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# Exposure to ionizing radiation and brain cancer incidence: The Life Span Study cohort

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ABSTRACT

*Background:* Ionizing radiation is a cause of cancer. This paper examines the effects of radiation dose and age at exposure on the incidence of brain cancer using data from the Life Span Study (LSS) of atomic bomb survivors.

*Methods:* The Radiation Effects Research Foundation website provides demographic details of the LSS population, estimated radiation doses at time of bomb in 1945, person years of follow-up and incident cancers from 1958 to 1998. We modelled brain cancer incidence using background-stratified Poisson regression, and compared the excess relative risk (ERR) per Gray (Gy) of brain dose with estimates from follow-up studies of children exposed to diagnostic CT scans.

*Results:* After exposure to atomic bomb radiation at 10 years of age the estimated ERR/Gy was 0.91 (90%CI 0.53, 1.40) compared with 0.07 (90%CI −0.27, 0.56) following exposure at age 40. Exposure at 10 years of age led to an estimated excess of 17 brain tumors per 100,000 person year (pyr) Gy by 60 years of age. These LSS estimates are substantially less than estimates based on follow-up of children exposed to CT scans.

*Conclusion:* Estimates of ERR/Gy for brain cancers in the LSS and haemangioma cohorts seem much smaller than estimates of risk for young persons in the early years after exposure to CT-scans. This could be due to reverse causation bias in the CT cohorts, diagnostic error, measurement error with radiation doses, loss of early follow-up in the LSS, or non-linearity of the dose-response curve.



## 1. Background

Ionizing radiation is well-known as a cause of cancer, and the excess relative risk (ERR) per unit of radiation dose is known to be greater following exposures in early life [1–4]. Computed tomography (CT) scans are now major determinants of exposure to ionizing radiation in developed countries. In Australia, CT scanning of children has increased by 7.1% per year after accounting for population growth [5]. Radiation doses are measured as absorbed energy; one Gray of absorbed dose corresponds to one Joule per kg of tissue. CT scans of the head in childhood expose the brain to organ doses of up to 40–50 milligray (mGy.) [6,7].

Although the incidence of brain cancers is increased following radiation exposure, there is continuing uncertainty about the dose-response relationship [2,8–14]. Braganza et al., 2012 reviewed the literature; their *meta*-analysis estimate, across different age-groups, suggested that the ERR per Gray of brain dose is between 0.19 and 5.6 [14]. Recent follow-up studies of large cohorts of children and adolescents exposed to diagnostic CT scans of the head have reported the ERR for brain cancer to be as large as 23 per Gy [2,8].

In this paper, we review the brain cancer incidence in the LSS cohort, analyze the effect of age at exposure and radiation dose on the incidence of brain cancer and seek to explain the differences between LSS risk estimates and those based on follow-up studies of CT-exposed cohorts.

## 2. Methods

*Life Span Study:* After the atomic bombings of Hiroshima and Nagasaki in August 1945 the Japanese and United States governments initiated the Life Span Study (LSS) of atomic-bomb survivors to study the health effects of ionizing radiation. Mortality follow-up of the LSS cohort began in 1950; follow-up for cancer incidence began in 1958, 13 years after the atomic bomb explosions [15].

*Cancer ascertainment*: Ascertainment of cases in the LSS depended on “active” surveillance by the Radiation Effects

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Research Foundation (RERF) personnel who visited local health-care organizations and searched for cancers in hospital records. From 1973 (Hiroshima) and 1974 (Nagasaki) there was mandatory reporting of cancer cases to tissue registries [16,17]. Reporting rules were based on those used by the U.S. Surveillance, Epidemiology and End-Results Registry (SEER). All CNS tumors were included, as classified by the International Classification of Diseases ICD-O-3 topography codes C70–C72, with behaviour codes 0, (benign), and 1 (uncertain or unknown nature) and 3 (malignant). Tumors of the spinal cord, and benign tumors of the central nervous system were included, while lympho-hematopoietic malignancies originating in the central nervous system were excluded [18].

*Diagnostic accuracy:* In earlier years, before the era of CT scans and magnetic resonance imaging (MRI), diagnostic misclassification was more probable. Desmueles et al. (1992) estimated that in the pre-CT/MRI era (before the late 1970s & 1980s), up to 20% of brain tumors could have been misclassified as other diseases (most commonly stroke) and that approximately 10% of those classified as brain tumors were wrongly diagnosed [19].

*LSS cohort*: We accessed the RERF website (www.rerf.jp) to obtain LSS data on cancer incidence (filename: lssinc07.csv). The LSS cohort includes 105,427 people who were registered residents at the time of bombings, resident in Hiroshima or Nagasaki at the time of the 1950 census, and who were alive and cancer-free in 1958. Survivors were classified in three groups: 1) Those exposed within 2.5 km of the epicenter of the blast; 2) Those "unexposed", who were between 2.5 and 10 km from the epicenter of the blast; and 3) Those Not-in-City (NIC), comprising residents of either Hiroshima or Nagasaki who were absent during the bombings. Follow-up was continued to the end of 1998.

*Radiation dose*: Estimates were based on the Reassessment of the Atomic Bomb Radiation Dosimetry for the Hiroshima and Nagasaki Dosimetry System 2002 (DS02) [20]. For each person, the weighted brain dose in the RERF data-file was based on the estimated gamma and neutron doses in Gy, with a weighting of 10 for the greater biological effectiveness of neutrons. We used the weighted brain dose in Gray (Gy; DS02 dosimetry estimates) for each stratum as a continuous variable; the few persons with unknown radiation doses were excluded from our analyses. The open-access dataset provided by the RERF provides frequency counts for incident cancers, stratified on a range of demographic and exposure variables, including city, sex, age at time of bomb (ATB; 15 categories ranging from 0 to 4 to 70+ years), radiation dose (22 categories ranging from 0 to 5 to >3000 mGy), 18 categories of attained age, ranging from 0 to 4 years to 85 + years; distance from ground zero (0–3000 m, 3000–10000 m, and not in city), and calendar year of follow-up (10 categories ranging from 1958–1960 to 1996–1998). Each stratum in the LSS dataset provided the person years, average age ATB, average attained age and average radiation dose weighted by person years.

*Statistical methods*: Previous analyses of LSS data used the AMFIT program in Epicure to fit background-stratified Poisson models [11,18]. Background stratification estimates parameters for only a subset of the available variables, treating the terms that were not included as nuisance terms; this approach is also known as conditional Poisson regression [21]. Results from SAS or Stata software are believed to be equivalent to those obtained with AMFIT; our findings re-validate that conclusion [21].

We used Stata (version 13) to fit background-stratified Poisson regression models to identify radiation dose effects on brain cancer incidence. We followed the usual convention of using a linear non-threshold model, which assumes that the excess relative risk (ERR) of cancer radiation increases linearly with radiation dose from zero effect at zero dose [8,13,18,22]. We calculated incidence rate ratios (IRR), where IRR = ERR + 1, with 90% confidence intervals, as 90% CI's are often used in this field of research [18]. The "*margins*" command (part of the post-estimation suite of commands) in Stata was used to calculate excess incidence rates (EIR), corresponding to the excess absolute rates presented in LSS publications and other radiation epidemiology studies [10,11,13,15,23]. The EIR represents the cumulative excess of cancers in the exposed group, expressed as a rate per person year Gy of exposure; it is to be distinguished from the IRR – the ratio of rates in exposed to rates in unexposed.

*Model fitting:* In each stratum we used the number of brain tumors as the outcome variable; we used person-year weighted mean values of explanatory variables: age at time of bomb (agex); brain dose in Gy (dose); attained age (attage), with person-years (pyr) as an offset. The use of person-year weighted means for quantitative explanatory variables made optimal use of the stratified data. City and sex were tested as explanatory variables, as well as interaction terms with dose, but as they did not influence the main effects of interest (agex, dose, attage) significantly, they were dropped from the final model. An interaction term between age at time of bomb and dose was used in the final model.

$$\log(\text{Brain Cancer Count}) = B_0 + B_1\ Dose + B_2\ agex + B_3(agex \times dose) + B_4\ attage + \log(pyr)$$

**Table 1**
Distribution of person-years and observed brain cancer cases by sex, city, age at time of bomb and dose estimates. (1958–1998).

| | | Exposed | | Unexposed | | Not-in-City | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cases | Person Years | Cases | Person Years | Cases | Person Years | Cases | Person Years |
| Sex | Male | 55 | 545279 | 23 | 233408 | 16 | 261594 | 94 | 1040281 |
| | Female | 110 | 929956 | 53 | 375349 | 24 | 419150 | 187 | 1724454 |
| City | Hiroshima | 124 | 1045948 | 57 | 394595 | 32 | 527059 | 213 | 1967602 |
| | Nagasaki | 41 | 429287 | 19 | 214161 | 8 | 153685 | 68 | 797133 |
| Age at time of bomb (yrs) | 0–4 | 14 | 224100 | 9 | 87168 | 3 | 89957 | 26 | 401225 |
| | 5–9 | 8 | 152769 | 8 | 63923 | 3 | 62376 | 19 | 279068 |
| | 10–14 | 16 | 178272 | 10 | 77753 | 5 | 81470 | 31 | 337495 |
| | 15–19 | 23 | 187256 | 10 | 79689 | 5 | 102999 | 38 | 369943 |
| | 20–29 | 30 | 241136 | 13 | 100404 | 8 | 121078 | 51 | 462618 |
| | 30–39 | 25 | 236494 | 10 | 95035 | 8 | 114822 | 43 | 446351 |
| | 40+ | 49 | 255206 | 16 | 104786 | 8 | 108041 | 73 | 468034 |
| Estimated brain doses (Gy) | <0.005 | 28 | 309443 | 76 | 608757 | 40 | 680744 | 144 | 1598943 |
| | 0.005–0.1 | 75 | 729604 | 0 | 0 | 0 | 0 | 75 | 729604 |
| | 0.1–0.2 | 33 | 299812 | 0 | 0 | 0 | 0 | 33 | 299812 |
| | 0.2–0.5 | 22 | 99113 | 0 | 0 | 0 | 0 | 22 | 99113 |
| | >1 | 7 | 37263 | 0 | 0 | 0 | 0 | 7 | 37263 |
| | Total | 165 | 1475235 | 76 | 608757 | 40 | 680744 | 281 | 2764735 |

The unexposed cohort was more than 2.5 km from the blast hypocenter. The Not-in-City cohort was absent from Hiroshima or Nagasaki, or more than 10 km from the hypocenter.

$\beta_0$ = constant (incidence rate per person year in the unexposed population), $\beta_1$ to $\beta_4$ = coefficients, or multipliers of effect for associated variables, pyr = person-years.

## 3. Results

There were 281 incident brain tumors (213 in Hiroshima and 68 in Nagasaki, see Table 1) during 2,764,735 person-years of follow-up between 1958 and 1998, for an overall incidence rate of 10 brain tumors per 100,000 person-years. Sixty-three percent of exposed persons had estimated brain doses of 100 mGy or less. The person-year weighted average age of the exposed cohort at the time of exposure was 22.9 years. The person-year weighted average brain dose for the entire cohort was only 0.11 Gy, but amongst those with significant exposure (>0.005 Gy), the person-year weighted average brain dose was 0.25 Gy. Significant follow-up occurred in persons aged more than 60 years (1,064,672 person-years or 38.5% of follow-up).

For persons considered to have been exposed to radiation (1,165,792 person years of follow-up), approximately 729,604 years of follow-up occurred in persons with brain doses of less than 100 mGy (not including those with exposures <0.005). Only 13,712 years of follow-up were for radiation doses of more than 2 Gy (1.18% of exposed follow-up years). The estimated IRR per Gy decreased with increasing age of exposure (see Fig. 1,Table 2) from 1.91 (90% CI 1.53, 2.40) following exposure at 10 years of age to 1.07 (90% CI 0.73, 1.56) for exposure at age 40. For children exposed at 10 years of age the estimated EIR was 17 brain tumors per 100,000 person-years Gy by an attained age of 60 years.

Following exposure at age 20 years the estimated IRR per Gy for brain tumors was increased by 58% (IRR = 1.58, 90% CI 1.30, 1.91) compared with unexposed persons (Fig. 1). By 60 years of age the estimated number of excess brain cancers was 8.31 (90% CI 3.40, 13.22) per Gy per 100,000 person yr (see Table 3). The estimated excess was 16.46 (90% CI 2.02, 30.91) at a dose of 2.5 Gy (see Table 3). Persons exposed at age 40 did not have an increased incidence of brain tumors by age 60 (Fig. 1 and Table 3).

As only 4.73 and 1.17% of follow-up time was in persons exposed to radiation of more than 1 & 2 Gy respectively, and as the linear model had wide confidence intervals at larger doses, the exact form of the dose-response relationship remains uncertain.

## 4. Discussion

This study examined how the incidence rate of brain cancer in the LSS cohort depended on the dose of atomic radiation and the age at time of bomb. The dose-response relationship, as measured by ERR per Gy, was greater following exposure at younger ages, as previously reported for the LSS cohort [11]. In the Australian cohort of 10.9 million, of whom 680,000 were exposed to CT scans, the

**Table 2**
Final Poisson model parameter estimates of incidence rate ratios of brain cancer with age at time of bomb by radiation dose interaction term.

| Predictor variable (units of measurement) | Estimated IRR (90% CI) | p-value |
|---|---|---|
| Attained age (years) | 1.05 (1.040, 1.059) | <0.001 |
| Age at time of bomb (years) | 0.98 (0.975, 0.994) | 0.006 |
| Radiation dose (Gy) | 2.32 (1.678, 3.221) | <0.001 |
| Interaction Term: age at time of bomb by radiation dose | 0.98 (0.966, 0.995) | 0.031 |

Attained age, age at time of bomb (agex), and radiation dose were the weighted means for each stratum. Parameters estimate the mean effects (with 90% confidence intervals) of each predictor variable on the incidence rate ratio (IRR), which measures the proportional increase in risk for the given exposure. For example, after fitting the effects of attained age, age at time of bomb and the interaction term, the parameter measuring the effect of radiation dose is estimated as 2.32 per Gray (Gy). The excess relative risk (ERR) is thus estimated as 1.32 per Gy. By comparison, the ERR increases by 0.05 per year of attained age, but decreases by 0.02 for each year of age at time of bomb.

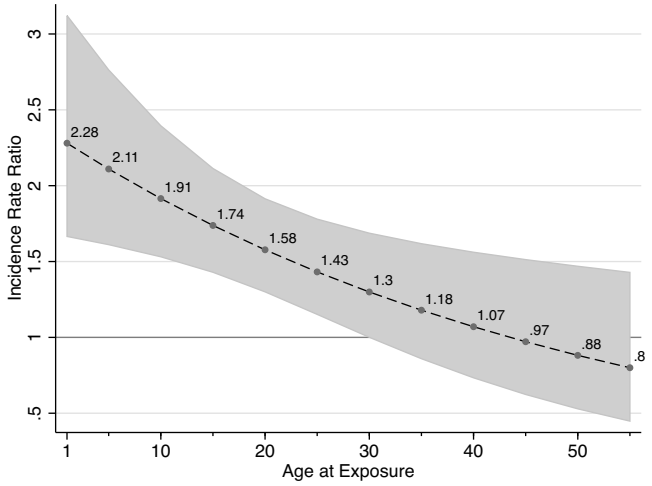


**Fig. 1.** Dependence of incidence rate ratio (IRR) for brain cancer (90% confidence intervals) on age at exposure using the Life Span Study Cohort dataset. The incidence rate ratio (IRR) was estimated by Poisson modelling for a notional dose of 1 Gray (Gy) using the linear non-threshold assumption. The excess relative risk (ERR) per Gy is estimated as IRR−1.

**Table 3**
Estimated excess brain cancer incidence rate per 100,000 person-years Gray for an attained age of 60 years by age at time of bomb.

| Age at time of bomb (years) | Excess Incidence Rate | 90% CI | | Excess Incidence Rate | 90% CI | |
|---|---|---|---|---|---|---|
| | 1 Gy | | | 2.5 Gy | | |
| 5 | 23.10 | 8.93 | 37.26 | 70.79 | −0.14 | 141.73 |
| 10 | 16.85 | 7.64 | 26.06 | 44.65 | 5.76 | 83.56 |
| 20 | 8.31 | 3.40 | 13.22 | 16.46 | 2.02 | 30.91 |
| 30 | 3.35 | −0.78 | 7.49 | 4.97 | −3.09 | 13.03 |
| 40 | 0.61 | −3.00 | 4.23 | 0.68 | −3.71 | 5.06 |

ERR for brain cancer was greater for those exposed before the age of 5 years [2]. In contrast, in the UK study [8] the ERR increased with age at CT exposure.

Exposure to radiation after the age of 40 does not seem to increase the incidence of brain tumors in LSS survivors. This could simply be due to limited numbers of cases, contributing to the wide confidence intervals. On the other hand, it is possible that radiation increases brain cancer risk most in those who are (genetically) susceptible to develop brain cancer at younger ages. On this view, if exposure is delayed beyond the age of 40, the average susceptibility of the population to radiation (and hence the ERR) would be less than at younger ages. This is consistent with other studies showing that the ERR decreases with increasing age at exposure (Mathews et al., 2013) [2].

Although the increased risks of cancer following early ages at exposure are seen in both the LSS and Australian CT study, there are major discrepancies in the estimates of effect per unit of radiation dose (ERR/Gy) based on the linear non-threshold assumption [1,24]. Table 4 summarises available estimates of effect for radiation-induced brain cancers; in each study the linear non-threshold assumption has been used to estimate the dose-response co-efficient, but effectively each co-efficient has been obtained by dividing the average ERR by the average dose for the study in question. The LSS study and the Karlsson (hemangioma treatment) study both had higher average brain doses than studies with CT scans as exposures, but their estimates of ERR per Gy were much lower than the estimates from the CT studies [2,8]. It has been suggested that the large increases in ERR per Gy after CT scans could be partly due to reverse causation, where symptoms of a pre-cancerous condition or early symptoms of a brain cancer trigger a CT scan in the years before a diagnosis is made [2,8]. In detailed analyses (Mathews et al., submitted) it appears that reverse causation cannot explain more than a small proportion of the excess cancers at lag periods of more than one year between CT exposure and cancer diagnosis.

How else might we account for dose-response estimates for brain cancers after CT scans that are larger than those seen in the LSS study and in the hemangioma cohort? For the LSS and other studies, which began in earlier times, it is possible that estimates of radiation effect were biased towards the null because a proportion of central nervous system conditions, such as stroke, were wrongly diagnosed as brain cancer [19]. For the haemangioma and tinea capitis studies (Table 4) it is also possible that the average dose response coefficients were reduced by dose-fractionation, used

**Table 4**
Published estimates of excess relative risk (ERR) for brain cancer incidence by radiation dose to the brain in Gray (Gy).

| | ERR/Gy (95% CI) | Type of Exposure | Dose Estimates | Age at Exposure | Comments |
|---|---|---|---|---|---|
| Karlsson et al. [13] | 2.7 (1.0, 5.6) | Radiotherapy for skin hemangioma | Mean absorbed intracranial dose 0.07 Gy, (range 0–11 Gy) | Mean 8 months (range 0.8 to 50 months) | 28,008 children, Exposure years 1930 to 1965; Cancer follow-up began in 1958, |
| Preston et al. [11] | 1.2 (0.3, 2.9) | Atomic radiation in Hiroshima and Nagasaki in 1945 | DS86 dosimetry Mean dose 0.12Gy | <20 years | Life Span Study Cohort, follow-up from 1958 to 1995. |
| Sadetzki et al. [10] | 1.98 (0.73, 4.69) | Radiation therapy for tinea capitis | Median brain dose 1.38 Gy (range 0.98-6 Gy) | Mean 7 yrs (range <1 to 15 years) | 10,834 exposed matched 1:1 to unexposed subjects. Follow-up for more than 40 years. |
| Pearce et al. [8] | 23 (10, 49) | Diagnostic computed tomography (CT) scan radiation | Average brain dose 0.06 Gy | Younger than 22 years | NHS Central Registry,176,587individuals exposed between 1985 and 2002 to 279,824 CT scans. Lag time was 5 years from first CT. |
| Mathews et al. [2] | 15 (7, 26) | Diagnostic CT scan radiation | Average brain dose 0.04Gy | <20 years | Australian Medicare Cohort, 10.9 million people of whom 680,000 were exposed to CT scans. Cutoff used is 10 years from first CT scan. |
| Huang et al. [9] | Hazard Ratio 2.56 (1.41, 4.54) comparing exposed and unexposed | Diagnostic CT scan radiation | None provided | ≤18 years | Taiwan National Health Insurance Research Database. 24,418 exposed children matched 1:4 to unexposed controls. |
| The Current Study | 1.11(0.61, 1.76) | Atomic radiation from the Hiroshima and Nagasaki bombings in 1945 | DS02 dosimetry. Person-year weighted mean brain dose 0.25Gy Mean 0.11 Gy (0.25 Gy if exposed to more than 5 mGy) | All ages, ERR presented in this table is for age at exposure at 5 yrs of age. Mean age of 22.9 years | Life Span Study Cohort. We found that the dose response relationship changed with age at exposure. |

The LSS data most closely matches the estimates found by Karlsson et al., 1998, considering that their mean ages at exposure was 8 months of age, and the current study included patients of all ages. The estimates presented by Mathews et al. (2013) used the 10 year lag period to more closely match the 13 year lag period in the LSS study.

routinely to minimise any acute side effects of radiation. In addition, as studies of CT exposed populations have relatively short follow-up (Mathews et al., 2013 had a mean follow-up of 9.5years), the attained age in the CT cohort is still substantially younger than in the LSS cohort. Accordingly the histological distribution of tumors in the CT cohort is likely to be substantially different from the LSS cohort. Similarly, the shorter length of follow-up in the CT scan studies could contribute directly to lag-related differences [2,8]. Furthermore, as the LSS cohort did not measure cancer incidence for the first 13 years after exposure, this could also have contributed to differences in outcome.

The linear non-threshold assumption, which underlies each of the separate dose coefficients in Table 4, gives such discrepant estimates of ERR/Gy that it cannot be true for all studies. Estimates from each study are most influenced by the observed ERR at the higher doses for that study, and the estimated gradient mostly reflects a straight line drawn back to zero effect at zero dose. If the linear non-threshold assumption is relaxed, a non-linear relationship could help to explain the discrepancies summarised in Table 4.

Brenner et al., 2003 describe five different dose response relationships that are plausible for low dose exposures [24]. The dose-response curve that could best represent dose-responses at low ($<100$ mGy) and high dose radiation is one that has a decreasing slope at higher doses (see Fig. 3, curve b in Brenner et al., 2003). Such a curve might be predicted by bystander and other models [24,25] or by differential genetic susceptibility to radiation carcinogenesis [2]. Therefore, to help explain the apparent discrepancies of Table 4, and to account for the larger estimates of ERR per Gy following CT scans, we suggest that the dose-response curve is steeper at the lower doses of acute radiation ($<100$ mGy) from diagnostic medical procedures [12,13]. On this view the lack of consistency between the LSS and CT scan cohorts [2,8] is at least partly a consequence of the non-linearity of the dose-response curve.

Other factors could contribute to the discrepancies summarised in Table 4 and help to explain the non-linearity. For example, it is possible that cancers in the early years after radiation occur preferentially in a sub-group of susceptible individuals or in those in whom stochastic effects are first expressed. Such cancers, which would be associated with a higher than average ERR per Gy, could have been missed in the LSS because of lack of follow-up in the early years after 1945, and missed because of a lack of statistical power in smaller studies of radiation and cancer.

In conclusion, we suggest that the ERR/Gy is much larger for brain cancers occurring in young persons in the early years after radiation exposure. The lower estimates of risk seen in the LSS and haemangioma cohorts may reflect diagnostic error, lack of early follow-up, lack of statistical power, non-linearity of the dose-response curve, or differences in the histological distributions of tumors.

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## Conflicts of interest

We have no conflicts of interest to declare.

## Authorship contributions

NRS—Jointly conceived the study, analysed the data, drafted and edited the paper, approved the final version.

ZB—provided advice on dose estimation, contributed to manuscript and approved the final version.

KS—provided statistical advice, contributed to manuscript and approved the final version.

JDM—Jointly conceived the study, reviewed data analyses, edited the paper and approved the final version.

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