Published OnlineFirst September 13, 2016; DOI: 10.1158/1055-9965.EPI-16-0451

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prenatal and Postnatal Medical Conditions and the Risk of Brain Tumors in Children and Adolescents: An International Multicenter Case–Control Study

Giorgio Tettamanti[1], Xiaochen Shu[1,2], Maral Adel Fahmideh[1], Joachim Schüz[3], Martin Röösli[4,5], Tore Tynes[6,7], Michael Grotzer[8], Christoffer Johansen[9,10], Lars Klaeboe[7,11], Claudia E. Kuehni[12], Birgitta Lannering[13], Lisbeth S. Schmidt[10], Danielle Vienneau[4,5], and Maria Feychting[1]

Abstract

Background: Previous studies have evaluated the effect of medical diagnostic radiation on brain tumors. Recent cohort studies have reported an increased risk associated with exposure to head CT scans.

Methods: Information regarding medical conditions, including prenatal and postnatal exposure to medical diagnostic radiation, was obtained from CEFALO, a multicenter case–control study performed in Denmark, Norway, Sweden, and Switzerland through face-to-face interview. Eligible cases of childhood and adolescent brain tumors (CABT) were ages 7 to 19 years, diagnosed between January 1, 2004 and August 31, 2008, and living in the participating countries ($n = 352$). The cases were matched by age, sex, and region to 646 population-based controls.

Results: Prenatal exposure to medical diagnostic radiation and postnatal exposure to X-rays were not associated with CABTs. A higher risk estimate of CABTs, although not statistically significant, was found for exposure to head CT scan (OR, 1.86; 95% confidence interval, 0.82–4.22). The associations with head injury, febrile seizure, fever in the first 12 weeks, and general anesthesia were close to unity.

Conclusions: Prenatal or postnatal medical conditions, including medical diagnostic radiation, were not associated with CABTs. On the basis of small numbers of exposed children, we observed a nonsignificant increased risk for CT scans of the head.

Impact: We have presented additional evidence, suggesting that exposure to head CT scan may be associated with the occurrence of CABTs. *Cancer Epidemiol Biomarkers Prev; 26(1); 110–5. ©2016 AACR.*

Introduction

Brain tumors are the most common solid tumors in children (1). The annual incidence rate of childhood brain tumors (CBT) varies by country, and the Nordic countries have among the highest observed incidence rates in the world, with slightly over 40 cases per million children diagnosed below 15 years of age (1, 2). Despite extensive epidemiological research, little is known about the etiology of CBTs: only some rare genetic syndromes and high-dose ionizing radiation to the head and neck were consistently reported to be associated with an increased risk of CBTs (3–5).

Previous studies have evaluated the effect of medical diagnostic radiation, which is regarded as moderate- and low-dose radiation, on the risk of brain tumors. No increased risk of CBTs was found among children exposed, *in utero* or after birth, to medical X-rays (6, 7). However, three cohort studies reported an increased risk of brain tumor associated with radiation exposure from CT scans during childhood and adolescence (8–10). In adults, an increased risk of adult glioma was observed among individuals who had three or more CT scans to the head and neck region, although limited to persons with a family history of cancer (11). Results from studies regarding the effect of head injury on the risk of brain tumor are conflicting: Although some case–control studies reported a positive association (12–14), two large cohort studies found nonsignificant results (15, 16).

The aim of this study was to evaluate the effects of specific prenatal and postnatal medical conditions, including exposure to medical diagnostic radiation, on the risk of childhood and adolescent brain tumors (CABT).

Materials and Methods

The present study was conducted using data from the CEFALO study, a multicenter case–control study performed in Denmark,

[1]Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [2]Department of Epidemiology, School of Public Health, Soochow University, Suzhou, China. [3]Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France. [4]Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland. [5]University of Basel, Basel, Switzerland. [6]National Institute of Occupational Health, Oslo, Norway. [7]The Cancer Registry of Norway, Oslo, Norway. [8]Department of Oncology, University Children's Hospital of Zurich, Zurich, Switzerland. [9]Oncology Clinic, Finsen Center, Copenhagen, Denmark. [10]The Danish Cancer Society Research Center, Copenhagen, Denmark. [11]Norwegian Radiation Protection Authority, Oslo, Norway. [12]Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Switzerland. [13]Department of Clinical Sciences, Pediatric Oncology, University of Gothenburg, Gothenburg, Sweden.

Note: G. Tettamanti and X. Shu share joint first authorship for this article.

Corresponding Author: Giorgio Tettamanti, Karolinska Institutet, Nobels väg 13, Stockholm 171 77, Sweden. Phone: 468-524-8811; Fax: 468-313-961; E-mail: giorgio.tettamanti@ki.se

doi: 10.1158/1055-9965.EPI-16-0451

Norway, Sweden, and Switzerland with the purpose to examine the association between mobile phone use and CABTs (17, 18).

All children and adolescents in the four countries, ages 7 to 19 years, diagnosed between January 1, 2004 and August 31, 2008, with a primary intracranial brain tumors defined according to the International Classification of Childhood Cancer, third edition (ICCC-3; ref. 19), group III, restricted to ICD-O-3 location C71, were eligible to be enrolled as cases. Information about cases was obtained both from population-based cancer registries and reports from pediatric oncology clinics and neurosurgery hospital departments. Participants with neurofibromatosis or tuberous sclerosis were excluded from the study. Two controls per case were randomly selected from the national population registers continuously throughout the study period and were matched to the case by age, sex, and geographical region. The reference date for the controls was defined as the date of diagnosis of their matched case. The participation rate among cases was 83%, while among controls was 71%. Participants did not receive any participation incentive.

The exposures of interest in this study were prenatal (i.e., during mother's pregnancy) and postnatal exposure to medical diagnostic radiation, such as X-ray (dental X-rays excluded), CT and PET scans, ultrasound, and MRI. Other exposures analyzed in this study were head injury (defined as a blow to the head that caused a concussion, a serious wound or a headache), febrile seizure, jaundice, fever in the first 12 weeks of life, and general anesthesia. Information regarding these exposures was collected through face-to-face interview, with the child and at least one parent, using the CEFALO questionnaire.

Regarding exposure to medical diagnostic radiation, initial information about the number of medical examinations (X-ray and/or scans) was collected, then for each examination further information regarding date of the examination, type of examination (X-ray, CT scan, PET scan, ultrasound, and MRI), and location of the examination (head or neck, thorax, abdomen, legs or arms, whole body, including head or neck, whole body excluding head or neck) was obtained. Children were defined as exposed to medical diagnostic radiation to the head and neck region if the examination was performed to these areas or if the whole body, including the head, was exposed. Because only one participant had a head PET scan, the effect of head PET scans on CABTs susceptibility was not evaluated.

Because CT scans and MRI are commonly used to diagnose brain tumors, a latency period of two years was used to exclude medical examinations that were probably performed because a tumor was suspected. This latency period was applied to both cases and controls. We also used a latency period of 2 years for febrile seizures, head injury and general anesthesia to prevent bias from reverse causality. Sensitivity analyses using different latency periods (1 and 5 years) were performed.

Odds ratios (OR) and 95% confidence intervals (CI) were used to estimate the association between the exposures of interest and CABTs. Because this was a matched case–control study and children were matched by age, sex, and region, conditional logistic regression was used to take into account the matching factors. Analyses were adjusted for parental age and highest attained educational level of the two parents (low, elementary school; intermediate, high school or apprenticeship; high, university or postgraduate university). Information regarding these potential confounders was obtained from the questionnaire and referred to parental age and education at the time of the interview. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc.). The study was approved by the national data protection boards and ethical committees in all participating countries.

Results

Characteristics of the 352 children and adolescent with a brain tumor and the 646 controls participating in the study are presented in Table 1. Among cases, there were more boys than girls (54% vs. 46%). Almost 40% of the cases were from Sweden, whereas only 12% were from Norway. Very few children, only 20 cases and 26 controls, had parents who both had a low education (i.e., elementary education), whereas the majority had at least one parent with a high educational level (i.e., university or postgraduate university).

Results regarding the effects of prenatal exposure to medical diagnostic radiation on CABTs are shown in Table 2. A lower risk estimate of CABTs, although not statistically significant, was found among children whose mothers did not have an ultrasound examination during pregnancy (OR, 0.64; 95% CI, 0.32–1.30). However, when the number of ultrasounds during pregnancy was considered, no dose–response relationship was observed. An 80% higher risk estimate of CABTs was found among children whose mothers had the first ultrasound after 25 weeks of gestation (OR, 1.79; 95% CI, 0.74–4.31), but again the association was not statistically significant. Maternal exposure to X-rays or other medical diagnostic examinations during pregnancy was not associated with CABTs (OR, 0.96; 95% CI, 0.54–1.68).

Table 1. Descriptive characteristics of the children enrolled in the CEFALO study

	CABT cases *n* (%)	Controls *n* (%)
Age, y		
7–12	170 (48.3)	318 (49.2)
13–19	182 (51.7)	328 (50.8)
Sex		
Male	190 (54.0)	353 (54.6)
Female	162 (46.0)	293 (45.4)
Country		
Denmark	85 (24.1)	170 (26.3)
Sweden	138 (39.2)	228 (35.3)
Norway	44 (12.5)	78 (12.1)
Switzerland	85 (24.1)	170 (26.3
Parental educational level		
Low[a]	20 (5.7)	26 (4.0)
Medium[b]	156 (44.3)	269 (41.6)
High[c]	176 (50.0)	346 (53.6)
Missing	—	5 (0.8)
Maternal age (years)		
<36	42 (11.9)	82 (12.7)
36–45	227 (64.5)	392 (60.7)
46+	77 (21.9)	153 (23.7)
Missing	6 (1.7)	19 (2.9)
Paternal age (years)		
<36	18 (5.1)	37 (5.7)
36–45	198 (56.2)	320 (49.5)
46+	130 (36.9)	261 (40.4)
Missing	6 (1.7)	28 (4.3)

NOTE: CABT denotes childhood and adolescent brain tumor. For parental educational level, the highest level of the two parents was chosen.

[a]Elementary school.

[b]High school or apprenticeship.

[c]University or postgraduate university.

Published OnlineFirst September 13, 2016; DOI: 10.1158/1055-9965.EPI-16-0451

Table 2. Prenatal exposure to medical diagnostic radiation and risk estimates of childhood and adolescent brain tumors

	Cases	Controls	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Ultrasound examination during mother's pregnancy				
Yes	335	592	1 (ref)	1 (ref)
No	14	34	0.71 (0.36–1.38)	0.64 (0.32–1.30)
Missing	3	20		
No. of times				
No ultrasound	14	34	0.76 (0.38–1.50)	0.71 (0.34–1.45)
1	114	212	1 (ref)	1 (ref)
2	96	139	1.36 (0.95–1.94)	1.46 (1.01–2.11)
3	44	94	0.95 (0.60–1.48)	0.96 (0.61–1.53)
4 or more	77	144	1.05 (0.70–1.58)	1.11 (0.73–1.68)
Missing	4	3		
Gestational week of the first ultrasound				
No ultrasound	14	34	0.91 (0.45–1.85)	0.76 (0.36–1.64)
1–12	109	206	1.13 (0.78–1.64)	1.18 (0.81–1.73)
13–24	151	288	1 (ref)	1 (ref)
25+	13	19	1.47 (0.63–3.40)	1.79 (0.74–4.31)
Missing	62	79		
Maternal X-ray or other scan during pregnancy				
Yes	31	57	0.91 (0.54–1.55)	0.96 (0.54–1.68)
No	306	556	1 (ref)	1 (ref)
Missing	15	33		
No. of times				
No X-ray or scan	306	556	1 (ref)	1 (ref)
1	30	51	1.00 (0.58–1.72)	1.00 (0.56–1.79)
2 or more	1	6	0.33 (0.04–2.77)	0.43 (0.05–3.98)
Missing	—	—		
X-ray or scan to the abdomen				
Yes	5	7	0.88 (0.25–3.04)	0.72 (0.17–2.97)
No X-ray or scan to the abdomen	332	606	1 (ref)	1 (ref)

[a]Conditional logistic regression model.
[b]Conditional logistic regression model adjusted for highest parental education, maternal age, and paternal age.

Table 3 shows the association between postnatal exposure to medical diagnostic radiation and CABTs. Children who had any type of X-ray or scan examination (CT scan, PET scan, MRI, or ultrasound) at least 2 years before the reference date, had a borderline statistically significant lower risk estimate of CABTs (OR, 0.76; 95% CI, 0.58–1.01). However, no association was

Table 3. Postnatal exposure to medical diagnostic radiation and risk estimates of childhood and adolescent brain tumors

	1-year latency period[a]			2-years latency period[b]			5-years latency period[a]		
	Cases	Controls	Adjusted OR[c] (95% CI)	Cases	Controls	Adjusted OR[c] (95% CI)	Cases	Controls	Adjusted OR[c] (95% CI)
X-ray or scan									
Yes	182	362	0.86 (0.65–1.14)	159	333	0.76 (0.58–1.01)	115	246	0.81 (0.60–1.08)
No	168	282	1 (ref)	191	311	1 (ref)	235	398	1 (ref)
Missing	2	2		2	2				
No. of X-ray or scan									
No X-ray or scan	168	282	1 (ref)	191	311	1 (ref)	235	398	1 (ref)
1	87	174	0.84 (0.60–1.18)	81	169	0.75 (0.54–1.06)	66	136	0.82 (0.58–1.15)
2	38	77	0.85 (0.54–1.34)	34	70	0.78 (0.48–1.25)	24	58	0.72 (0.43–1.19)
3 or more	57	111	0.90 (0.60–1.35)	44	94	0.78 (0.51–1.21)	25	52	0.81 (0.49–1.36)
X-ray or scan (head or body+head)									
Yes	47	80	1.19 (0.78–1.80)	41	76	1.09 (0.71–1.67)	28	55	0.97 (0.60–1.57)
No	303	564	1 (ref)	309	568	1 (ref)	322	589	1 (ref)
X-ray (head or body+head)									
Yes	21	47	0.97 (0.53–1.80)	18	44	0.85 (0.45–1.60)	13	34	0.82 (0.40–1.69)
No X-ray or scan to the head	304	570	1 (ref)	310	574	1 (ref)	323	592	1 (ref)
CT (head or body+head)									
Yes	16	14	1.95 (0.90–4.22)	14	13	1.86 (0.82–4.22)	10	10	1.68 (0.69–4.09)
No X-ray or scan to the head	304	571	1 (ref)	310	575	1 (ref)	323	593	1 (ref)
MRI (head or body+head)									
Yes	7	10	1.75 (0.60–5.11)	5	10	1.25 (0.38–4.05)	2	5	0.93 (0.17–5.21)
No X-ray or scan to the head	304	570	1 (ref)	310	574	1 (ref)	323	592	1 (ref)
Ultrasound (head or body+head)									
Yes	5	10	0.80 (0.23–2.79)	4	10	0.79 (0.22–2.76)	2	9	0.47 (0.09–2.32)
No X-ray or scan to the head	304	570	1 (ref)	310	574	1 (ref)	323	592	1 (ref)

NOTE: Medical diagnostic examinations that were performed during the latency period were not taken into account.
[a]Sensitivity analysis.
[b]Main analyses.
[c]Conditional logistic regression models adjusted for highest parental education, maternal age, and paternal age.

Published OnlineFirst September 13, 2016; DOI: 10.1158/1055-9965.EPI-16-0451

found between X-ray or any type of scan examination of the head and neck region and CABTs (OR, 1.09; 95% CI, 0.71–1.67). Instead, in crude analysis, children who had a CT scan of the head and neck region had a two times higher risk estimate of CABTs (OR, 2.13; 95% CI, 0.96–4.77). However, after adjusting for parental age and educational level the positive association was somewhat reduced (OR, 1.86; 95% CI, 0.82–4.22). The association was less pronounced when a 5-year latency period was considered (OR, 1.68; 95% CI, 0.69–4.09) and slightly more pronounced for a 1-year latency (OR, 1.95; 95% CI, 0.90–4.22). MRI and ultrasound examinations of the head and neck region were not associated with CABT susceptibility, though a non-statistically significant increased risk estimate of CABTs was found for MRI when a 1-year latency period was considered (OR, 1.75; 95% CI, 0.60–5.11). However, there was no association when a 5-year latency period was used (OR, 0.93; 95% CI, 0.17–5.21).

As illustrated in Table 4, no positive association was found between head injury two years before the reference date and CABTs (OR, 1.18; 95% CI, 0.90–1.54). Moreover, number of head injuries and factors indicating a severe head injury (i.e., loss of consciousness, vomit, and headache) were not associated with CABTs. When a longer latency period was used, weaker associations were observed.

Jaundice, fever in the first 12 weeks, and general anesthesia were not associated with CABT (data not shown). No overall association was found between febrile seizure and CABTs (OR, 1.14; 95% CI, 0.67–1.95). For a first febrile seizure at 2 years of age or later, the OR was nonsignificantly raised (OR, 1.99; 95% CI, 0.76–5.21), whereas the corresponding OR for a first febrile seizure in the first 2 years of life was slightly reduced (OR, 0.91; 95% CI, 0.49–1.73; not shown in table).

Discussion

Many of the prenatal and postnatal factors that have been analyzed in the study were not associated with childhood and adolescent brain tumors. When considering all types of medical diagnostic examinations that were performed to the head and neck region, no association was found; however, children who had a CT scan to the head and neck region had a higher risk estimate of CABTs, although not statistically significant. Moreover, the association between CT scan and CABTs became weaker when a longer latency period was used.

Contrary to the overall established carcinogenicity of ionizing radiation (20), a modest lower risk estimate of CABTs was found among children who had an X-ray or scan examination 2 years before the reference date. A similar finding was also observed in the German part of the Interphone study, in which a negative association between exposure to medical diagnostic radiation and risk of adult glioma was found (21). However, both in the Interphone study and in our study, recall bias may have caused this negative association: In fact, as it was also noted in the interphone study, brain tumor cases may have had problems in answering to questions regarding medical diagnostic exposures. Moreover, we also found no association when we considered only X-ray or scan examinations that were performed to the head and neck region, suggesting that the protective effect of X-ray or scan examinations on CABTs was probably a chance finding. Historically, a consistent positive association between prenatal

Table 4. Head injuries and risk estimates of childhood and adolescent brain tumors

	1-year latency period[a]			2-years latency period[b]			5-years latency period[a]		
	Cases	Controls	Adjusted OR[c] (95% CI)	Cases	Controls	Adjusted OR[c] (95% CI)	Cases	Controls	Adjusted OR[c] (95% CI)
Head injury									
Yes	165	277	1.18 (0.90–1.54)	157	265	1.17 (0.89–1.54)	116	205	1.06 (0.79–1.43)
No	186	366	1 (ref)	194	378	1 (ref)	235	438	1 (ref)
Missing	1	3		1	3		1	3	
No. of times									
No head injury	186	366	1 (ref)	194	378	1 (ref)	235	438	1 (ref)
1	101	170	1.17 (0.85–1.60)	106	172	1.20 (0.88–1.64)	88	147	1.12 (0.81–1.55)
2	47	71	1.35 (0.88–2.07)	36	61	1.18 (0.74–1.88)	20	38	1.01 (0.55–1.86)
3 or more	17	36	0.97 (0.52–1.80)	15	32	0.98 (0.51–1.90)	8	20	0.76 (0.33–1.78)
Loss of consciousness[d]									
Yes	30	42	1.36 (0.82–2.27)	25	37	1.28 (0.73–2.21)	17	26	1.17 (0.61–2.23)
No	126	229	1.09 (0.81–1.48)	124	223	1.10 (0.82–1.48)	94	172	1.02 (0.74–1.40)
No head injury	186	366	1 (ref)	194	378	1 (ref)	235	438	1 (ref)
Missing	10	9		10	9		10	9	
Vomiting[d]									
Yes	44	78	1.16 (0.76–1.78)	38	71	1.10 (0.70–1.72)	22	54	0.82 (0.48–1.41)
No	118	194	1.20 (0.90–1.62)	116	90	1.20 (0.89–1.61)	91	148	1.14 (0.83–1.57)
No head injury	186	366	1 (ref)	194	378	1 (ref)	235	438	1 (ref)
Missing	4	8		4	8		4	8	
Headache[d]									
Yes	77	127	1.22 (0.85–1.75)	66	119	1.14 (0.78–1.66)	39	79	0.95 (0.61–1.50)
No	68	116	1.21 (0.83–1.76)	67	113	1.22 (0.84–1.77)	54	93	1.12 (0.75–1.67)
No head injury	186	366	1 (ref)	194	378	1 (ref)	235	438	1 (ref)
Missing	21	37		21	37		21	37	

NOTE: Head injuries that occurred during the latency period were not taken into account.
[a]Sensitivity analysis.
[b]Main analyses.
[c]Conditional logistic regression models adjusted for highest parental education, maternal age, and paternal age.
[d]Symptoms caused by the head injury.

Published OnlineFirst September 13, 2016; DOI: 10.1158/1055-9965.EPI-16-0451

abdominal X-rays and risk of childhood cancer has been reported (22–25). However, in our study, as well as in other recent investigations (6, 7), no association was found. The most likely explanation for this discrepancy is that radiation doses from X-ray examinations have substantially decreased over time. Moreover, abdominal X-ray examinations have been replaced by ultrasounds as a tool in obstetric care: In our study, only 12 mothers had an abdominal X-ray examination during pregnancy.

We found an indication of a positive association between CABTs and head CT scans performed at least 2 years before the reference date. When a latency period of 5 years was used, the effect of CT scans on CABTs risk decreased, but an almost seventy percent higher risk estimate was still observed. Even though our findings were not statistically significant, they are in agreement with previously reported results from three recent cohort studies (8–10). A retrospective cohort study performed in Great Britain found an almost three times higher risk of brain tumors among children and young adults who received a cumulative dose of 50–74 mGy (a dose equivalent to 2–3 head CT scans), compared with those who received a dose of less than 5 mGy (9). Moreover, a Taiwanese and an Australian cohort study also investigated the effect of pediatric CT examination on the risk of brain tumors among children and young adults and found that exposure to CT scan was associated with an almost three times higher risk of brain tumors, even though in the Taiwanese study the increased risk was observed only for benign tumors (8, 10). The fact that we found an indication of a positive association between head CT scans and CABTs, but no association between head X-rays and CABTs is not surprising. In fact, radiation doses from X-rays examinations are considerably lower than those from CT scans (26). However, a study has shown that radiation doses from CT scans have reduced over time in Great Britain (27): Although, to the best of our knowledge, no study has evaluated the trend in CT scan doses in the countries that participated in the CEFALO study, a similar decreasing trend in radiation doses from CT scans has likely occurred also in these countries.

With regard to the potential effect of head injury on the risk of brain tumors results from previous studies are conflicting (12–16). Case–control studies have shown that head injuries were associated with an increased risk of glioma in adults (12), meningioma in men (13), or brain tumors in children (14). However, only a small but not statistically significant increased risk of brain tumors was found in a Danish cohort study (15), and no association was reported by a Swedish cohort study (16): Both cohort studies were nationwide and used administrative data, that is, register data, to identify individuals who had a head injury or a brain tumor. In line with findings from these cohort studies, head injury and indicators of severe head injury (such as loss of consciousness, vomiting, and headache) were not associated with CABT susceptibility.

We also found an almost two times higher risk estimate of CABTs, even though not statistically significant, among children who had the first febrile seizure at 2 years of age or later. However, this finding was based on small numbers (10 exposed cases and 11 exposed controls), and a nonsignificantly reduced risk estimate was found for first febrile seizure in the first 2 years of life. To the best of our knowledge there is no biological explanation for such an age-specific association. Therefore, chance is a likely explanation for this finding.

One of the strengths of the present study was that we were able to obtain detailed information about the exposures of interest. All the information captured in the CEFALO questionnaire was reported by both the children and by at least one of their parents. Moreover, interviews were conducted by trained interviewers to ensure a uniform data collection.

All medical diagnostic examinations (X-rays, CT scans, MRIs, and ultrasounds) that were performed 2 years before the date of diagnosis (or reference date for the controls) were excluded to prevent reverse causality bias. In fact, medical diagnostic examinations could have been performed in response to early unspecific symptoms induced by a micro-tumor that was not yet seen on the imaging: this is less likely for imaging performed many years before the diagnosis. The fact that no association was found between CABTs and MRI to the head, an examination that is often performed if a brain tumor is suspected, suggests that medical examinations that were part of the cancer diagnostic procedure most likely did not influence the exposure assessment.

Previous studies used different latency periods: One year (10), 2 years (28), and 5 years (9). For this reason, we performed sensitivity analyses using different latency periods. In these analyses, we observed a positive association between MRI and CABTs when a 1-year latency period was used, whereas there was no association when MRI performed 2 or 5 years before the reference date were considered. This is a clear indication that the association observed using a 1-year latency period was because children were exposed to MRI because a brain tumor was suspected. Therefore, using a short latency period may result in spurious associations. However, this reverse causality bias was not observed for CT scan, as results found using a 1-year latency period were similar to the ones observed in the main analysis. Moreover, using a 5-year latency period might be too conservative, as some of the CABT cases caused by the exposure to head CT scans might have been excluded, especially those who have been diagnosed at a very young age. This could explain the lower risk estimate observed in this sensitivity analysis.

A limitation of our study is that some exposures were very uncommon. For example, only 14 cases of CABTs had at least one head CT scans 2 years before the reference date. For this reason, some of the positive associations reported could simply be chance findings, whereas some of the null findings could be caused by the fact that we did not have enough statistical power to detect modest increased risks. Moreover, due to the low number of exposed cases it was not possible to perform any CABT subtype or sex-stratified analyses. Another limitation is that information about the exposures analyzed in this study was self-reported by the child and their parents. Therefore, it is possible that recall bias could have influenced the associations reported in the study and both inflated or attenuated the results, for example, if parents of CABT cases would have over-reported certain exposures or could have mistakenly reported the date of certain examinations involving medical diagnostic radiation. Moreover, no information regarding radiation doses was available.

In conclusion, in this multicenter case–control study we mostly found that specific prenatal or postnatal medical conditions, including exposure to medical diagnostic radiation (both prenatal and postnatal), were not associated with CABT susceptibility. A nonstatistically significant increased risk estimate of CABTs was found for exposure to head CT scans. This finding is based on small numbers and should be interpreted with caution; however, it is in line with results reported by three recent cohort studies on the effect of pediatric CT scans on brain tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: X. Shu, J. Schüz, M. Röösli, T. Tynes, L. Klaeboe, M. Feychting

Development of methodology: X. Shu, J. Schüz, M. Röösli, T. Tynes, L. Klaeboe, C.E. Kuehni, L.S. Schmidt, M. Feychting

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Schüz, M. Röösli, T. Tynes, M. Grotzer, C. Johansen, L. Klaeboe, C.E. Kuehni, B. Lannering, L.S. Schmidt, M. Feychting

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Tettamanti, X. Shu, J. Schüz, M. Röösli, T. Tynes, C.E. Kuehni, L.S. Schmidt, M. Feychting

Writing, review, and/or revision of the manuscript: G. Tettamanti, X. Shu, M. Adel Fahmideh, J. Schüz, M. Röösli, T. Tynes, M. Grotzer, C. Johansen, L. Klaeboe, C.E. Kuehni, B. Lannering, L.S. Schmidt, D. Vienneau, M. Feychting

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X. Shu, M. Röösli, T. Tynes, L. Klaeboe, L.S. Schmidt, M. Feychting

Study supervision: X. Shu, J. Schüz, M. Röösli, T. Tynes, L. Klaeboe, L.S. Schmidt, M. Feychting

Acknowledgments

We would like to thank Michaela Prochazka, Tina Veje Andersen, Tone Eggen, Denis Infanger, Daniela Jenni, and Nicole Jakubowitz for coordinating the fieldwork of the CEFALO studies in their respective countries.

Grant Support

The Swedish part of the CEFALO study was supported by grants from the Swedish Council for Working Life and Social Research (grant numbers 2004-0504 and 2007-0224), the Swedish Research Council (K2008-70X-15366-04-3), the Swedish Cancer Society (09 0666), the Swedish Childhood Cancer Society (grant numbers PROJ06/050 and PROJ09/086), and the Swedish Radiation Protection Authority (SSI P 1572; to M. Feychting). The Danish CEFALO study was supported by the Danish Strategic Research Council (grant numbers 2103-05-0006, 2064-04-0010; to J.H. Olsen). The Swiss part of the CEFALO study was supported by the Swiss Federal Office of Public Health (grant number 05.001626), the Swiss Research Foundation on Mobile Communication (grant number A2006.18), and the Swiss National Science Foundation (grant number PDFMP3_122873; to M. Röösli). The Norwegian CEFALO study was supported by the Research Council of Norway (grant number 175163/V40; to T. Tynes).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 31, 2016; revised August 23, 2016; accepted September 1, 2016; published OnlineFirst September 13, 2016.

References

1. Johnson KJ, Cullen J, Barnholtz-Sloan JS, Ostrom QT, Langer CE, Turner MC, et al. Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomarkers Prev 2014;23:2716–36.
2. Schmidt LS, Schmiegelow K, Lahteenmaki P, Trager C, Stokland T, Grell K, et al. Incidence of childhood central nervous system tumors in the Nordic countries. Pediatr Blood Cancer 2011;56:65–9.
3. Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood–a review. Toxicol Appl Pharmacol 2004;199:118–31.
4. Pollack IF, Jakacki RI. Childhood brain tumors: epidemiology, current management and future directions. Nat Rev Neurol 2011;7:495–506.
5. Gurney JG, Smith MA, Olshan AF, Hecht SS, Kasum CM. Clues to the etiology of childhood brain cancer: N-nitroso compounds, polyomaviruses, and other factors of interest. Cancer Invest 2001;19:630–40.
6. Linet MS, Kim KP, Rajaraman P. Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations. Pediatr Radiol 2009;39 Suppl 1:S4–26.
7. Schulze-Rath R, Hammer GP, Blettner M. Are pre- or postnatal diagnostic X-rays a risk factor for childhood cancer? A systematic review. Radiat Environ Biophys 2008;47:301–12.
8. Huang WY, Muo CH, Lin CY, Jen YM, Yang MH, Lin JC, et al. Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. Br J Cancer 2014;110:2354–60.
9. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 2012;380:499–505.
10. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 2013;346:f2360.
11. Davis F, Il'yasova D, Rankin K, McCarthy B, Bigner DD. Medical diagnostic radiation exposures and risk of gliomas. Radiat Res 2011;175:790–6.
12. Hu J, Johnson KC, Mao Y, Guo L, Zhao X, Jia X, et al. Risk factors for glioma in adults: a case-control study in northeast China. Cancer Detect Prev 1998;22:100–8.
13. Preston-Martin S, Pogoda JM, Schlehofer B, Blettner M, Howe GR, Ryan P, et al. An international case-control study of adult glioma and meningioma: the role of head trauma. Int J Epidemiol 1998;27:579–86.
14. Gurney JG, Preston-Martin S, McDaniel AM, Mueller BA, Holly EA. Head injury as a risk factor for brain tumors in children: results from a multicenter case-control study. Epidemiology 1996;7:485–9.
15. Inskip PD, Mellemkjaer L, Gridley G, Olsen JH. Incidence of intracranial tumors following hospitalization for head injuries (Denmark). Cancer Causes Control 1998;9:109–16.
16. Nygren C, Adami J, Ye W, Bellocco R, af Geijerstam JL, Borg J, et al. Primary brain tumors following traumatic brain injury–a population-based cohort study in Sweden. Cancer Causes Control 2001;12:733–7.
17. Aydin D, Feychting M, Schuz J, Tynes T, Andersen TV, Schmidt LS, et al. Mobile phone use and brain tumors in children and adolescents: a multicenter case-control study. J Natl Cancer Inst 2011;103:1264–76.
18. Christensen JS, Mortensen LH, Roosli M, Feychting M, Tynes T, Andersen TV, et al. Brain tumors in children and adolescents and exposure to animals and farm life: a multicenter case-control study (CEFALO). Cancer Causes Control 2012;23:1463–73.
19. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer 2005;103:1457–67.
20. Friis S, Kesminiene A, Espina C, Auvinen A, Straif K, Schuz J. European Code against Cancer 4th Edition: medical exposures, including hormone therapy, and cancer. Cancer Epidemiol 2015;39 Suppl 1:S107–19.
21. Blettner M, Schlehofer B, Samkange-Zeeb F, Berg G, Schlaefer K, Schuz J. Medical exposure to ionising radiation and the risk of brain tumours: interphone study group, Germany. Eur J Cancer 2007;43:1990–8.
22. Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. Br Med J 1958;1:1495–508.
23. Macmahon B. Prenatal X-ray exposure and childhood cancer. J Natl Cancer Inst 1962;28:1173–91.
24. Harvey EB, Boice JDJr, Honeyman M, Flannery JT. Prenatal X-ray exposure and childhood cancer in twins. N Engl J Med 1985;312:541–5.
25. Rodvall Y, Pershagen G, Hrubec Z, Ahlbom A, Pedersen NL, Boice JD. Prenatal X-ray exposure and childhood cancer in Swedish twins. Int J Cancer 1990;46:362–5.
26. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med 2007;357:2277–84.
27. Lee C, Pearce MS, Salotti JA, Harbron RW, Little MP, McHugh K, et al. Reduction in radiation doses from paediatric CT scans in Great Britain. Br J Radiol 2016;89:20150305.
28. Journy N, Rehel JL, Ducou Le Pointe H, Lee C, Brisse H, Chateil JF, et al. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br J Cancer 2015;112:185–93.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Prenatal and Postnatal Medical Conditions and the Risk of Brain Tumors in Children and Adolescents: An International Multicenter Case–Control Study

Giorgio Tettamanti, Xiaochen Shu, Maral Adel Fahmideh, et al.

Cancer Epidemiol Biomarkers Prev 2017;26:110-115. Published OnlineFirst September 13, 2016.