Contamination of Poliovirus Vaccines With Simian Virus 40 (1955-1963) and Subsequent Cancer Rates

Howard D. Strickler, MD, MPH; Philip S. Rosenberg, PhD; Susan S. Devesa, PhD; Joan Hertel; Joseph F. Fraumeni, Jr, MD; James J. Goedert, MD

Context.—Poliovirus vaccine contaminated with live simian virus 40 (SV40), a macaque polyomavirus that is tumorigenic in rodents, was used extensively in the United States between 1955 and 1963. Simian virus 40 DNA has recently been detected in several rare human tumors, including ependymomas, osteosarcomas, and mesotheliomas.

Objective.—To determine the risk of ependymoma, osteosarcoma, and mesothelioma among Americans who as children received SV40-contaminated poliovirus vaccine.


Setting.—United States.

Participants.—Birth cohorts that were likely to have received SV40-contaminated poliovirus as infants, born 1956 through 1962 (60,811,730 person-years of observation); as children, born 1947 through 1952 (46,430,953 person-years); or that were unexposed, born 1964 through 1969 (44,959,979 person-years).

Main Outcome Measures.—Relative risk (RR) of each cancer among exposed compared with unexposed birth cohorts.

Results.—Age-specific cancer rates were generally low and were not significantly increased in birth cohorts exposed to SV40-contaminated vaccine. Specifically, compared with the unexposed, the relative risk of ependymoma was not increased in the cohorts exposed as infants (RR, 1.06; 95% confidence interval [CI], 0.69-1.63), or as children (RR, 0.98; 95% CI, 0.57-1.69) nor did the exposed have an increased risk of all brain cancers. Osteosarcoma incidence also showed no relation to exposure as infants (RR, 0.87; 95% CI, 0.71-1.06) or children (RR, 0.85; 95% CI, 0.59-1.22). Last, mesotheliomas were not significantly associated with exposure, although the cohorts studied have not yet reached the age at which these tumors tend to occur.

Conclusions.—After more than 30 years of follow-up, exposure to SV40-contaminated poliovirus vaccine was not associated with significantly increased rates of ependymomas and other brain cancers, osteosarcomas, or mesotheliomas in the United States.

DNA SEQUENCES homologous to simian virus 40 (SV40), a macaque polyomavirus that can induce cancer in rodents,1,2 were recently detected in several rare human tumors, including ependymomas,3-5 osteosarcomas,6 and mesotheliomas.7 Tens of millions of Americans were exposed to this virus between 1955 and 1963 as a consequence of adventitious contamination of the early poliovirus vaccines, produced in Asian macaque kidney cell cultures. By 1961, between 80% to 90% of all US children younger than 20 years had been injected at least once with formalin-inactivated poliovirus vaccine (IPV) containing SV40.8 Because SV40 is relatively resistant to formalin killing, the IPV contained variable amounts, commonly low titers, of live SV40. The oral poliovirus vaccine began mass distribution in the United States in 1963 and was SV40-negative.8 Earlier studies of cancer risk following exposure to SV40-contaminated vaccines were generally limited by small sample size or short follow-up.9-15 One exception, a large study in the German Democratic Republic with 22 years of follow-up, found no significant differences in cancer rates between the 885,783 individuals who received SV40-contaminated poliovirus vaccine as infants, compared with similarly aged individuals born a few years later, who received only SV40-negative vaccine.16 No epidemiologic studies, however, have evaluated the specific types of cancers found recently to contain SV40 DNA. In addition, many of the earlier investigations, including the German study, examined mainly oral poliovirus vaccine. The impact of the major single-source exposure to SV40 in the United States, in...
METHODS

The risk of immunization with SV40-contaminated IPV was determined according to birth cohort based on published information, and was used to define 3 comparison groups: (1) individuals at high risk of exposure in infancy, born 1956 through 1962; (2) those at high risk of exposure as children, born 1947 through 1952; and (3) unexposed individuals born a few years later, 1964 through 1969. Cancer incidence and mortality rates in these 3 cohorts were then compared on an age-specific basis (as described below).

Cancer incidence rates in the United States were obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, which since 1973 has collected detailed information regarding new cancer cases diagnosed among residents of 9 representative areas with approximately 10% of the total US population. Additional incidence data were obtained from the Connecticut Tumor Registry, the only cancer registry in the United States that was well established prior to 1955. Cancer mortality data for the entire country were obtained from the National Center for Health Statistics, and the population and demographic data from the US Bureau of the Census.

The cancers studied included ependymomas, osteosarcomas, and mesotheliomas, which have been reported to contain SV40 DNA. In addition, all primary brain cancers were studied as a group, since it has been suggested that a variety of brain tumors might contain SV40 DNA. For each birth cohort, we calculated age-specific cancer incidence rates by single year of age per 100,000 person-years at risk. We used Poisson regression to assess whether the age-specific incidence rates varied according to birth cohort, and fitted a sequence of models to assess whether the relationship between the log of the incidence rate and age was best described as uniform, linear, quadratic, or as a cubic spline with 2 or 3 segments. We used the likelihood ratio test to determine the best-fit model for age and the significance of birth cohort. In summary, we optimally controlled for the effects of age to best assess whether exposure history (determined by year of birth) was related to the incidence of cancer. For individual age-specific incidence or mortality figures of special interest, 95% confidence intervals (CIs) were determined assuming a Poisson distribution. Last, time trends in age-specific cancer incidence in Connecticut from 1950 through 1969 were examined for any changes in rates that could be attributed to SV40-contaminated vaccine exposure.

RESULTS

The observed and fitted (smoothed) age-specific cancer incidence rates in the SEER catchment area for 1973 through 1993 are presented by birth cohort in Figure 1. In general, the exposed groups did not experience elevated rates of cancer, and the likelihood ratio tests found no significant increases in cancer risk among the cohorts exposed as infants (60,811,730 person-years of observation for each cancer studied) or children (46,390,953 person-years), compared with the unexposed birth cohort (44,959,979 person-years).

Ependymoma incidence rates, based on 200 total cases in the data set, were similar in each of the 3 comparison groups (Figure 1, A), with observed fluctuations reflecting the small numbers of this rare tumor at any given age. For example, at age 13 years there were 5 cases (95% CI, 2.15-15.43) compared with 2 cases (95% CI, 0.55-16.53) in the cohorts that were exposed as infants and unexposed, respectively. Ependymoma incidence was best fitted using a quadratic model for age, and showed no overall difference among the cohorts ($\chi^2$, 0.19 on 2 df; $P = .91$). Specifically, incidence in the cohorts exposed as infants (RR, 1.06; 95% CI, 0.69-1.63) or children (RR, 0.98; 95% CI, 0.57-1.89) was not elevated as compared with the unexposed cohort (goodness of fit, 70.2 on 77 df).

Since the SEER program began in 1973, these data could not be used to study ependymoma incidence in the age group at highest risk, children under the age of 4 years. To address this limitation, we studied time trends in incidence among children 0 to 4 years of age in Connecticut, from 1950 to 1969 (Figure 2). Ependymoma incidence in this age group (based on 22 cases and 5,036,496 person-years of observation) was actually higher during the period 1950 through 1954, just prior to the mass immunization program, than in 1960 through 1964, when the greatest effect of SV40 exposure on ependymoma incidence would be expected; ie, as a result of exposures during both 1954 through 1959 and 1960 through 1963. Similar data for individuals 5 to 9 and 10 to 14 years of age in Connecticut also showed no relation between ependymoma incidence and the period of vaccine contamination.

Brain cancer incidence (Figure 1, B), was best fitted using a 2-segment spline function for age (goodness of fit, 62.71 on 75 df). These tumors were relatively common (4162 total cases) and the variation according to birth cohort was statistically significant ($\chi^2$, 10.89 on 2 df; $P = .004$). However, compared with the unexposed cohort, incidence was incrementally lower in the cohorts exposed to SV40-contaminated vaccine as infants (RR,
spline with 2 segments (goodness of fit, the data set, were well fit using a cubic years (Figure 1, C). The age-specific in-age groups at highest risk of developing from the others based on a total of 4643 infants continued to decrease over time. showing that brain cancer deaths among contaminated vaccine, the rate was 1.04, not yet vaccinated than in young children exposed as infants (1.27 per 100 000 per- birthday. However, brain cancer mortality was higher in this group (2.04 per 100 000 person-years). Brain cancer mortality, therefore, was greater among young children not yet vaccinated than in young children injected with contaminated IPV during infancy. Notably, in the cohort born after 1963 and never exposed to SV40-contaminated vaccine, the rate was 1.04, showing that brain cancer deaths among infants continued to decrease over time. Each rate was significantly different from the others based on a total of 4643 brain cancer deaths and 333 163 427 person-years of observation. Osteosarcomas were studied in the age groups at highest risk of developing the disease, the teenage and young adult years (Figure 1, C). The age-specific incidence data, based on 522 total cases in the data set, were well fit using a cubic spline with 2 segments (goodness of fit, 94.87 on 75 df). However, Poisson regression showed no significant differences in risk ($\chi^2$, 2.12 on 2 df; $P = .346$) between the unexposed cohort and the cohorts exposed as infants (RR, 0.87; 95% CI, 0.71-1.06) or children (RR, 0.85; 95% CI, 0.59-1.22). Note the initial peak at 10 years of age in the cohort exposed as infants represented just 2 cases (95% CI, 0.55-16.53). Similarly, trends in osteosarcoma incidence rates over time in Connecticut showed no increases in risk ($\chi^2$, 2.90 on 2 df; $P = .23$) in the linear age model that provided the best fit (goodness of fit, 60.13 on 78 df). The risk in the cohorts exposed as infants (RR, 3.00; 95% CI, 0.67-13.11) or children (RR, 2.45; 95% CI, 0.50-12.03) was elevated as compared with the unexposed. However, the birth cohorts studied have not yet reached the age at which most mesotheliomas occur, resulting in few cases (a total of 71) and imprecise estimates of risk.

**COMMENT**

Contamination of the early poliovirus vaccines with SV40 has reemerged as a public health concern following recent reports that SV40 DNA may be present in osteosarcomas, mesotheliomas, ependymomas, and perhaps other types of brain cancer. Extensive parental exposure of infants is a particular cause for concern as animal studies have shown that injected neonates are particularly susceptible to SV40-induced tumors. However, more than 30 years after this extensive single-source exposure in the United States, the birth cohorts exposed as infants or children showed no significant increase in those cancers reported to have high prevalence of SV40 DNA.

This result is reassuring, as it is likely that we would have observed an effect on cancer rates if one existed. As discussed, almost all US children under the age of 20 years in 1961 had been injected 1 or more times with SV40-contaminated IPV. Furthermore, because of the large number of individuals studied and the long period of follow-up, each cohort contributed a large number of person-years to the data. To help judge the uncertainty in our analyses of incidence rates, we calculated the 95% CIs around the estimates of cancer risk in the exposed birth cohorts. For ependymomas and osteosarcomas, even the upper limit of risk was quite small, and for brain cancers there was a significant inverse relation. Few cases of mesothelioma occurred in any groups.

A causal relation between SV40 exposure and ependymomas in children would involve a short incubation time, if the recent detection of SV40 DNA in ependymomas in infants is to be believed. Therefore, the absence of an SV40-contaminated vaccine effect on ependymoma cancer rates in the Connecticut children 0 to 4 years of age is consistent with the cohort analyses. Together the null results argue against a relation between vaccine-related SV40 exposure and the development of ependymomas.

In addition, overall brain cancer incidence rates were actually lower in the exposed birth cohorts. This pattern seems unlikely to represent a protective effect of SV40-contaminated vaccines, but it probably reflects the increase in brain cancer incidence over calendar time that has been well described in the literature. To specifically evaluate brain cancers in young children and infants we assessed cancer mortality rates, but no relation was seen between SV40-contaminated vaccine exposure and the development of brain cancers in children under 5 years of age.

The age-specific incidence of osteosarcoma was not significantly different in exposed or unexposed cohorts, including the teenage years when osteosarco-

mas are most common. In addition, trends in osteosarcoma incidence in Connecticut showed no changes that could be attributed to the period of vaccine contamination. The interpretation of this finding is limited, since the postulated incubation time of SV40-induced osteosarcoma is not as defined as it is for ependymoma. However, the overall pattern observed for osteosarcoma incidence argue against an association with vaccine-related SV40 exposure.

Mesothelioma incidence rates showed a nonsignificant increase among the exposed groups. Few individuals developed mesothelioma in any of the comparison groups, however, and the modest case numbers made estimates of RR imprecise. Mesotheliomas could not be directly studied in the older age groups, which are ordinarily at highest risk, since individuals in the exposed cohorts were at most 46 years of age in 1993. This is important, as mesothelioma incidence has increased dramatically over time, but only among older individuals who were unlikely to have received the contaminated vaccines. Therefore, other factors, notably asbestos exposure, likely explain the increases in mesothelioma incidence rates that have been observed. Final conclusions about the relation of mesotheliomas to SV40-contaminated vaccines will not be possible until the individuals exposed as infants and children reach a more advanced age.

Several limitations to this investigation need to be considered. It is important that this report not be viewed as strong evidence against the role of SV40 as a human pathogen. For example, SV40 may have been in the human population for some time, unrelated to vaccine exposure, as suggested by the finding of SV40 antibodies in serum samples from the world that were collected before introduction of poliovirus vaccines. It is also possible that SV40 only has tumorigenic potential in humans exposed un-
der different conditions and higher levels of virus than were associated with poliovirus vaccine. Vaccine-related exposure to SV40 in many countries has involved either oral administration or mostly low viral titers in injected inoculations. In general, the unavailability of specific information regarding the actual SV40 titer of each inoculation has limited the power of population-based studies of this kind. Finally, comparisons among birth cohorts measure the net impact of all protective and adverse factors that influence the risk of cancer in the cohorts, and not just the factor under investigation (ie, SV40 exposure).

In summary, our study failed to detect any significant increases in the risk of cancers reported to contain SV40 DNA among the birth cohorts exposed to SV40-contaminated vaccine. In effect, ependymomas and osteosarcomas have remained rare cancers, while the rising rates for mesotheliomas have involved older age groups unlikely to have received SV40-contaminated vaccine. Thus, approximately 30 years after millions of Americans were parenterally exposed as infants or children, the absence of a discernible effect in our study adds to the evidence that no relation exists between exposure to SV40-contaminated vaccine and the development of cancer. As the exposed cohorts mature, however, it will be important to continue monitoring of cancer risks.

References