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Exposure to Medical Radiation during Fetal Life, Childhood and Adolescence and Risk of Brain Tumor in Young Age: Results from The MOBI-Kids Case-Control Study

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Keywords
Brain cancer · Children-adolescent health · Environmental exposure · Epidemiology studies · Medical radiation

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Abstract

Background: We explored the association between ionizing radiation (IR) from pre-natal and post-natal radio-diagnostic procedures and brain cancer risk within the MOBI-kids study. ***Methods:*** MOBI-kids is an international (Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, New Zealand, Spain, The Netherlands) case-control study including 899 brain tumor (645 neuroepithelial) cases aged 10–24 years and 1,910 sex-, age-, country-matched controls. Medical radiological history was collected through personal interview. We estimated brain IR dose for each procedure, building a look-up table by age and time period. Lifetime cumulative doses were calculated using 2 and 5 years lags from the diagnostic date. Risk was estimated using conditional logistic regression. Neurological, psychological and genetic conditions were evaluated as potential confounders. The main analyses focused on neuroepithelial tumors. ***Results:*** Overall, doses were very low, with a skewed distribution (median 0.02 mGy, maximum 217 mGy). ORs for post-natal exposure were generally below 1. ORs were increased in the highest dose categories both for post and pre-natal exposures: 1.63 (95% CI 0.44–6.00) and 1.55 (0.57–4.23), respectively, based on very small numbers of cases. The change in risk estimates after adjustment for medical conditions was modest. ***Conclusions:*** There was little evidence for an association between IR from radio-diagnostic procedures and brain tumor risk in children and adolescents. Though doses were very low, our results suggest a higher risk for pre-natal and early life exposure, in line with current evidence.

Introduction

The use of radio-diagnostic tools has drastically improved patient care and has become a fundamental part of clinical evaluation. However, this has resulted in an increase in the number of diagnostic procedures, and consequently, of ionizing radiation (IR) exposure [1–3]. This has become a public health and radiation protection concern [2], as there is growing evidence that IR may induce cancer even at low-to-moderate doses, such as those delivered in common diagnostic examinations [3]. Concern is particularly high in pediatric populations [4], as exposure in childhood is known to entail higher risk of radiation-induced cancer than exposure later in life [5]. It is well known that radiation can cause brain tumors in adults, particularly following exposure in early life [5, 6].

Brain tumor is the second most frequent tumor in childhood and adolescence, after leukemia [7]. Previous studies have attempted to quantify brain tumor risk in young people from radio-diagnostic procedures. Case-control studies generally found a dose-related increased risk of brain tumors in offspring of mothers exposed to IR during pregnancy [8]; the effect of post-natal exposure is less conclusive [8–10]. Recent large-scale pediatric computed tomography (CT)-scan cohort studies reported a dose-related increases in brain tumor risk that are higher (per unit radiation dose) [11–16], though statistically compatible, than those derived from the atomic bomb survivor study, which underpins much of radiological protection up to now.

The results of CT-scan studies published to date have been criticized because of potential for bias resulting from: confounding by indication due to underlying medical conditions related both to CT-scan exposure and brain cancer risk; reverse causation, which occurs when the CT-scan was in fact related to the symptoms or diagnosis of the tumors; as well as missing doses [17]. Analyses of data from the United Kingdom and French pediatric CT cohorts and simulation studies indicate that genetic predisposing conditions have little effects on radiation-risk estimates [11, 16, 18], but may act as effect modifiers [16, 19]. Apart from genetic predisposing conditions, several neurological and congenital conditions are associated with childhood brain cancer or higher CT-scan exposure [20–24], and could potentially confound estimates of brain cancer risk from medical radiation.

Here, we aimed to estimate the risk of brain tumor in children and young adults from exposure to pre- and post-natal medical diagnostic IR within one of the largest international case-control study on brain tumor in young people, the MOBI-Kids study. The analysis conducted here includes detailed cumulative brain dose estimation based on typical time-age radiographic protocols. In addition, the role of medical history, as a potential confounder of the relation between medical radiation dose and brain tumor risk is, for the first time, examined in detail.

Materials and Methods

Study Design

We recruited 899 cases of brain tumors, aged 10–24 at diagnosis, from 14 countries (Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, New Zeeland, Spain, The Netherlands) between May 2010 and March 2016. For each case, 2 controls were selected among patients undergoing appendectomy in hospitals from the geographical area covered by the neurosurgery/oncology departments where cases were identified. Controls were matched by sex, age (1-year category up to age 19,

2 years thereafter), date of surgery/interview and region of residence. Controls with previous brain tumor diagnosis were not eligible. Participants with language difficulties or a known brain tumor predisposing syndrome (e.g., neurofibromatosis) were excluded. All histological brain tumor types were included. The main objective of MOBI-Kids was to study brain tumor risk from mobile phone use, thus midline tumors close to the sellar region were not included, because of the low radio-frequency exposure in these areas. Further methodological details have been published elsewhere [25].

Data Collection

Data were collected through a personal interview conducted by trained personnel. Two questionnaires were used: the main questionnaire, administered to the participant (or a parent, depending on the age of the study subject and his/her health condition), captured information on demographic factors, use of mobile communication devices, medical and radiological history and other environmental exposures; the second, for parents, collected data on preconception, pre-natal and early life factors.

The medical radiation section of the main questionnaire included a screening question to identify subjects who had ever undergone a particular procedure (e.g., "Have you ever had X-rays of the head or neck?"). If the answer was positive, the interviewee was asked about the body part examined (head, neck, whole body), age and reason of examination. Procedures included conventional X-ray, CT-scan, magnetic resonance imaging (MRI), angiography and dental X-ray (bite-wing X-ray, panoramic, full mouth and dental-CT). To help the interviewee identify the correct examination, pictures of the machine were shown. In the maternal questionnaire, the subject's mother was asked if she had radiation imaging/therapy during her pregnancy. If so, questions were asked, for each trimester of pregnancy, about the type of procedure, the body part, the number of examinations and whether the mother's abdomen was shielded during the procedures. The mother was also asked if her child underwent any radiological procedures during its first year of life. As subjects would typically be unable to report procedures early in life, we considered exposures in the first year of life only if it was reported by the parents (online suppl. File 1; for all online suppl. material, see www.karger.com/doi/10.1159/000506131).

Dose Estimation

For the dose estimation, we had, for each subject, a list of procedures reported during the interview, with details on the time period where they were performed and the body part examined. We aimed to perform the risk analysis using as exposure metric the cumulative dose to the brain, expressed in mGy. Thus, for each examination, brain doses were estimated based on typical protocols by time period and age at exposure as follows [8, 26].

We searched the literature for publications reporting, for each examination type in a given time-age frame, either a distribution of technical parameters used by radiologists (i.e., X-ray tube voltage, X-ray beam energy, filtration, X-ray tube distance) [27] or an estimation of brain dose [28]. Technical parameters extracted from publications were used to estimate brain dose using the PCXMC software by entering the measures of central tendency (median or mean) of these technical parameters [29]. For each "examination × age × time period" frame, we obtained values of the brain absorbed dose simulated from a set of parameters, which would have been the most representative of radiological practice at the time. Thus, we scored each publication with a "relevance score" (ranging from 0 to 5). To build the look-up table, we calculated the mean of the absorbed dose among the simulations coming from publications with the highest "relevance score" for each period of time and age range.

We obtained a look-up table where, for each examination, time period (1980–1989; 1990–1999; 2000–2010) and age category (fetal, 0–0.5, 0.5–2.5, 2.5–7.5, 7.5–12.5, 12.5–18 years of age, and adults), a brain dose could be attributed (online suppl. File 2).

The list of questions asked in the questionnaires, and all steps of the calculation of dose including the assumption made are reported in online supplement File 3. The dose estimation process implemented here and results for intraoral dental examination are published elsewhere [30].

Post-natal cumulative brain dose up 2 year before interview was calculated for each participant by summing the doses received for each examination the subject underwent. Fetal cumulative dose was calculated separately, using the approach described above, relying on a revision of typical fetal dose values during X-ray examination published in a doctoral thesis [31].

Definition of Covariates

We identified the following a priori variables as being possibly associated with brain tumor risk: parental education, as a proxy of socio-economical status (SES) [32], presence of any neurological or psychological disease [20, 21, 23], genetic diseases [22].

Parental education was estimated as the highest of mother's or father's education level, categorized into low (primary education), medium (secondary education), and higher (university or more), along with a fourth category including missing or not classifiable.

The medical history section of the main questionnaire included a screening question formulated as: "Has a doctor ever told you that you have one of the following diseases?" with a list of conditions, including neurological, psychological and genetic diseases. For each condition reported, information was asked on the exact diagnosis and date. For the analysis of neurological diseases, we only considered diseases diagnosed at least 2 years before diagnosis, to avoid inclusion of neurological brain tumor symptoms. A full list of reported neurological, psychological and genetic conditions can be found in online supplement File 4.

As the presence of a brain tumor could influence the interview conditions, the interview quality score and identity of the interviewee (index, parent[s], and index with parent) were explored as covariates. At the end of the main questionnaire, the interviewer evaluated 2 dimensions of interview quality: motivation ("was the interviewee responsive?") and memory ("how well did the interviewee remember the information about questions asked?"). We derived a single score by calculating the mean between the 2 scores. If the case interview was done with a parent present, the interviewer was also asked to evaluate the quality of the parents' answers. In this case, we considered the parental score rather than that of the index.

Power Calculation

We performed a post hoc power calculation using the Power [33] software. Considering the number of cases we have and the estimated dose distribution in our study population, the estimated power to reject the hypothesis of no effect if the effect magnitude is as high as that reported in a recent CT-cohort study (RR of 3.3 for 100 mGy of dose – Pearce et al. [34]) is 85%, with an α of 0.05.

The power is actually less than that because of possible exposure misclassification related to the actual technical parameters used in the radiological examination. If, instead, we hypothesize that the true risk (in absence of any dosimetric error) is closer to that seen in other populations such as the atomic bomb survivors (RR at 100 mGy of 2.5 or 2), the study power decreases considerably to 60 and 40% respectively.

Statistical Analysis

We estimated the association between categories of estimated post-natal and pre-natal brain doses and risk of brain tumors using conditional logistic regression stratified by sex, attained age and country. ORs and Likelihood ratio test 95% CIs are shown throughout. The main analyses focused on risk of neuroepithelial tumors, which represent 75% of the tumors in the study. Embryonal tumors are the second largest group recruited, representing 14% of all tumors; the numbers of cases for each other subtype are very low, with only 45 cases of meningioma. Neuroepithelial tumors have a different age distribution than embryonal tumors and likely a different etiology. Thus, we focused our analyses on the more homogeneous group of neuroepithelial tumors. Supplementary analyses were also conducted for embryonal tumors and for all histological brain cancer types.

For post-natal exposure, cumulative dose was categorized into 4 groups using 20, 50, and 100 mGy as a priori cut-off points for consistency with previously published studies [13]; for pre-natal dose, only 2 categories were considered, using 5 mGy as the cut-off point, given the low levels of these doses. In the main analyses, doses were lagged by 2 years, whereas in a sensitivity analysis doses were lagged by 5 years, taking as a reference the date of diagnosis for cases and of appendectomy for controls.

The potential confounding effect of the covariates identified above were evaluated by testing for an association between each covariate and the lagged categorical cumulative dose (with 20 and 50 mGy cut-off points) using multinomial logistic regression. We used likelihood ratio tests to compare the null model which includes only sex, age, and country and the models where the covariate was added. Each covariate was tested separately.

Heterogeneity of risk by time since exposure was tested by including 3 dose variables (corresponding to the cumulative dose received in different windows of time before diagnosis: 2–5, 6–10, and over 10 years) in the model and comparing to the model with cumulative dose only. Heterogeneity of risk by age at exposure (0–5, 6–15, and >15 years of age) was evaluated in the same way.

Additional analyses were conducted to evaluate the sensitivity of the results to different assumptions. This included using (1) alternative exposure scenarios such as cumulative dose including procedures with missing date as performed before 2 years from diagnosis; cumulative fetal dose setting dose to 0 when the mother reported abdominal lead apron protection; using total number of head CTs instead of dose; and (2) alternative subsets, such as only participants with high interview quality score; only participants for whom the interview was conducted with parents present; excluding subjects with any reported genetic condition; excluding subjects reporting any neurological condition diagnosed 5 year before cancer/appendicitis; adjusting for parental education. Risk of neuroepithelial tumors was also estimated in relation to number of MRIs as a "negative control" (MRI does not emit IR).

Statistical analysis was conducted with the R software [35].

Results

A total of 899 cases and 1,910 controls were recruited. Participation rate was 72% in cases and 54% in controls. Details of reason for non-participation are described elsewhere [36]. We excluded 9 cases and 5 controls reporting a previous cancer and 4 controls whose age at appendectomy was missing. With stratification by attained age, sex and country, 859 cases (645 neuroepithelial, 124 embryonal) and 1,730 controls (1,700 for neuroepithelial and 865 for embryonal cases) were included in the analysis; 31 cases and 171 controls were excluded as they belonged to a stratum lacking of at least one control or case. Countries with the highest number of neuroepithelial cases were Spain (143), Italy (122), France (74), Israel (74), and Germany (68).

Characteristics of the participants are reported in Table 1, by case/control status and tumor morphology (neuroepithelial, embryonal and all brain tumors). There were slightly more males than females. Parents of controls tended to have slightly higher education level than cases parents. Prevalence of neurological, psychological and genetic disease was similar between cases and controls. The index was interviewed alone more often in controls; however, no difference in quality of interview was found between cases and controls.

Overall cumulative brain dose was very low and the dose distribution was skewed (Fig. 1) with 2 peaks: the first, including 75% of participants, is below 1 mGy; the second, less prominent, is around 30 mGy and includes subjects who underwent at least 1 CT-scan.

Table 2 describes the distribution of doses. Median post-natal dose was similar (0.02 mGy) in cases and controls for all 3 tumor groupings when doses were lagged by either 2 or 5 years. The percentage of controls with at least one CT-scan was higher than in cases (6.5 vs.3.7% in the neuroepithelial sample). Only a small proportion of subjects received pre-natal doses. Median pre-natal dose was higher among cases than that in controls (Table 2).

Concerning potential confounders, statistically significant associations with doses were found for neurological disease, psychological disease and quality of interview, but not for parental education, genetic diseases or identity (subject, parent, other) of the interviewee (online suppl. File 5).

Table 3 reports ORs and 95% CI by post-natal and pre-natal by dose level based on categorical and continuous analyses for neuroepithelial, embryonal, and brain tumors overall. For post-natal dose, there was no evidence of a trend with dose; ORs were below 1 in all but the highest dose category, where they were systematically above 1, based on

Table 1. Characteristics of the study population

Variable	Neuroepithelial		Embryonal		All brain tumours[a]	
	cases	controls	cases	controls	cases	controls
Number	645	1,700	124	865	859	1,730
Gender, male, *n* (%)	352 (54.6)	969 (57.0)	88 (71.0)	535 (61.8)	487 (56.7)	991 (57.3)
Age at diagnosis, median (IQR)	15.7 (12.7–20.0)	15.8 (12.9–20.3)	14.6 (11.6–17.7)	15.1 (12.3–19.7)	15.7 (12.7–20.1)	15.7 (12.9–20.9)
Parental education, *n* (%)						
Low	216 (33.5)	483 (28.4)	53 (42.7)	252 (29.1)	300 (34.9)	493 (28.5)
Medium	189 (29.3)	400 (23.5)	26 (21.0)	218 (25.2)	242 (28.2)	405 (23.4)
High	196 (30.4)	630 (37.1)	39 (31.5)	292 (33.8)	262 (30.5)	643 (37.2)
Other/don't know	44 (6.8)	187 (11.0)	6 (4.8)	103 (11.9)	55 (6.4)	189 (10.9)
Any neurological disease, *n* (%)	69 (10.7)	147 (8.6)	7 (5.6)	75 (8.7)	88 (10.2)	149 (8.6)
Missing	0 (0.0)	12 (0.7)	1 (0.8)	6 (0.7)	1 (0.1)	12 (0.7)
Difference in years between age at diagnosis of the cancer/appendicitis and the neurological disease, median (IQR)	6.4 (3.5–10.0)	8.0 (4.6–11.7)	11.3 (5.8–16.8)	7.1 (4.6–10.4)	6.4 (3.6–10.5)	8.0 (4.7–11.7)
Any psychological disease, *n* (%)	23 (3.6)	69 (4.1)	7 (5.6)	31 (3.6)	33 (3.8)	70 (4.0)
Missing	2 (0.3)	16 (0.9)	1 (0.8)	7 (0.8)	3 (0.3)	16 (0.9)
Any genetic disease, *n* (%)	12 (1.9)	28 (1.6)	4 (3.2)	12 (1.4)	16 (1.9)	28 (1.6)
Missing	6 (0.9)	18 (1.1)	2 (1.6)	8 (0.9)	9 (1.0)	18 (1.0)
Identity of the interviewee, *n* (%)						
Index only	176 (27.3)	773 (45.5)	22 (17.7)	326 (37.7)	237 (27.6)	791 (45.7)
Index with proxy/proxy only	468 (72.6)	916 (53.9)	102 (82.3)	533 (61.6)	621 (72.3)	928 (53.6)
Missing	1 (0.2)	11 (0.6)	0 (0.0)	6 (0.7)	1 (0.1)	11 (0.6)
Interview quality score						
1 (poor)-6 (very good), median (IQR)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)

[a] All brain cancer includes all histological tumor type: 645 neuroepithelial, 124 embryonal, 45 meningiomas, 45 other non-neuroepithelial.
IQR, interquartile range.

small numbers of cases. Continuous analyses showed no evidence of a dose-response relationship. Adjustment for neurological, psychological and genetic conditions modified the risk estimates only slightly. Analyses with a 5-year lag showed similar results, though risk estimates in the highest dose category were lower and CIs wider.

For fetal exposure above 5 mGy, unadjusted ORs of 1.52 (95% CI 0.56–4.14), 2.04 (0.22–18.63), 1.34 (0.52–3.48) were found for neuroepithelial, embryonal and all brain cancer cases respectively. Results did not change substantially after adjustment.

Table 4 shows results of analyses of the potential modifying effect of time since exposure and age at exposure in neuroepithelial cases. For doses received in the first 5 years of life, the OR in the above 50 mGy category was 1.29 (0.49–3.40) based on a very small number of cases. The ORs were above 1 (with large CIs) for doses above 50 mGy cumulated in the 2–5 and 6–10 years before diagnosis windows. For doses above 50 mGy received >10 years before diagnosis, the OR was below 1 but not statistically significantly (Table 4).

Results of sensitivity analyses for neuroepithelial tumors are shown in online supplement File 6. Risk estimates were generally statistically compatible with those of the main analyses. Assigning 0 dose for pre-natal procedures with a lead apron protection resulted in an OR of 2.1 (0.45–6.04) for doses above 5 mGy category. The OR was 0.53 (0.26–1.05) for exposure to one CT-scan compared to none and 0.72 (0.45–1.15) for one MRI scan.

Discussion

We explored the association between categories of cumulative brain IR dose from medical diagnostic exposures during pre-natal and post-natal life and brain cancer risk among young people in one of the largest population based case-control studies of this disease to date [10, 37, 38]. Cumulative brain dose derived from common medical diagnostic examinations was generally low, with 90% of subjects having cumulative lifetime doses below or equal to 1 mGy. In comparison, the average annual per capita dose in the world is 1–2 mGy from natural and human made sources [39], excluding radon, which does not contribute to brain dose.

Overall, no statistically significant differences were found across categories of exposure and continuous analyses showed no evidence of a dose-response relationship.

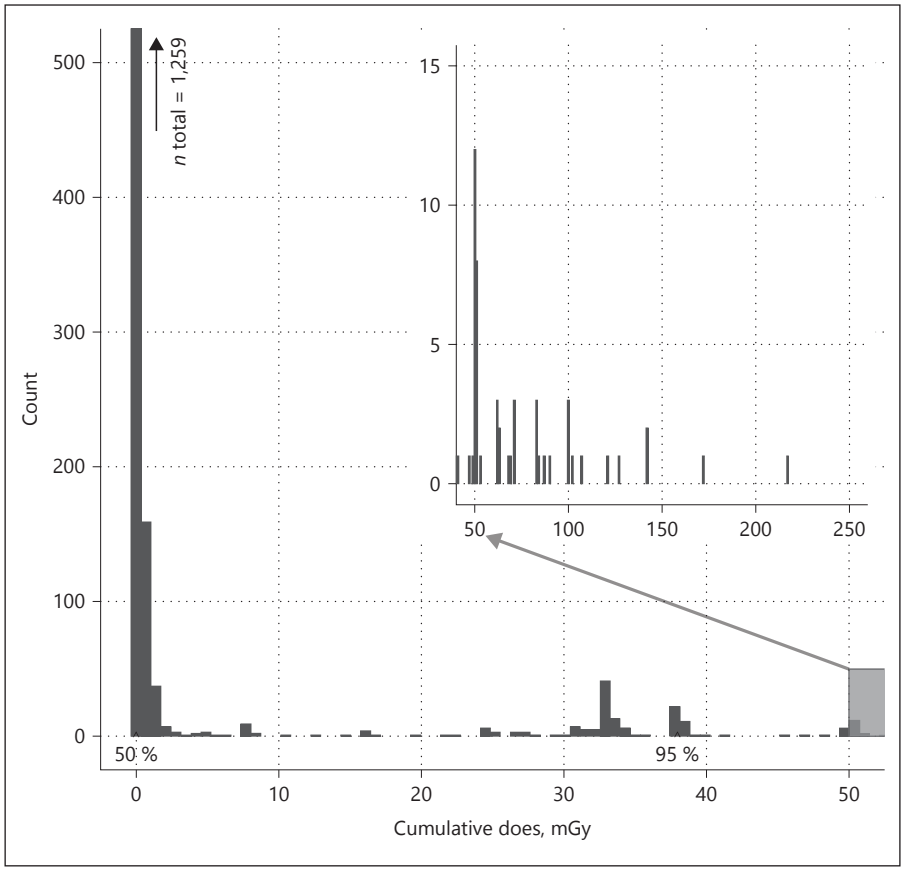

Fig. 1. Distribution of cumulative brain dose (2 year lag period) in cases and controls. Seven hundred and fifty-nine subjects with dose = 0 are excluded.

Table 2. Distribution of dose and number of radiological examinations by brain tumor morphology among cases and controls

Variables	Neuroepithelial		Embryonal		All brain cancer	
	cases	controls	cases	controls	cases	controls
Number	645	1,700	124	865	859	1,730
Exposed (2 years lag), *n* (%)	432 (67.0)	1,154 (67.9)	74 (59.7)	570 (65.9)	564 (65.7)	1,173 (67.8)
Distribution of dose in the exposed, median (IQR)						
Cumulative dose in mGy (2 years lag)	0.02 (0.01–0.14)	0.02 (0.01–0.66)	0.02 (0.01–0.05)	0.02 (0.01–0.66)	0.02 (0.01–0.17)	0.02 (0.01–0.66)
Cumulative dose in mGy (5 years lag)	0.02 (0.01–0.06)	0.02 (0.01–0.07)	0.02 (0.01–0.05)	0.02 (0.01–0.07)	0.02 (0.01–0.06)	0.02 (0.01–0.07)
Prenatal exposure						
Exposed prenatally, *n* (%)	17 (2.6)	48 (2.8)	2 (0.2)	20 (2.3)	20 (2.3)	49 (2.8)
Cumulative fetal dose in mGy, median (IQR)	1.40 (0.01–12.70)	0.05 (0.00–12.70)	6.38 (3.21–9.54)	0.33 (0.01–3.15)	0.73 (0.01–12.70)	0.05 (0.00–12.70)

IQR, interquartile range.

The OR was systematically above 1 for cumulative doses above 100 mGy, with very large CIs, based on small numbers. The sensitivity analyses did not substantially modify the results.

These findings are in line with previous case-control studies on childhood/adolescent brain tumor risk following medical diagnostic radiation exposure, which generally reported non-statically significant increased risks [10, 37]. Compared to those studies, we included a much larger number of cases and we performed an analysis based on category of absorbed dose to the brain instead of using number of examinations. In addition, we took into account medical history variables as potential confounders of the association.

We also found reduced ORs, statistically significant in some analyses, for the 20–50 mGy categories, and for hav-

Table 3: OR and 95% CI for neuroepithelial, embryonal and all brain tumors by cumulative dose for post-natal and pre-natal exposure

	Crude[a]					Adjusted[b]				
	cases	controls	OR	95% CI	*p* value	cases	controls	OR	95% CI	*p* value
Neuroepithelial tumors										
Postnatal 2 years lag										
Categorical analysis, mGy										
0–20	607	1,552	1			597	1,529	1		
20–50	25	113	0.61	0.38–0.96		24	112	0.56	0.35–0.9	
50–100	9	28	0.79	0.36–1.73		9	28	0.73	0.33–1.6	
≥100	4	7	1.93	0.53–7.07		4	7	1.64	0.45–6.06	
Continuous (per mGy)	645	1,700	1.00	0.99–1.00	0.32	634	1,676	0.99	0.99–1.00	0.17
Postnatal 5 years lag										
Categorical analysis, mGy										
0–20	618	1,608	1			607	1,585	1		
20–50	17	62	0.84	0.48–1.49		17	61	0.82	0.46–1.45	
50–100	8	25	0.84	0.37–1.91		8	25	0.77	0.33–1.78	
≥100	2	5	1.35	0.24–7.62		2	5	1.16	0.2–6.63	
Continuous (per mGy)	645	1,700	1.00	0.99–1.01	0.57	634	1,676	1.00	0.99–1.01	0.41
Fetal										
Categorical analysis, mGy										
0–5	639	1,686	1			628	1,662	1		
≥5	6	14	1.52	0.56–4.14		6	14	1.55	0.57–4.23	
Embryonal tumors										
Postnatal 2 years lag										
Categorical analysis, mGy										
0–20	120	801	1			117	788	1		
20–50	2	54	0.31	0.07–1.3		2	52	0.35	0.08–1.48	
≥50	2	10	1.37	0.26–7.23		2	10	1.49	0.26–8.56	
Continuous (per mGy)	124	865	1.00	0.99–1.02	0.91	121	850	1.00	0.99–1.02	0.75
Fetal										
Categorical analysis, mGy										
0–5	123	860	1			120	845	1		
≥5	1	5	2.04	0.22–18.63		1	5	1.5	0.14–16.28	
All brain tumors										
Postnatal 2 years lag										
Categorical analysis, mGy										
0–20	806	1,580	1			792	1,559	1		
20–50	35	114	0.66	0.44–0.99		34	113	0.63	0.41–0.95	
50–100	11	29	0.72	0.35–1.47		11	29	0.68	0.33–1.4	
≥100	7	7	2.98	0.96–9.29		7	7	2.58	0.82–8.13	
Continuous (per mGy)	859	1,730	1.00	1.00–1.01	0.75	844	1,708	1.00	1.00–1.01	0.52
Fetal										
Categorical analysis, mGy										
0–5	852	1,716	1			837	1,694	1		
≥5	7	14	1.34	0.52–3.48		7	14	1.35	0.52–3.51	

[a] Conditional logistic regression stratified by sex, attained age (1 year group until the age of 19, then by 2 years), and country.
[b] Models adjusted for presence of neurologic, mental, and genetic disease.

ing had one head CT-scan. The findings were generally consistent across the sensitivity analyses and remained after excluding interviews with poor quality. This observation likely reflects a difference in the percentage of controls undergoing one CT-scan (6.4%), compared to cases (3.8%), possibly due to chance, selection bias or unmeasured confounding. Indeed, selection bias was observed in an adult brain cancer case-control study [40], where controls who had experienced previous head injury (and consequently underwent head and neck examination)

Table 4. Effect modification by time since exposure and age at exposure for neuroepithelial

	Cases	Controls	OR	95% CI
ORs and 95% CI for dose cumulated in different windows of age at exposure[1, 2]				
0–5 ages, mGy				
0–50	627	1,663	1	
≥50	7	13	1.29	0.49–3.4
6–15 ages, mGy				
0–50	631	1,657	1	
>50	3	19	0.39	0.11–1.37
>15 ages, mGy				
0–50	633	1,673	1	
≥50	1	3	1.09	0.09–13.33
LRT results[3]			**0.80**	
ORs and 95% CI for dose cumulated in different time windows before diagnosis[1, 2]				
2–5 years, mGy				
0–50	632	1,674	1	
≥50	2	2	3.4	0.44–26.53
6–10 years, mGy				
0–50	631	1,671	1	
≥50	3	5	2.7	0.58–12.63
>10 years, mGy				
0–50	627	1,652	1	
≥50	7	24	0.68	0.28–1.65
LRT results[3]			**0.60**	

Bold indicate significant values.

[1] Conditional logistic regression stratified by sex, attained age (1 year group until the age of 19, then by 2 years), and country.

[2] Model adjusted for presence of neurologic, mental and genetic disease.

[3] LRT results refer to the *p* value of the LRT test between the null model (with the lifetime cumulative exposure) and the model with the cumulative exposure in different windows periods.

LRT, Likelihood ratio test.

were more likely to participate than those who had not. It is conceivable that a similar phenomenon might at least partly explain our results, where potential controls with a history of head injury or other neurological diseases may be more interested in participating in a brain cancer case-control study.

SES may confound the association between radiation dose and brain tumor risk in this study as parents of controls tended to have higher education levels (thus, likely, higher level of SES) compared to parents of cases. However, recent reports, show no consistent association between SES and CT-scan exposure [18, 41–44]. We tested if parental education was related to cumulative dose, and found no association. Adjustment for parental education did not substantially change the results.

Regarding time since exposure, the risk of brain tumors for subjects with doses of 50 mGy or more appears to decrease with increasing time since exposure; the small numbers and very large CIs preclude any clear conclusions. We detected a non-statistically significant increased risk for exposure above 50 mGy cumulated up to 5 year of age, in line with current evidence suggesting increased sensitivity from exposures early in life [5].

Though only a low percentage (about 2%) of parents reported pre-natal radiation exposure, an OR of 1.55 (0.57–4.23) was found for subjects with the highest pre-natal doses (>5 mGy) for all outcomes considered. This result, based on very small numbers of subjects, appeared to be robust to sensitivity analyses.

Evidence of an association between pre-natal diagnostic X-rays exposure and subsequent cancer risk in the offspring mainly come from the Oxford Survey of Childhood Cancer study, the findings of which [45], based on generally higher doses than observed here, have resulted in a drastic reduction of the use of diagnostic IR procedures in pregnant women [46]. While

this reduction is clearly beneficial for patients, it limits the power of more recent studies, including ours, to detect an increased risk for pre-natal exposures [8–10, 37].

Strengths and Limitations

Our work is subject to certain limitations. This study, one of the largest population based case-control study of brain tumors in young people, had low statistical power to detect an association with diagnostic IR exposure, due to the very low dose levels received [47]. Our dose distribution likely reflects current and recent past childhood/adolescent population exposure levels, where the majority of subjects received very low levels of dose from common X-ray examinations (including dental) and only a small proportion underwent CT-scans.

Our estimated doses are subject to error and we identified 2 main sources of uncertainty. First, using self-reported information may have induced recall errors (systematic and random). If these are non-differential with respect to case-control status, this would likely bias risk estimates towards the null. Second, the estimated dose accounted only for a *time* × *age* variability, but not for the full range of variability (related to patient characteristics, country variability in radiographer practice, or actual technical parameters used in the specific patients examinations) and are thus subject to Berkson error – which is unlikely to affect the risk estimates in a linear dose-response model, though it may affect the width of the CIs.

CT-scan cohort studies have been criticized for not taking into account medical conditions that could predispose to cancer and prompt to radiological examination (confounding by indication) and because of the possibility of reverse causation [12, 17, 34].

Confounding by indication due to a genetic syndrome known to predispose to brain cancer (e.g., neurofibromatosis) is unlikely in the present study because participants with these conditions were excluded by design. In addition, we adjusted the analysis for the presence of other medical conditions.

Regarding the issue of reverse causation, in the main analysis, we have lagged doses for a period of 2 years before diagnosis (and for 5 years in a sensitivity analysis). Most symptoms for brain tumors tend to appear only a few months before the diagnosis [48, 49] and this was also seen in the MOBI-kids population [50]. Therefore, reverse causation seems unlikely here, particularly in analyses with a 5-year lag. However, the decreased OR with increasing time since exposure may suggest a certain degree of reverse causation. We conducted a sensitivity analysis by excluding subjects who reported a neurological disease diagnosed 5 year before cancer/appendicitis, assuming that these diseases could potentially represent early cancer symptoms. Results of the sensitivity analysis were comparable to those of the main analysis. Thus, the finding of decreasing ORs with increasing time since exposure is difficult to interpret as it is based on small numbers of subjects; however, it could also reflect a poorer recall of the procedures back in time.

Recall Error

Both cases and controls may be already familiar with medical history questions because they have been recruited in hospitals, and, when hospitalized, it is common to be asked by a doctor to report previous diseases. For the same reason, participants may all be familiar with radiological history questions. It is true that cases may tend to distinguish better MRI from CT-scans because both procedures may be required for cancer diagnosis; however, this would introduce lower response accuracy in controls, rather than explaining differential over or under-reporting in one of the 2 groups.

The accuracy of reporting medical radiological history may also be affected by interview conditions. For medical radiological history, particularly in early life, the parents' answers are likely to be more accurate than the participant's. Indeed, recalling examinations during childhood might be problematic for the participants. Interviews of subjects aged <18 years of age were generally conducted in the presence of a parent (80%; or with the parent[s] alone) while only 25% of young adults were interviewed with parents. In addition, older cases tended to be interviewed in the presence of parents more often than controls, because of their poorer health conditions, and thus information collected for cases would tend to be more accurate than for controls, in particular for young adults. We conducted 2 sensitivity analyses: one restricted to interviews with parents and the other restricted to high quality interview. Results were similar to those of the main analysis.

Dose Estimation

Variability of doses by country has not been taken into account, due to the scarcity of literature relevant for our dose estimation methodology. However, a recent study showed that, for head CT-scans, dose variation across country is limited, suggesting that protocols for head CTs are standardized across countries [51]. We based our head-CT dose estimation on the work published by Lee et al. [52] and doses are comparable to those from ongoing work in Australia and Europe [53, 54].

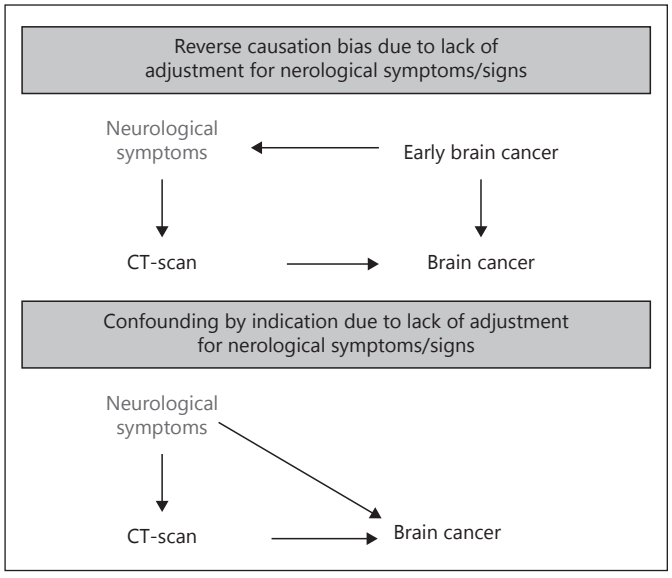

Fig. 2. Direct acyclic graphs showing issue of confounding by indication and reverse causality. CT, computed tomography.

Another issue for consideration is that we could not capture eventual retakes of the same image. Retakes are done when using contrast technique or because of the poor image quality. This is unlikely to cause substantial misclassification for non-CT images (doubling the dose of a head X-ray will not lead to a subject changing dose category), but it is important for CT-scans, where doubling the dose can shift participants into higher dose categories. As a result, we could have underestimated the dose for some participants, albeit non-differentially between cases and controls.

Despite the limitations discussed, our work, presents 2 important original aspects. It is the first brain tumor case-control study of medical IR diagnostic exposure to use time-period based dose estimation; even if it comes with some uncertainty, this is a valid alternative to using merely number of examinations [8, 26]. Indeed, using the number of examinations leads to exposure misclassification due to the wide range of doses for each procedure. The other important aspect of our study is the collection of detailed medical history, including the list of diseases diagnosed in each subject. This allowed previous medical history to be taken into account, which could confound the association between IR dose and brain tumor risk.

Role of Medical Conditions

Some neurological and psychological conditions have been suggested to increase brain tumor risk [20, 21, 23, 55]. These may be early signs/symptoms of the tumor; however, a causal association has not been excluded. Neurological and psychological conditions have never been taken into account in diagnostic radiation studies of brain tumors. We found that these diseases were related to higher IR exposure from medical procedures, with a stronger association for neurological diseases. Thus, we adjusted our analyses for the presence of these diseases to overcome possible bias due to confounding by indication (in the case that the association between neurological disease and brain cancer is interpreted as causal) or reverse causation bias (if the presence of neurological/psychological conditions represents early signs/symptoms; Fig. 2). We also adjusted for the presence of any genetic/congenital disease because these may be associated with brain cancer or with exposure to CT-scans [22, 24]. After adjustment, there was a slight decrease in point estimates in all categories, suggesting possible confounding; however, the change in risk estimates was modest.

Conclusion

In this large multi-center case-control study, with very low average doses, we found little evidence of an increased risk of pre-natal and post-natal exposure to external IR dose from diagnostic medical procedures.

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Statement of Ethics

Ethical approval was obtained from all the relevant Ethics Committees in the participating countries. The study protocol followed was in accordance with the ethical standards of the responsible committees on human experimentation and with the Helsinki Declaration. Written consent was obtained from all participants (or their parents) for each part of the study, including the interview, whose data have been used for the present publication.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

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