
Re: Trends in U.S. Pleural Mesothelioma Incidence Rates Following Simian Virus 40 Contamination of Early Poliovirus Vaccines

We read with interest the recent article in the Journal by Strickler et al. (1), in which the authors performed a retrospective age-period-cohort analysis to estimate the incidence of pleural mesothelioma in individuals potentially exposed to simian virus 40 (SV40)-contaminated poliovirus vaccines. The authors concluded that "Age-specific trends in U.S. pleural mesothelioma incidence rates are not consistent with an effect of exposure to SV40-contaminated poliovirus vaccine" and suggested that "monitoring of vaccine-exposed cohorts should continue." We wish to raise two issues about this and similar studies (2-4) that address "exposure" to SV40-contaminated polio vaccines and the incidence of human cancers. First, although a cohort study is recognized as the best design to identify incidence and natural history of disease (with a known exposure) and may be used to assess multiple outcomes after a single exposure (5), the prevalence of SV40 infections in the human population is not known, and the available data about prevalence are limited and inconclusive (2-4). Second, an important confounding factor in the epidemiologic assessment of malignant mesothelioma is that the actual number of people infected with SV40 through the use of contaminated polio vaccines is not known and may be less than the "exposed" population size assumed in the study by Strickler et al. (1). For example, in the United States, not all vaccine lots were contaminated with SV40, formalin inactivation was expected to reduce the titer of live SV40 in the lots that were contaminated, and successful infection rates by live SV40 are unknown (2-4). Therefore, an inability to identify the population that was actually infected with SV40 through the use of contaminated polio vaccines precludes a meaningful calculation of cancer incidence in relation to exposure to those vaccines. Furthermore, the Institute of Medicine

(IOM) Immunization Safety Review Committee found that epidemiologic studies of cancer rates in people potentially "exposed" to SV40-contaminated vaccines, such as the analysis by Strickler et al. (1), are inadequate to evaluate a causal relationship between exposure and disease (2). These limitations led the IOM to "not recommend additional epidemiological studies of people potentially exposed to contaminated polio vaccine" (2). However, the IOM concluded that "the biological evidence is strong that SV40 is a transforming virus" and that "the biological evidence is of moderate strength that SV40 exposure could lead to cancer in humans under natural conditions" (2). Future studies are needed to determine the prevalence of SV40 infections in different human populations. The IOM recognized that gaps in our understanding of the pathogenesis of SV40 in humans are important and recommended "targeted biological research," including "further study of the transmissibility of SV40 in humans" (2).

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In a recent article in the Journal, Strickler et al. (1) estimated age- and sex-specific pleural mesothelioma incidence rates from 1975 through 1997. These trends were then compared with trends in prevalence of exposure to simian virus 40 (SV40)-contaminated poliovirus vaccine. The authors concluded that "Age-specific trends in U.S. pleural mesothelioma incidence rates are not consistent with an effect of exposure to SV40-contaminated poliovirus vaccine." In our opinion, the observed plateau in pleural mesothelioma incidence after 1992 is not in conflict with a possible effect of SV40 for three reasons. First, because pleural mesothelioma is a disease of the elderly, even an increasing incidence among the youngest individuals would lead to a number of cases too small to modify the general trend. The exposure prevalence by age may be better evaluated by disaggregating the data into age groups (Table 1). Among individuals in the 25- to 44-year age groups, half the cohort (i.e., those aged 25-34 years) includes few exposed people in the last two periods of observation (i.e., 1991-1994 and 1995-1997). Moreover, in this group, few cases are able to modify the age-specific trend. For this reason, the 3-year period, 1995-1997, should be excluded from the analysis. Among those in the 45- to 54-year age group, trends show a decrease among males and a slight increase among females [Fig. 2, B in (1)]. In the oldest age groups, the prevalence of SV40 exposure increases over time, as does the trend of pleural mesothelioma incidence. Second, it is important to consider the latency period of pleural mesothelioma. In occupational studies of long-term asbestos exposure, time since first exposure ranges from 10 to 60 or more years (2,3). Epidemiologic data suggest that the latency period for pleural mesothelioma is longer than 40 years, particularly if an individual inhaled asbestos at a very young age. The

Table 1. Rough estimates of the prevalence of exposure to SV40-contaminated poliovirus vaccine by age at exposure and year of birth in different age groups*

Years of observation	Years of birth	Age at exposure, y	Prevalence of exposure, %	Years of birth	Age at exposure, y	Prevalence of exposure, %
Age group		25-29			30-34	
1975-1978	1946-1953	8-15	95	1941-1948	13-20	90
1979-1982	1950-1957	4-11	92.5	1945-1952	9-16	95
1983-1986	1954-1961	0-7	87.5	1949-1956	5-12	95
1987-1990	1958-1965	0-3	85	1953-1960	1-8	90
1991-1994	1962-1969	—	—	1957-1964	0-4	85
1995-1997	1966-1972	—	—	1961-1967	—	—
Age group		35-39			40-44	
1975-1978	1936-1943	18-25	75	1931-1938	23-30	65
1979-1982	1940-1947	14-21	85	1935-1942	19-26	67.5
1983-1986	1944-1951	10-17	90	1939-1946	15-22	80
1987-1990	1948-1955	6-13	95	1943-1950	11-18	90
1991-1994	1952-1959	2-9	90	1947-1954	7-14	95
1995-1997	1956-1962	0-5	85	1951-1957	4-10	92.5
Age group		45-49			50-54	
1975-1978	1926-1933	28-35	60	1921-1928	33-40	55
1979-1982	1930-1937	24-31	60	1925-1932	29-36	60
1983-1986	1934-1941	20-27	60	1929-1936	25-32	60
1987-1990	1938-1945	16-23	75	1933-1940	21-28	62.5
1991-1994	1942-1949	12-19	90	1937-1944	17-24	75
1995-1997	1946-1952	9-15	92.5	1941-1947	14-20	85
Age group		55-59			60-64	
1975-1978	1916-1923	38-45	40	1911-1918	43-50	30
1979-1982	1920-1927	34-41	50	1915-1922	39-46	35
1983-1986	1924-1931	30-37	55	1919-1926	35-42	45
1987-1990	1928-1935	26-33	60	1923-1930	31-38	55
1991-1994	1932-1939	22-29	60	1927-1934	27-34	60
1995-1997	1936-1942	19-25	65	1931-1937	24-30	60
Age group		65-69			70-74	
1975-1978	1906-1913	48-55	15	1901-1908	53-60	10
1979-1982	1910-1917	44-51	20	1905-1912	49-56	12.5
1983-1986	1914-1921	40-47	25	1909-1916	45-52	20
1987-1990	1918-1925	36-43	45	1913-1920	41-48	30
1991-1994	1922-1929	32-39	55	1917-1924	37-44	45
1995-1997	1926-1932	29-35	60	1921-1927	34-40	55
Age group		75-79			80-84	
1975-1978	1896-1903	58-65	5	1891-1898	63-70	5
1979-1982	1900-1907	54-61	7.5	1895-1902	59-66	7
1983-1986	1904-1911	50-57	10	1899-1906	55-62	8
1987-1990	1908-1915	46-53	15	1903-1910	51-58	10
1991-1994	1912-1919	42-49	30	1907-1914	47-54	15
1995-1997	1916-1922	39-44	35	1911-1917	44-50	20

*Years of observation were grouped as in Fig. 2, B (1). Year of birth was calculated in the vaccination period with SV40-contaminated poliovirus vaccine (from 1955 through 1963). Age at exposure was calculated in 1961, and prevalence of exposure (%) was crudely estimated from Fig. 1 (1), on the basis of the age-specific prevalence of exposure to potentially SV40-contaminated poliovirus vaccine in the United States in 1961. — = indeterminate.

latency period may be different in the case of a viral contamination; however, in such a case, a similarly long-term presence of SV40 in the body compartments can be hypothesized. Among young individuals inoculated with SV40-contaminated vaccine, the virus could remain silent for many years and then possibly interact with asbestos that remains in the pleura as well. Indeed, SV40 is able to initiate oncogenic transformation of cells. The large T antigen of SV40 inactivates the p53 and Rb tumor suppressor genes and promotes immortalization of cells (4-6). However, additional cellular changes are necessary for a tumor to develop. The timing of these events could occur slowly, in-

ducing mesothelioma even 60 years after the first exposure. Third, the Institute of Medicine recently concluded that epidemiology that is based on the differences between exposed and non-exposed cohorts is of dubious significance because it is impossible to clearly separate these two cohorts (7). Recent data [reviewed in (5)] suggest that SV40 may have contaminated some vaccines even after 1963, and/or that human-to-human transmission of SV40 may occur.

Regardless of the route of infection, the molecular pathologic evidence indicates that SV40 is a factor in the pathogenesis of some mesotheliomas (5,6). We believe, however, that the epidemiologic data currently available are insuf-

ficient to draw definitive conclusions about the possible contribution of SV40-contaminated poliovaccines to the overall increase in the incidence of mesothelioma in the past 40 years.

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RESPONSE

We thank Dr. Puntoni and his colleagues and Drs. Vilchez and Butel for their interest in our study of pleural mesothelioma risk subsequent to immunization with simian virus 40 (SV40)-contaminated poliovirus vaccine. Widespread SV40 contamination of poliovirus vaccine manufactured between 1955 and 1963 resulted in a massive single-source exposure. As of 1961, most U.S. residents under the age of 40 years and nearly 90% of those under the age of 20 years had been injected with poliovirus vaccine potentially containing live SV40. Published estimates (1) indicate that approximately 10%–30% of vaccine lots [some published data (2) place the fig-

ure higher] contained live SV40. Because vaccinees received multiple immunizations (a series of three injections and a booster), a high percentage of those immunized with poliovirus vaccine between 1955 and 1963 were injected at least once with live SV40. The inability to precisely identify those, if any, who became infected does not invalidate our comparison of cancer rates according to probability of exposure, which ranged from very high (e.g., >90%) to very low (e.g., <5%), based on the year of birth.

We observed that pleural mesothelioma incidence rates were not associated with exposure to SV40-contaminated poliovirus vaccine. Could SV40 be a major independent cause of mesothelioma nonetheless? For this possibility to be so, alternative routes of exposure to SV40 would have to exist, and SV40 would have to be circulating in the general population. In any case, the persistent rarity of pleural mesothelioma cases among women suggests that the cumulative independent effects of known and hypothesized SV40 exposures on rates of pleural mesothelioma have, to date, been negligible.

Could SV40 be in circulation in the general population and interact with other risk factors, particularly asbestos, to cause mesothelioma? We think this is an open question. However, as reviewed in our paper (3), detection of SV40 DNA in approximately equal numbers of asbestos-positive and asbestos-negative mesothelioma tumors argues against such an interaction.

We agree with Puntoni et al. that the latency period for malignancies can be very long, even decades. Nonetheless, most readers are probably reassured that we found no association between mesothelioma and SV40-contaminated poliovirus vaccine in 40 years of follow-up data. Their suggestion, to discard the most recent data (1995–1997) for the youngest age group (25–44 years), would have no impact on our overall results or conclusions. Moreover, their

comments do not take into account our age–period–cohort analyses, in which the contribution of each age group and calendar period was weighted by the size of the group, and exposure trends were assessed by individual year of birth.

In our opinion, achieving the Institute of Medicine's primary research recommendation—development of sensitive, specific, and reproducible tests for detection of SV40 antibodies as well as DNA (4)—will ultimately help resolve remaining questions about the role of SV40 infection in the etiology of human cancer.

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