

CORRESPONDENCE

Re: Cancer Incidence in Denmark Following Exposure to Poliovirus Vaccine Contaminated With Simian Virus 40

We read with interest the recent article by Engels et al. (1) in which the authors performed a retrospective birth-cohort analysis in Denmark following exposure to poliovirus vaccine contaminated with simian virus 40 (SV40) to clarify whether SV40 infection increases risk of mesothelioma, choroid plexus tumors, and non-Hodgkin's lymphoma, or of cancers arising in children. The authors concluded that "exposure to SV40-contaminated poliovirus vaccine in Denmark was not associated with increased cancer incidence."

It is important to point out that several limitations have been recognized for this and similar epidemiologic studies addressing exposure to SV40-contaminated poliovirus vaccines and the incidence of human cancers (Table 1) (2-4). Indeed, an evaluation by the Institute of Medicine Immunization and Safety Review Committee found that the epidemiologic data used in birth-cohort studies to examine cancer rates in individuals potentially exposed to SV40-contaminated vaccines are inadequate to evaluate a causal relationship (2). The validity of observational studies, such as the retrospective analyses by Engels et al. (1), depends on the accuracy of the existing knowledge of the biologic properties of SV40 and the identification of the human population infected with the virus (2,4,5). There-

fore, supportive evidence from experimental studies is required to draw causal inferences in human disease (4,6). Indeed, a recent case-control study (5) of 1793 cancer patients indicated that there is a statistically significant excess risk of SV40 associated with primary brain cancers (odds ratio [OR] = 3.8, 95% confidence interval [CI] = 2.6 to 5.7), primary bone cancers (OR = 24.5, 95% CI = 6.8 to 87.9), malignant mesothelioma (OR = 15.1, 95% CI = 9.2 to 25.0), and non-Hodgkin's lymphoma (OR = 5.4, 95% CI = 3.1 to 9.3).

A known confounding factor in the observational study by Engels et al. (1) is that the actual number of people infected with live SV40 through the use of contaminated poliovirus vaccines in Denmark or other countries is not known (2-4). It is also recognized that not all vaccine lots were contaminated with SV40, that formalin inactivation may have reduced the titer of live SV40 in the vaccine lots that were contaminated, and that successful infection rates by live SV40 are unknown (2-4). For example, only 19% of newborn children and 15% of infants aged 3-6 months at the time of receiving a known contaminated oral poliovirus vaccine excreted infectious SV40 in their stools for up to 5 weeks after vaccination (4), indicating an established infection. Therefore, an inability to identify the population actually infected with SV40 in Denmark through the use of contaminated poliovirus vaccines precludes a meaningful calculation of cancer incidence in relation to exposure to those vaccines. Furthermore, there is ample evidence that some individuals acquire SV40 infection from sources other than poliovirus vaccines (2,5), indicating that the individuals in the unexposed group identified by Engels et al. (1) may also have been infected with SV40. These shortcomings led the Institute of Medicine

committee to recommend that no additional epidemiologic studies of individuals potentially exposed to contaminated poliovirus vaccine be initiated (2). Hence, future studies need to focus on how SV40 is transmitted in humans today, how it is distributed throughout the infected host, how the virus interacts with different tissues, and how the host responds immunologically to this infection.

REGIS A. VILCHEZ
AMY S. ARRINGTON
JANET S. BUTEL

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NOTES

Affiliation of authors: R. A. Vilchez (Departments of Medicine and Molecular Virology and Microbiology), A. S. Arrington, J. S. Butel (Department of Molecular Virology and Microbiology), Baylor College of Medicine, Houston, TX.

Correspondence to: Regis A. Vilchez, MD, Department of Medicine, Section of Infectious Diseases, One Baylor Plaza, BCM-286, Rm. N1319, Houston, TX 77030 (e-mail: rvilchez@bcm.tmc.edu).

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Table 1. Limitations of birth cohort studies and the link between SV40 and some human malignancies (2-4)

1. Assumption: SV40 "exposure" equals infection
2. Assumption: SV40 "exposure" was fixed and limited (poliovaccines used 1955-1963)
3. Not all vaccine lots contained infectious SV40
4. Amount of live SV40 varied among contaminated lots
5. No. of individuals who received contaminated vaccine is unknown
6. No. of individuals who became infected with SV40 is unknown
7. Different age groups were inoculated with contaminated vaccine
8. Other sources of SV40 infection are possible for "unexposed" group
9. Coding and diagnostic criteria of cancers, particularly for lymphomas, have changed over time
10. Background increase in cancer incidence

RESPONSE

Unfortunately, Vilchez et al. have incorrectly generalized from a recent Institute of Medicine (IOM) report (1) to criticize our study (2). That report noted that there were several limitations to previous U.S.-based retrospective cohort studies, most importantly that not all U.S. poliovirus vaccines between 1955 and 1962 contained live simian virus 40 (SV40) and that the extent of use of SV40-contaminated poliovirus vaccine in the United States was poorly documented.

Our retrospective cohort study in Denmark overcomes these limitations. As previously described (2), by April 1962, 84%–100% of Danish children had received at least one dose of poliovirus vaccine. In addition, SV40 contamination of poliovirus vaccine was much more frequent in Denmark than it was in the United States because Danish vaccines were manufactured in monolayer cultures that pooled kidney tissue from dozens of monkeys. We also described (2) frequent SV40 seroconversions following receipt of the Danish vaccine, further illustrating widespread contamination. We concluded that, by 1962, almost all Danish children had received one or more inoculations with poliovirus vaccine containing live SV40.

Why then, did these SV40-exposed children (i.e., born 1946–1961) have similar cancer incidence to children born later (i.e., born 1964–1970) who did not receive SV40-contaminated vaccine? The argument by Vilchez et al. on this matter is vague. They suggest that successful infection rates by live SV40 are unknown. This statement is true; however, in the absence of data on whether SV40 can be acquired by other routes, we suggest that direct injection of live SV40 early in life would be the most likely route and time course that could lead to SV40 infection.

In addition, Vilchez et al. comment that there is ample evidence that some individuals acquire SV40 infection from sources other than poliovirus vaccines. In fact, the data on this issue are somewhat contradictory, as reviewed by the IOM (1). Specifically, whereas some laboratories have reported detection of SV40 DNA in tumors from individuals too young to have received SV40-contaminated vaccines, other laboratories have not detected SV40 in any hu-

man tumors. SV40 antibodies found in asymptomatic individuals may represent cross-reactive antibodies to the human polyomaviruses BK and JC. Indeed, recognizing these issues, the IOM highlighted the need for the development and use of sensitive and specific standardized techniques for SV40 DNA detection, including masking of specimens, use of positive and negative control tissues, and replicate testing, and the development of sensitive and specific serologic tests.

Given the limitations of laboratory studies of SV40 in humans (1), the possibility that SV40 infection can be acquired by routes other than through SV40-contaminated vaccinations remains uncertain. Nevertheless, as we argue (2), if any SV40 infections occurred in Denmark after 1962, they would likely have been less frequent, have occurred at older ages, and have arisen from smaller inocula of virus than infections transmitted by SV40-contaminated vaccination. Vilchez et al. further suggest that changes in cancer registration, coding, or diagnosis could have obscured an effect of SV40 on cancer risk. However, as we note in our study (2), such an effect would likely be small and would not hide a large effect of SV40, if one were present. Therefore, our comparison of vaccine-exposed and unexposed individuals remains informative. The similar cancer incidence among these groups argues against a role for SV40 in human cancer.

Vilchez et al. also cite their own recently published study (3) to argue that, contrary to our results, SV40 infection is associated with increased cancer risk. Although they characterize this work as a case-control study and imply that it includes new data on 1793 cancer patients, their article is actually a meta-analysis of previously published laboratory studies on the detection of SV40 in human tumors. As reviewed elsewhere (1,4), many of these individual laboratory studies have important limitations, including an absence of appropriate negative control tissues and masking of specimens. Substantial variability among the results of these various studies is apparent. It is also surprising that Vilchez et al. did not comment on the fact that in the only multi-laboratory study that evaluated mesothelioma tumors under masked conditions, SV40 was not reproducibly detected in any

specimen (5). Because the sensitivity, specificity, and reproducibility of molecular methods for detecting SV40 infection in human tumors remain uncertain, we concur with the IOM's recommendations (1) that urge the improvement and standardization of laboratory methods.

ERIC A. ENGELS
MORTEN FRISCH

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Editor's note: Dr. Frisch is employed by Statens Serum Institut, the manufacturer of poliovirus vaccine used in Denmark since 1955.

Affiliations of authors: E. A. Engels, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD; M. Frisch, Department of Epidemiology Research, Danish Epidemiology Science Center, Statens Serum Institut, Copenhagen, Denmark.

Correspondence to: Eric A. Engels, MD, MPH, Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS 8010, Rockville, MD 20892 (e-mail: engelse@exchange.nih.gov).

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