

Polio vaccines, Simian Virus 40, and human cancer: the epidemiologic evidence for a causal association

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In 1960, it was discovered that Simian Virus 40 (SV40) contaminated up to 30% of the poliovirus vaccines in the US. This contamination arose because the vaccines were produced in monkey kidney cell cultures harboring SV40 between 1955 and 1963. During this period, approximately 90% of children and 60% of adults in the USA were inoculated for polio and possibly exposed to SV40. Many epidemiologic and molecular pathogenesis studies have been conducted in order to identify potential cancer risks since this 'natural' experiment began. Productive SV40 infection has the potential to initiate malignancy in a variety of target tissues. Epidemiological studies that investigated the relationship between SV40 infection and cancer risks have yielded mixed results. Studies can be grouped into three categories based on their exposure definition of SV40 infection: (1) use of vaccination or birth cohorts as proxy variables for infection, (2) follow-up of children of pregnant women who received polio vaccines, and (3) direct molecular detection of the virus or serologic detection of anti-SV40 antibody responses. A meta-analysis of five published studies did not support the hypothesis that SV40 exposure increases the overall risk of cancer incidence or cancer mortality. The analysis of specific cancer sites is largely inconclusive because of substantial problems that most studies have had in reliably defining exposure, defining latency effects, or dealing with confounding and other biases. A new generation of molecular epidemiologic studies is necessary to properly address these issues.

Oncogene (2004) 23, 6535–6540. doi:10.1038/sj.onc.1207877

Keywords: Simian Virus 40; poliovirus vaccines; causality; mesothelioma; ependymoma; neoplasms

Introduction

In 1960, it was discovered that Simian Virus 40 (SV40) contaminated 10–30% of the poliovirus vaccines in the USA (Sweet and Hilleman, 1960). This contamination arose because the vaccines were produced in monkey

kidney cell cultures harboring SV40 between 1955 and 1963. During this period, approximately 90% of children and 60% of adults (~98 million children and adults) in the USA were inoculated for polio and possibly exposed to SV40-contaminated vaccines (Shah and Nathanson, 1976). The large-scale exposure of the population to SV40 has risen much scientific and public health concern, because the macaque polyomavirus has been proven to be oncogenic in rodents and capable of transforming human cells *in vitro*. Eddy *et al.* (1962) reported that hamsters injected with monkey cells infected with SV40 developed sarcoma and ependymoma. Other *in vitro* experiments have supported these findings and have also found that SV40 is capable of transforming human cells (Kirschstein and Gerber, 1962; Carbone *et al.*, 1997; Butel and Lednický 1999). Moreover, these transformed cells were capable of tumor growth when injected into terminally ill human volunteers (Jensen *et al.*, 1964). Some researchers, though not all, have detected SV40 DNA sequences in several rare human tumors, including ependymomas, osteosarcomas, and mesotheliomas.

Despite SV40's ability to transform both rodent and human cells, the question of whether SV40 causes cancer in humans remains controversial. Several observational epidemiological studies have been published on SV40 infection and the risk of human cancer, but the results have been conflicting and inconclusive. In 2002, the Vaccine Safety Review Committee of the Institute of Medicine (IOM), National Academy of Sciences, USA, reviewed these epidemiological studies with the sole intent of assessing the potential impact on cancer risks of the distribution of polio vaccines manufactured in 1955–1963 (IOM, 2002). The IOM concluded that 'the evidence was inadequate to conclude whether or not the contaminated polio vaccine caused cancer because the epidemiological studies are sufficiently flawed.' In this report, we present a systematic review of the current epidemiological evidence for an association between SV40 and human cancer using meta-analysis techniques to derive a global pooled estimate of the relative risk (RR) of cancer from the observational studies published before April 2004. We hasten to add, however, that the knowledge base of epidemiologic studies on SV40 and cancer is far from ideal in terms of the reliability of exposure measures. Therefore, the analysis presented herein is intended to provide a general overview of how

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the epidemiologic estimates of effect are distributed about the null hypothesis, and to provide some insights into the heterogeneity of results.

Exposure assessment in epidemiologic studies of SV40 and cancer

Epidemiological studies that investigated the relationship between SV40 infection and the incidence of cancer or cancer death have yielded mixed results. An important caveat is the fact that many investigations could only address the issue of SV40 infection indirectly, via its presumed relationship with the polio vaccination eras. Current studies can be grouped into three categories based on their exposure definition of SV40 infection. First, since it is generally believed that contaminated polio vaccines were the main source of SV40 infection in humans, most studies have defined SV40 exposure based on vaccination or birth cohorts (Fraumeni *et al.*, 1963; Innis, 1968; Mortimer *et al.*, 1981; Strickler *et al.*, 1998, 1999; Fisher *et al.*, 1999; Carroll-Pankhurst *et al.*, 2001; Engels *et al.*, 2003a, b). Such studies are, strictly speaking, ecologic investigations, since exposure is ascertained in aggregate for an entire subcohort, rather than individually. As an alternative approach for determining exposure, two studies investigated whether children of pregnant women receiving the polio vaccine had an increased risk of developing malignant tumors (Heinonen *et al.*, 1973; Farwell *et al.*, 1979). Finally, more recently three studies have directly screened human sera to determine the presence of anti-SV40 antibodies by serology or of target tissue for SV40 DNA sequences by amplified or nonamplified DNA hybridization techniques (Procopio *et al.*, 2000; Carter *et al.*, 2003; Rollison *et al.*, 2003).

The relationship of poliovirus vaccination and cancer incidence or mortality

Nine studies compared the rate of cancer incidence or cancer death among individuals born during the years of SV40 contamination of polio vaccine (1955–1963) and individuals born before or after the polio vaccine contamination period. Two studies found an increased risk of cancer among children vaccinated with polio vaccine. A hospital-based case–control study, conducted by Innis *et al.* in Australia, compared the immunization status of 816 children with various malignancies to 816 controls matched on age, sex, and hospital admission (Innis, 1968). This study found that children of all ages inoculated with polio vaccine had a 40% greater 10-year risk of developing cancer. This increase in risk was most prominently observed in children over 1 year of age (69% greater risk), while infants did not show any increase in cancer risk. Since vaccination status was obtained from medical records and the actual SV40 contamination status of the polio vaccine was not known, these results may be biased by the potential misclassification of SV40 exposure. The selection of controls is also of concern if cases and controls do not come from the same catchment area. This might occur if

the hospitals are specialized cancer centers, which would imply that the cases would have originated from a much broader area than the neighboring controls. In a study conducted in Denmark, Engels *et al.* (2003a) found that ependymoma incidence was 2.6 times higher for children aged 0–4 years born between the years 1955 and 1962. However, the authors pointed out that the incidence of ependymoma peaked in 1969, when SV40 contamination of polio vaccines cleared. This suggests that the increased incidence of ependymoma may not be due to SV40, but some other factor; or alternatively, but rather unlikely, that the association would be of very short latency.

Epidemiological studies mostly sponsored by the US National Cancer Institute have demonstrated an increased incidence of cancer in birth cohorts exposed to the SV40-contaminated vaccines, but none showed statistical significance (Fraumeni *et al.*, 1963; Strickler *et al.*, 1998; Fisher *et al.*, 1999; Carroll-Pankhurst *et al.*, 2001; Engels *et al.*, 2003a, b). Table 1 highlights the study characteristics and findings. Three studies conducted in the US found elevated risks of death due to cancer in people born during the period when vaccines were deemed contaminated. Fraumeni *et al.* (1963) published the first epidemiological study, which provided US cancer mortality rates in 1956 and 1959 and estimated the per capita dose of polio vaccine containing SV40 in 16 states in 1955. The risk of mortality due to all cancers (except leukemia) was similar in 1956 and 1959. If we compare the mortality risk due to all cancers (except leukemia) in exposed and unexposed cohorts in 1959, the RR is 1.33, while a comparison of deaths due to leukemia shows a 50% risk increase in leukemia mortality. Carroll-Pankhurst *et al.* (2001) used the National Death Index (NDI) to compare the observed and expected causes of death in people who had presumably received SV40-contaminated poliovirus vaccine as newborns in 1960 or 1962 and found a 26% increase in mortality risk due to all cancers. By using data from the SEER program and from US national mortality statistics, Strickler *et al.* (1998) showed that exposed infants had three times greater risk of death due to mesothelioma and children had a 2.45 times greater risk than the presumably unexposed cohorts. This increase in risk was not observed in deaths due to ependymoma and osteosarcoma. Fisher *et al.* (1999) found an elevated risk of some cancers in people born during the contaminated years. Although not provided in the paper, we were able to calculate the RRs of 1.25 (95% confidence interval (CI): 0.6–2.5) and 3 (95% CI: 0.6–14.8) for ependymoma and mesothelioma, respectively, using the authors' data. However, an elevated risk is not observed when all cancers are taken into account (RR=0.89, 95% CI: 0.86–0.92), which could have been due to a dilution effect of the excess risks by combining cancers potentially linked with SV40 with a preponderance of neoplasms unrelated to the virus. Other studies did not find any excess risk of mortality or incidence in individuals exposed to SV40 (Mortimer *et al.*, 1981; Engels *et al.*, 2003a, b).

Table 1 Characteristics of epidemiological studies of SV40 and cancer published until April 2004

Study (first author and year)	Geographical area	Study design	Source population	Exposure assessment ^a	Cancer type	Outcome	RR (95% CI)
Carroll-Pankhurst <i>et al.</i> (2001) ^b	USA	Cohort	Population	Vaccination era	All cancers	Death	1.26 (0.4–3.9)
Carter <i>et al.</i> (2003) ^b	USA	Case-control	Hospital	Laboratory test	Osteosarcoma	Occurrence	0.30 (0.1–1.0)
					Prostate cancer	Occurrence	0.65 (0.1–2.7)
Engels <i>et al.</i> (2003b)	Denmark	Cohort	Population	Vaccination era	Non-Hodgkin's lymphoma	Occurrence	0.97 (0.8–1.2)
Engels <i>et al.</i> (2003a)	Denmark	Cohort	Population	Vaccination era	All cancers	Occurrence	0.86 (0.8–0.9)
					Mesothelioma	Occurrence	0.48 (0.1–1.8)
					Ependymoma	Occurrence	1.25 (0.8–2.0)
					Osteosarcoma	Occurrence	0.95 (0.5–1.7)
			Aged 0–4	Vaccination era	All cancers	Occurrence	1.01 (0.9–1.2)
					Ependymoma	Occurrence	2.59 (1.4–4.9)
Farwell <i>et al.</i> (1979) ^b	USA	Case-control	Population	In utero	CNS tumors	Occurrence	2.15 (0.8–6.5)
Fisher <i>et al.</i> (1999) ^b	USA	Cohort	Population	Vaccination era	All cancers	Occurrence	0.89 (0.86–0.92)
					Ependymoma	Occurrence	1.25 (0.6–2.5)
					Osteosarcoma	Occurrence	1.07 (0.7–1.6)
					Mesothelioma	Occurrence	3.00 (0.6–14.8)
Fraumeni <i>et al.</i> (1963) ^b	USA	Cohort	Population	Vaccination era	All cancers (except leukemia)	Death	4.00 (0.5–35.8)
					Leukemia	Death	1.50 (0.7–3.5)
Heinonen <i>et al.</i> (1973) ^b	USA	Cohort	Population	In utero	All cancers	Occurrence	2.48 (1.1–5.6)
Innis (1968) ^b	Australia	Case-control (hospital)	Infants	Vaccination era	All cancers	Occurrence	1.04 (0.6–2.0)
			Children		All cancers	Occurrence	1.69 (1.3–2.3)
			All ages		All cancers	Occurrence	1.40 (1.1–1.8)
Rollison <i>et al.</i> (2003)	USA	Nested case-control	Population	Laboratory test	CNS tumors	Occurrence	1.00 (0.3–3.3)
Strickler <i>et al.</i> (1998)	USA	Cohort (population)	Infants	Vaccination era	Ependymoma	Death	1.06 (0.6–1.7)
			Children		Ependymoma	Death	0.98 (0.6–1.7)
			Infants	Vaccination era	Osteosarcoma	Death	0.87 (0.7–1.1)
			Children		Osteosarcoma	Death	0.85 (0.6–1.2)
			Infants	Vaccination era	Mesothelioma	Death	3.00 (0.7–13.1)
			Children		Mesothelioma	Death	2.45 (0.5–12.0)
Strickler <i>et al.</i> (1999)	USA	Cohort (population)	Infants	Vaccination era	Medulloblastoma	Occurrence	0.74 (0.6–1.0)
			Children		Medulloblastoma	Occurrence	0.56 (0.3–0.9)

^aSee the text for details on the method used for assessing exposure. ^bRate ratio estimates and corresponding 95% confidence intervals were calculated using the data provided in the article

The relationship of SV40 exposure in utero and childhood malignancy

Two studies were undertaken to investigate the relationship of SV40 exposure of children *in utero*, by polio vaccine inoculation of their mothers during pregnancy, and the increase of childhood malignancy (Heinonen *et al.*, 1973; Farwell *et al.*, 1979) (Table 1). To examine this relationship, Heinonen *et al.* conducted a follow-up study of 50 897 pregnancies and found that children whose mothers were vaccinated during pregnancy with killed polio vaccine had a greater risk than unexposed children (RR = 2.45, 95% CI: 1.10–5.58) for the development of childhood malignancy. The RR was even greater for the children of the 6834 mothers immunized during the first 4 months of pregnancy (rates of 13.2 *versus* 3.1 per 10 000; RR = 4.3, $P < 0.01$), or during the first 3 months (15.6 per 10 000), with an RR = 5, $P < 0.01$. As well, the study found that no malignancies occurred among the children born to 3056 women who received oral polio vaccine. The authors suggested that SV40 could be a possible cause of the increased risk in childhood cancer; however, this study was not designed to confirm this relationship. Cases of malignancy may have been missed since the investigators could only

obtain mortality data on children after 1 year of follow-up and no information could be obtained from abortions. This may have resulted in selection and misclassification biases, which would have distorted the study estimates. Misclassification of exposure may also occur since children were likely vaccinated after birth. If the mother of these children were not vaccinated, then the children would be considered unexposed, irrespective of their own immunization status.

In a case-control study done in 1979, Farwell *et al.* used the Connecticut Tumor Registry to identify 120 children, born in 1956–1962, who had developed central nervous system (CNS) neoplasms before 20 years of age. Of these, 40 children were selected and matched with two controls by sex, date of birth, and town of birth. Vaccination status of the mothers was obtained from a questionnaire sent to the obstetricians who delivered the children. Among the 52 cases, 19 (37%) children were exposed to SV40 compared to the 38 controls, where eight (21%) were found to be exposed. This study found that exposed children had more than twice the risk of developing CNS tumors than unexposed children; however, the results were not statistically significant. By matching on date of birth, the authors were able to control for the cohort effect. But as in the Heinonen

et al. (1973) study, misclassification of exposure is likely, since the children may have been exposed to SV40 from their own vaccination after delivery.

Epidemiological studies using serologic or molecular techniques to detect SV40

Recent epidemiological studies have sought to better ascertain actual SV40 exposure by using molecular techniques to detect SV40 DNA sequence or Tag protein in the study subjects or serologic techniques to detect anti-SV40 antibodies. Depending on the sensitivity and specificity of the tests being used, the problems of exposure misclassification, encountered in previous studies, may be considered as minimized.

A case-control study by Carter *et al.* (2003) did not find a significant increase in osteosarcoma or prostate cancer risk when they screened serum samples for SV40 virus-like particles. Rollison *et al.* (2003) measured SV40-neutralizing antibodies by using plaque neutralization assays of cases and their matched controls and found no increase in risk of CNS tumors.

Although not germane to the argument of an etiologic association, a cohort study of mesotheliomas conducted in Italy, using polymerase chain reaction (PCR) and southern blot analysis to identify SV40 DNA found a 4-fold increase in the risk of death from mesotheliomas of biphasic or sarcomatous morphology in patients with SV40 positive tumors compared with those with negative samples (Procopio *et al.*, 2000).

Global estimate of RR for SV40 and cancer

In order to obtain insights into the general distribution and tendency of RR estimates among the several studies reporting on the SV40-cancer association, we conducted a crude meta-analysis to summarize the main findings of all epidemiologic investigations. Studies were included if they met the following criteria: (1) the exposure measured was the infection of SV40 or a proxy of SV40 infection, (2) the outcome under investigation was the incidence or prevalence of human cancers or cancer death, (3) the SV40 exposure groups were clearly identified, and (4) the cancer outcome groups were clearly identified. We sought the following information from each article: authors; year of publication, geographic region; study design; number and characteristics of the cancer cases and controls (or population); type of cancer; exposure definition; and cancer outcome (incidence or death). When available, covariate-adjusted RR estimates (rate ratios or odds ratios depending on study type) were extracted and used in the calculation of a global effect measure. To maintain homogeneity among all the studies being compared, we identified the main findings as the most general results before stratification by age group or cancer type. In the event that a study had more than one main finding, we selected the finding based on the larger sample size. Both fixed (Mantel-Haenszel method) and random effects models (DerSimonian-

Laird method) were used to calculate the summary risk ratios, but only the latter was reported to account for the differences in sampling within studies and the variation in effect across studies. This is a prudent assumption given the different study characteristics, as seen in Table 1.

A summary effect of five studies did not support the hypothesis that SV40 exposure increases the overall risk of cancer or cancer mortality. The Cochran's Q test was used to test homogeneity of the summary risk estimate. The pooled estimate yielded an RR of 0.95 (95% CI: 0.85-1.07). There was evidence of heterogeneity (P -value < 0.0001), which was not surprising given the substantial methodological differences across studies and populations studied. As seen in Figure 1, the data used to calculate the pooled estimate are heavily influenced by two negative studies (Fisher *et al.*, 1999; Engels *et al.*, 2003a). This is an important consideration because both studies contributed 40% of the entire weight of the analysis. It should be noted that the results from this pooled analysis represent a very broad estimate of the findings and should be interpreted with caution. Analyses stratified on cancer type and covariates indicative of study design and exposure assessment approach are required before any firm conclusions can be reached. A stratified analysis, based on three studies (Strickler *et al.*, 1998; Fisher *et al.*, 1999; Engels *et al.*, 2003a), found that there was an elevated but statistically nonsignificant increase in the RR of mesothelioma for individuals exposed to SV40 (RR = 1.42, 95% CI: 0.43-4.68). However, more elaborate meta-analyses and meta-regression techniques should be applied in order to obtain an improved overview of the validity of the association for SV40 and individual cancer sites while controlling for methodological differences across studies.

Challenges in epidemiological studies

The primary issue of concern in all the aforementioned studies is the virtual inability to clearly distinguish SV40 infected and noninfected cohorts (IOM, 2002; Carbone *et al.*, 2003). The best distinction that can be made by most studies is based on the separation of pre-1963 and post-1963 polio vaccine cohorts; the validity of these studies rests on the main assumption that individuals who received polio vaccine between 1955 and 1963 were infected with SV40. However, misclassification of SV40 exposure is likely since only 30% of the polio vaccines were contaminated with SV40. Another source of misclassification may come from the assumption that contaminated polio vaccine was the only source of SV40 infection. In fact, there is evidence of SV40 infection in individuals born after the polio vaccines were cleared of SV40 (Butel and Lednicky, 1999). Since the risk of SV40-infected polio vaccines changed before and after 1963, there is a concern that secular trends were introduced in the studies. Individuals who received the vaccine later will have been less likely to be exposed to SV40.

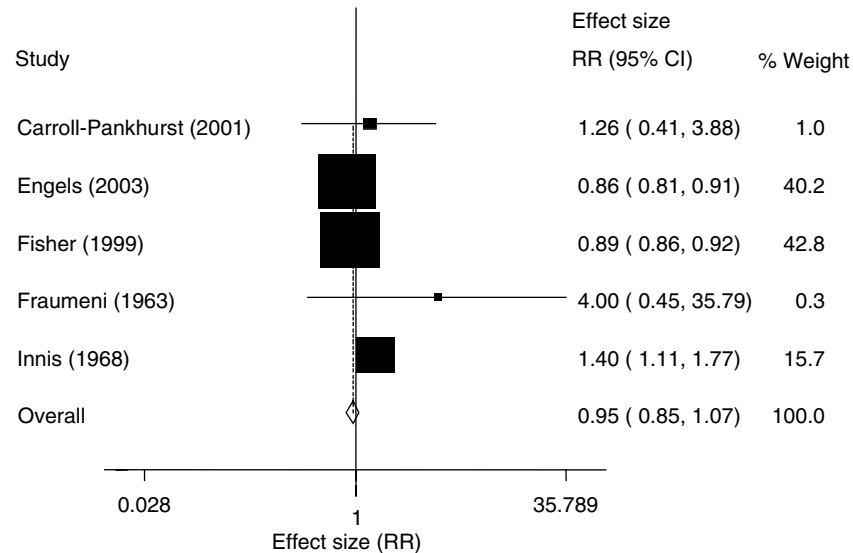


Figure 1 Pooled RR estimate for the association between presumed SV40 exposure and all cancers

Also contributing to the heterogeneity in results is the substantial variability in the level of contamination of polio vaccine lots, from hundreds to millions of SV40 particles (Carbone, personal communication). The likelihood of a productive infection will be influenced by the initial dose. Once productive infection starts, millions of SV40 particles are made in the permissive human cells, but a threshold of a sufficiently large viral dose will be necessary to enable the onset of a productive infection (Gazdar *et al.*, 2002). Therefore, even if one is able to determine that a given cohort received contaminated vaccines, it is still necessary to ascertain how contaminated the vaccine was.

Historical improvements in cancer diagnosis and treatment may have also contributed to the heterogeneity of results over time. Given that progress in therapy has been the greatest for pediatric malignancies, any study that attempts to make inferences on the basis of mortality trends over decades will be biased towards a null effect because any increases in incidence rates are largely offset by the decreases in mortality. Finally, all studies are limited by the rarity of cancers under investigation. The low numbers of cancer cases or cancer deaths do not permit robust estimation of RRs. A case-control study is an efficient design for the study of rare cancers but, unfortunately, it is a less than ideal study design to probe for the risk effects of possibly long or variable latency, as may be the case for SV40 in mesothelioma (Puntoni *et al.*, 2003).

Another issue that is germane to the assessment of the association is the challenge of exposure measurement. The evidence base for a causal relation between SV40 and neoplasms such as mesothelioma relies on the demonstration of the virus in tumor tissue. The

contention that false-positive results may have plagued most studies has been appropriately challenged by an inter-laboratory investigation (Testa *et al.*, 1998) that used state-of-the-art methods and stringent quality control measures to show that the virus is unequivocally present in the target mesothelioma tissue and sufficiently infrequent in cells from adjacent areas (Gazdar *et al.*, 2002; Cerrano *et al.*, 2003). Such methods, which incorporate direct DNA detection and functional assays to demonstrate that virus is not merely a contaminant, are necessary for a new generation of epidemiologic studies that should attempt at assessing with minimal biases the nature of association at the population level. In fact, the undertaking of new studies with high-quality exposure ascertainment should be a higher priority than revisiting the descriptive epidemiologic data by vaccination cohorts, which is irremediably plagued by validity problems. The latter research undertaking will remain useful, however, if future studies of vaccination cohorts attempt to explore the wide geographical variability in the timing of clearance of SV40 from vaccine lots manufactured in different countries. Regardless of the approach used, issues of properly defining the latency for SV40-induced carcinogenesis will remain an intellectually challenging opportunity for innovative research in the field.

Acknowledgements

We are grateful to Professor Michele Carbone, Loyola University, for valuable technical comments and editorial advice. Mr Tam Dang-Tan and Professor Eduardo L Franco are recipients of Doctoral Fellowship and Distinguished Scientist awards, respectively, from the Canadian Institutes of Health Research.

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