Null Results in Brief

Polio Vaccination and Risk of Brain Tumors in Adults: No Apparent Association

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Introduction

There is a concern that massive vaccination against polio between 1954 and 1962 in the United States might have resulted in the unintentional exposure of millions of people to SV40 through contaminated vaccines (1). The long-term health effects of such exposure are still being debated (1–3). SV40 DNA sequences reportedly have been identified in several rare types of human tumors (1, 3), including those of the brain (2), and SV40 has been shown to transform a variety of cell types *in vitro* and *in vivo* (1, 3). However, epidemiological evidence of oncogenicity in humans is inconclusive. Previous epidemiological studies largely failed to demonstrate an association between vaccine-related exposure to SV40 and subsequent cancer development (4, 5), although several studies could not rule out the possibility of an increase in certain subtypes of brain tumors (6, 7). Most of these studies had a cohort design that was not optimal for the study of rare cancers because of the limited statistical power of even very large cohorts. In addition, very few of the earlier studies had long enough follow-up to allow for a long cancer induction period. Here, we test the hypothesis that polio vaccination during the early years of its use increased the risk of brain tumors, particularly glioma, using data from a large case-control study of adult brain tumors conducted in the United States between 1994 and 1998, more than 30 years after the period in which contaminated vaccine may have been given.

Materials and Methods

Details of this study were described previously (8). Briefly, cases were adult patients (mean age at diagnosis = 52 years) with incident, histologically confirmed glioma (n = 489), meningioma (n = 197), or acoustic neuroma (n = 96). They were diagnosed between June 1994 and August 1998 at three United States hospitals [Brigham and Women's Hospital (Boston, MA), St. Joseph's Hospital and Medical Center (Phoenix, AZ), and Western Pennsylvania Hospital (Pittsburgh, PA)]. Controls were selected from patients admitted to the same hospitals for a variety of nonmalignant conditions and frequency-matched to the total case series (1:1 ratio) by age (10-year intervals), sex, race/ethnicity, and distance of residence from the hospital (the latter to control for differences in referral patterns). All study participants were queried about history of polio vaccination, including year and vaccination route. We also include results for self-reported vaccination by year of birth. Because most people were vaccinated for polio as infants or young children, year of birth serves as a surrogate for possible exposure to contaminated *versus* uncontaminated vaccine (4). Information on sociodemographic characteristics and other possible risk factors also was collected. Unconditional logistic regression models were fitted to estimate ORs[2] and compute 95% CIs and likelihood-ratio tests. This study had 95% power to detect an OR of 2.0 for glioma associated with polio vaccination during the 1954–1962 period (two-sided test of significance, α = 0.05).

Results

Table 1 presents ORs for the risk of brain tumors associated with self-reported history of polio vaccination. There was little evidence of an association between any type of tumor and history of polio vaccination, particularly for glioma and meningioma. The ORs for acoustic neuroma, adjusted for education, were nonsignificantly increased for early vaccination and birth year prior to 1940. For glioma, the ORs for polio vaccination varied little by sex, age at tumor diagnosis, histological subtype (astrocytic *versus* other), or histological grade (high *versus* low; data not shown). When analyzing the joint effect of vaccine administration route and calendar period of vaccination, there was no meaningful increase in risk of glioma for the 1954–1962 period with either injected (OR, 0.8; 95% CI, 0.5–1.3) or oral vaccine (OR, 1.4; 95% CI, 0.8–2.3). Exclusion of proxy respondents or cases with medical record notation of impaired mental status due to their brain tumor had little effect on the observed ORs. Results also were insensitive to whether any of the subgroups of controls with common discharge diagnoses (injuries or diseases of the circulatory, musculoskeletal, or digestive systems) were excluded.

Discussion

In this large hospital-based case-control study, we found no significant associations between history of polio vaccination and risk of adult glioma, meningioma, or acoustic neuroma. Several issues that could have influenced our findings should be considered. History of polio vaccination was ascertained retrospectively and was self-reported. Nondifferential errors in reporting of early childhood events could have obscured a true association, particularly one of modest strength. However, prevalence of self-reported polio vaccination among controls

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[2] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Association between self-reported history of polio vaccination and risk of glioma, meningioma, and acoustic neuroma among patients from hospitals in Boston, Phoenix, and Pittsburgh, United States, 1994–1998

Condition	Controls[a] (N = 799)	Glioma			Meningioma			Acoustic neuroma		
		Cases[a,b] (N = 489)	OR[c]	95% CI[d]	Cases[a] (N = 197)	OR[c]	95% CI	Cases[a] (N = 96)	OR[e]	95% CI
Polio vaccination										
No[f]	102	65	1.00[f]		33	1.00[f]		8	1.00[f]	
Yes	614	361	1.08	0.75–1.56	153	1.10	0.68–1.82	79	1.46	0.63–3.38
Route										
Oral	201	144	1.33	0.89–2.00	59	1.22	0.70–2.12	32	1.55	0.66–4.00
Injection	276	121	0.77	0.51–1.16	57	0.90	0.52–1.57	30	1.37	0.56–3.58
Both	56	43	1.38	0.81–2.36	14	1.03	0.47–2.21	4	0.62	0.15–2.24
Year of vaccination										
<1954	154	94	1.05	0.68–1.63	49	1.10	0.62–1.96	28	1.95	0.80–5.15
1954–1962	223	133	1.08	0.71–1.66	53	0.95	0.53–1.70	33	1.30	0.54–3.41
1963+	164	95	1.26	0.78–2.05	32	1.58	0.79–3.18	7	0.69	0.20–2.33
Year of birth										
<1940	184	132	1.15	0.77–1.72	62	1.19	0.71–2.02	31	1.94	0.84–4.94
1941–1962	321	172	0.93	0.57–1.53	82	0.94	0.49–1.84	42	0.75	0.28–2.16
1963+	109	57	1.02	0.55–1.88	9	0.76	0.26–2.16	6	1.02	0.24–4.36

[a] Numbers may not add up to column totals because of missing data.
[b] The high-grade glioma cases (N = 354) include 241 patients diagnosed with glioblastoma (236) or gliosarcoma (5), 70 patients diagnosed with anaplastic astrocytoma, 25 patients diagnosed with anaplastic oligodendroglioma or mixed glioma, 9 patients diagnosed with embryonal tumors, 3 patients diagnosed with anaplastic ependymomas, and 6 others. The low-grade gliomas (N = 135) include 46 oligodendrogliomas, 34 astrocytomas, 17 gangliogliomas, 14 mixed gliomas, 7 ependymomas, 4 neurocytomas, and 13 others.
[c] ORs were adjusted for matching factors.
[d] 95% CIs were computed using profile likelihood function.
[e] ORs were adjusted for matching factors and education as indicated in Ref. 8.
[f] Referent group.

less than 20 years of age in 1961 was 85% (data not shown), which is similar to estimated values reported in the literature for the same time period (1). It also is possible that other types of vaccination were confused with polio vaccination, although this seems less likely for p.o.-administered polio vaccine, as it was the only oral vaccine administered to the general public. In addition, when we used the birth year categories adopted from Ref. 4 as a surrogate indicator for the likelihood that persons who reported having been vaccinated received contaminated vaccine, we did not find any deviation in risk estimates from unity. Our results could not be generalized to ependymomas and choroid plexus tumors, which are the types of brain tumor known to be induced by SV40 in laboratory animals. These tumors are very rare in humans and were uncommon in our case series (Table 1). Lastly, the major shortcoming of all epidemiological studies of SV40 to date, including ours, is the lack of data on individual exposure to SV40 among persons reporting a history of vaccination. It is known that not all of the vaccine lots were contaminated and that the lots that were contaminated varied substantially in the amount of the live SV40 (1). We cannot rule out the possibility of an increased risk among a small proportion of highly exposed individuals.

Strengths of the current study include a large series of cases with malignant or benign brain tumors, high response rates (92% among cases and 86% among controls), a relatively small percentage of proxy interviews (at most, 24% among glioma cases), allowance for possible mental impairment in some glioma patients, detailed information on many potential confounding factors, and timing of the study relative to the period when contaminated vaccine was used, which enabled us to evaluate possible long-term effects of exposure.

In conclusion, our results are consistent with the majority of previous epidemiological studies, mainly of large cohorts, that did not show convincing evidence of increased risk of brain tumors after vaccination for polio, the only major known source of human exposure to SV40 (4, 5). Although both injected (Salk) and unlicensed oral (Sabin) polio vaccines were contaminated with SV40, animal experiments suggest a greater risk associated with the injected vaccine, especially when given in infancy (4). In our study, risks for both injected and oral vaccine given during the 1954–1962 period, when they were most likely contaminated, and for birth years 1941–1962, when the majority were exposed to the potentially contaminated vaccine during infancy or early childhood, were around unity. However, whether additional sources of SV40 exposure might exist and contribute to risk remains unknown, as does the possible existence of modifying factors that influence individual susceptibility (1). To clarify the etiological significance of SV40 exposure in human tumorigenesis, future epidemiological studies should incorporate new genetic and serological markers of previous SV40 exposure.

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