Cancer Epidemiology 42 (2016) 60–65

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

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

Nicolas R. Smoll[a], Zoe Brady[a,b], Katrina Scurrah[a], John D. Mathews[a,*]

[a] School of Population and Global Health, University of Melbourne, Level 3, 207 Bouverie Street, The University of Melbourne, Victoria 3010, Australia
[b] Department of Radiology, The Alfred, 55 Commercial Rd, Prahran, Victoria 3181, Australia

ARTICLE INFO

Article history:
Received 10 November 2015
Received in revised form 1 March 2016
Accepted 10 March 2016
Available online xxx

Keywords:
Ionizing radiation
Brain tumors
Lifespan study
CT scan
Radiation-induced cancer

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

* Corresponding author.
E-mail address: mathewsj@unimelb.edu.au (J.D. Mathews).

http://dx.doi.org/10.1016/j.canep.2016.03.006
1877-7821/

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.