CHAPTER 24

Epidemiologic Studies of Polyomaviruses and Cancer:
Previous Findings, Methodologic Challenges and Future Directions

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Abstract
Polyomavirus infection became the focus of epidemiologic studies of cancer several decades ago, soon after the discovery of simian virus 40 (SV40) in 1960 and its ability to induce tumors in experimentally infected animals in 1961. Between 1963 and 2003, eight case-control and eleven cohort studies investigated the possible associations between polyomavirus infection and multiple types of cancer, including lymphoma, brain tumors, and mesothelioma. Two of these studies included measures of infection with the human polyomaviruses, JC virus and BK virus. Overall, the results from these studies were mostly null, although limitations in study design and exposure assessment complicate their interpretation. This chapter includes a review of results from previous epidemiologic studies of polyomavirus infection and human cancer, discussion of the methodologic challenges in study design, and proposed future directions for epidemiologic research.

Introduction
Polyomavirus infection became the focus of epidemiologic studies of cancer several decades ago, soon after the discovery of simian virus 40 (SV40) in 1960 and its ability to induce tumors in experimentally infected animals in 1961. Early polio vaccines were prepared from virus pools grown in monkey kidney tissue which harbored SV40, resulting in the accidental contamination of polio vaccines administered to millions of Americans in the late 1950s to early 1960s. Fraumeni and colleagues were the first to address the concern that widespread exposure to SV40-contaminated polio vaccine may be associated with increased cancer incidence in their cohort study published in 1963. Findings from this initial study were reassuring, since there were no increases in cancer incidence observed within states thought to have the highest levels of SV40 polio vaccine contamination. However, only four years had elapsed since the widespread exposure to SV40 at the time of this study, and the possibility remained that a cancer epidemic was forthcoming.

Subsequent epidemiologic studies of SV40 exposure and cancer published in the late 1960s, 1970s and early 1980s were mostly negative. Concern was quieted until the advent of polymerase chain reaction (PCR) techniques and the subsequent detection of SV40 genomic sequences in ependymomas and osteosarcomas by Bergsagel et al in 1992. The literature quickly expanded with reports of PCR-detected SV40 sequences in several types of cancer, including brain tumors, mesothelioma, hematologic malignancies, and other types of cancer, as reviewed...
in previous chapters in this book. In response to the renewed concern over the possible association between SV40 exposure and cancer, several cohort studies incorporating longer follow-up time were conducted and published in the 1990s. As before, findings from these cohort studies were mostly negative, but all were predicated on the assumption that human exposure to SV40 was limited to those individuals who were vaccinated for polio in 1955-63. Epidemiologic studies conducted up to this point have been previously reviewed (refs. 17,18).

Eight additional epidemiologic studies of polyomaviruses and cancer were published in 2003, seven of which incorporated some measure of exposure to SV40. Two studies included measures of infection with the related human polyomaviruses, JC virus (JCV) and BK virus (BKV), as potential risk factors for cancer. These viruses are highly prevalent in the human population and have the same transforming capabilities as SV40. This chapter includes a review of results from previous epidemiologic studies of polyomavirus infection and human cancer, discussion of the methodologic challenges in study design, and proposed future directions for epidemiologic research.

**Previous Findings**

The results from case-control and cohort studies of polyomavirus infection and cancer are presented separately in Tables 1 and 2, respectively, and studies are ordered chronologically within these two tables. When comparing results across studies, it is important to consider several sources of heterogeneity in the study designs, including selection of cases and controls for case-control studies (i.e., hospital-based versus population-based), the type of cancer studied (i.e., cancer site, incidence vs. mortality, adult vs. pediatric), the geographic location of the study (differences in SV40 exposure vary by country), length of follow-up (length of time between exposure and outcome), and adjustment for potential confounders (i.e., approaches to teasing apart age and cohort effects). Variations in methods of exposure assessment are important considerations in the interpretations of these results, thus the case-control and cohort studies discussed below are grouped by method of exposure assessment.

**Case-Control Studies (Table 1)**

**Maternal or Childhood Polio Vaccination and Childhood Cancers**

The earliest case-control studies investigated the association between childhood cancer and receipt of polio vaccine potentially contaminated with SV40 by either the mother during pregnancy or the child after birth. Stewart and Hewitt (1965) observed no association between polio vaccination as recorded on the medical records and deaths from childhood leukemia or other cancers in the United Kingdom. Using the same measure of exposure in Australia, Innis (1968) observed no increased risks of childhood cancer in children immunized against polio at ages younger than 1 year, and a significant increase in childhood cancer risk associated with polio immunization at ages greater than 1 year. Farwell et al. (1979) conducted a case-control study in Connecticut and observed an overall increase in childhood tumors of the central nervous system (CNS) associated with maternal receipt of injected polio vaccine (IPV) during pregnancy, an increase which was statistically significant for medulloblastomas. This increased risk of medulloblastomas was not replicated in a cohort study of incidence rates in Connecticut conducted years later and reviewed below.

**Self-Reported History of Polio Vaccination and Adult Cancers**

Self-reported history of polio vaccination was not associated with multiple subtypes of adult non-Hodgkin's lymphoma (NHL) in a population-based case-control study in San Francisco (2003). Results remained unchanged after restriction of analyses to individuals vaccinated prior to 1963 and those vaccinated in childhood. Similarly, a hospital-based case-control study of adult gliomas conducted within three U.S. cities (2003) did not observe a statistically significant association with self-reported history of polio vaccination, regardless of route of administration, year of vaccination, or year of birth.