

LETTER TO THE EDITOR

Lack of Serological Evidence for an Association Between Simian Virus 40 and Lymphoma

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Dear Sir,

We thank Vilchez and Butel for their interest in our recent report "Lack of serological evidence for an association between simian virus 40 and lymphoma."¹ Contrary to what Vilchez and Butel suggest, our report was not a "preliminary" analysis but a full completed analysis of our case-control data.

The Immunization Safety Review led by the U.S. Institute of Medicine of the National Academies concluded recently that "the evidence is inadequate to accept or reject a causal relationship between SV40-containing polio vaccines and cancer" and recommended that the development of sensitive and specific serologic tests for SV40 be a primary research objective.² The serological assay that we used was demonstrated to be 100% sensitive and 100% specific for SV40 infection in the natural host, the rhesus macaque. The assay employed as an antigen virus-like particles (VLPs) that were formed by self-assembly of the SV40 VP1 major capsid protein. VLPs morphologically resemble authentic virions. Because viral infections induce a humoral immune response against surface-exposed epitopes on virions, one would expect that SV40 infection in humans would elicit at least some response to the antigens used in the assay, as we clearly demonstrated in rhesus macaques. Furthermore, using identical VLP-based enzyme immunoassays for the human polyomaviruses BKV and JCV, we detected very high viral antibody titers in human sera. Indeed, our finding of low SV40 antibody titers in human sera and the demonstration that cross reactivity with BKV antibodies may account for part of the SV40 reactivity does not suggest difficulties with the assays. Rather, our results argue against the frequent presence of current SV40 infection in Spain.

Regardless of the level of exposure of the Spanish population to SV40 contaminated polio vaccines, our results indicate that exposure to SV40 from routes other than vaccination is

unlikely to have taken place in the Spanish population as suggested by Vilchez and Butel. The absence of detectable SV40 in sewage from Spain and elsewhere, when BKV and JCV can be found readily, also argues against ongoing transmission of SV40 in humans.³ We are aware of no published data to support the claim by Vilchez and Butel that "SV40 infections are occurring in children and adult populations today."

Vilchez and Butel use the term "confounding" incorrectly when they state that geographical differences in the use of SV40-contaminated poliovirus vaccines create varying results across studies.⁴ A factor causes confounding within a study only if it is related to both the exposure (*i.e.*, SV40) and outcome (*i.e.*, cancer). For any given study based in a single geographical region (such as Spain in our study), all subjects, regardless of exposure or outcome status, have the same geography. Because each study thus stratifies on geography, an examination of the association between exposure and outcome within each study is entirely unconfounded. The effect of SV40 exposure on cancer risk might conceivably vary by geography through an interaction with another cancer-causing agent (*i.e.*, effect modification).⁴ In the case of lymphoma, however, it is unclear what such a factor would be. In any event, the prevalence per se of SV40 exposure should not affect the magnitude of association.

The availability of sensitive and specific serologic assays for SV40 infection will prove valuable in future investigations of SV40 to study the magnitude of effect of SV40 on cancer risk. SV40 serology can also be useful in examining the natural history of SV40 in humans.

Yours sincerely,

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