H + \alpha_N + \beta_\gamma D_\gamma + \beta_\nu D_\nu$			
$\hat{\alpha}_H$ } Difference $\hat{\alpha}_N$ }	0.04 (0.24) 1.32 (0.60) } NC	0.44 (0.24) 2.13 (0.80) } *	0.46 (0.25) 2.03 (0.78) } Sug
$\hat{\beta}_\gamma 10^{-2}$(Gy)	1.27** (0.44)	0.56^{NS} (0.91)	0.87^{NS} (1.12)
$\hat{\beta}_\nu$(Gy)	0.06** (0.02)	0.74** (0.24)	1.18** (0.46)
Log likelihood value	−278.5	−258.7	−261.4

The binary response score was 1 if an opacity was present and 0 otherwise. City is 1 for Hiroshima and 2 for Nagasaki. $\hat{\alpha}_o$, $\hat{\alpha}_c$, $\hat{\alpha}_{aH}$, and $\alpha_{\alpha N}$ denote the estimates for 100 individuals. AgeH is age ATB in Hiroshima and AgeN is age ATB in Nagasaki. Standard errors are given in parentheses beneath each individual estimate. Significance levels: $^{NS}(P>0.10)$, $^{Sug}(P<0.10)$, *(P<0.05), and **(P<0.01).

Appendix 4. The estimation of RBE and 95% lower and upper bounds in a linear-linear model with two thresholds

The RBE of neutrons is defined as the ratio of X rays or gamma rays (D_γ) to neutrons (D_ν), D_γ/D_ν, in an absorbed dose that produces the same prescribed biological effect in tissue. Therefore, the estimated RBE depends upon the modeling relationship applied to the data analysis. In the L-L model with two thresholds (Model C), which is the most suitable from the model fit and radiobiological standpoint, the RBE is defined as

$$\psi = \frac{\beta_\nu}{\beta_\gamma} + \frac{T_\gamma}{(D_\nu - T_\nu)} \quad ,$$

which holds for $(D_\nu - T_\nu) > 0$ under a given T_γ and T_ν. The $100(1-\alpha)\%$ confidence limits for $\log \psi$ are estimated by

$$\exp [\log \hat{\psi} - t_\alpha \sqrt{V(\log \psi)}\,] \leq \psi - T_\gamma/(D_\nu - T_\nu) \leq \exp [\log \psi + t_\alpha \sqrt{V(\log \psi)}\,] \quad ,$$

where t_α denotes the $100(1-\alpha)\%$ value of normal deviate, and $V(\log \psi)$ the estimate of asymptotic variance of $\log \psi$, i.e.,

$$V(\log \hat{\psi}) = V(\hat{\beta}_\gamma)/\beta_{\gamma^2} + V(\hat{\beta}_\nu)/\beta_{\nu^2} - 2\ \mathrm{Cov}(\hat{\beta}_\gamma, \hat{\beta}_\nu)/\beta_\gamma \beta_\nu \quad .$$

Hence, the estimates of inequality are given by

$$\exp [\log \psi - t_\alpha \sqrt{V(\log \psi)}\,] + \hat{T}_{\gamma L}/(D_\nu - \hat{T}_\nu) \leq \psi \leq$$

$$\exp [\log \psi + t_\alpha \sqrt{V(\log \psi)}\,] + T_{\gamma U}/(D_\nu - T_\nu) \quad ,$$

where $\hat{T}_{\gamma L}$ and $\hat{T}_{\gamma U}$ denote the lower and upper bounds of T_γ.

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