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Patterns of polyomavirus SV40 infections and associated cancers in humans: a model

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Abstract

A model is described that predicts patterns of polyomavirus SV40 infections and associated cancers in humans. The model proposes that SV40 infections were established in humans primarily by exposure to contaminated oral poliovaccines and that infections persist today in geographic regions where poor sanitation or living conditions allow maintenance of infections transmitted by a fecal/urine–oral route. Predictions from the model include that SV40 infections and virus-associated malignancies will be restricted geographically and demographically and that in developed countries, such as the US, SV40 prevalence rates will be generally very low. The model highlights the importance of selection of populations for investigations of SV40 human infections. This model can explain inconsistencies in the published literature of SV40 infections in humans and can guide the design of future studies.

Introduction

The origins of polyomavirus SV40 are closely linked to the development and production of several viral vaccines in the 1950s and early 1960s, most predominantly the inactivated (IPV) and live attenuated oral (OPV) poliovaccines. These vaccines were produced using primary cultures of monkey kidney cells which were sometimes carrying unrecognized infections by SV40. These contaminated vaccines were used in humans prior to the discovery of SV40, creating opportunities for introduction of SV40 as a cross-species infection into vaccinees. As SV40 has oncogenic potential in animal models and transforming ability in cell cultures, a question of public health significance is whether those vaccine exposures established SV40 as an infectious pathogen in humans.

SV40 markers have been detected in human specimens, including human cancers, dating back to the 1970s. More recent studies using molecular techniques to detect the presence of SV40 DNA or antigen expression in human specimens have yielded variable results. Seroprevalence estimates of human infections have also varied. Because of these inconsistent findings, no consensus has emerged about the role of SV40 as a potential human pathogen.

A model is presented here that can explain many of the discrepant results and guide future investigations to better define the prevalence of SV40 infections and the possible role of the

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virus in human neoplasia. Re-evaluation of reported data from the perspective of the model can resolve inconsistencies in the published literature.

Model to predict contemporary SV40 infections in humans

The model can be stated as follows: SV40 infections were established in humans primarily by exposure to contaminated oral poliovaccine and that infections persist today in certain geographic regions where poor sanitation or living conditions allow maintenance of cycles of infections transmitted by a fecal/urine–oral route. The model is summarized schematically in Figure 1.

This model postulates that seeding of SV40 human infections was mediated primarily by exposure to contaminated OPV rather than exposure to the killed poliovaccine. One consideration underlying this premise was the amount of live SV40 present in the different vaccines. Not all lots of IPV were contaminated as not every preparation of primary monkey kidney cells contained SV40; it has been estimated that ~30% of IPV lots contained residual infectious SV40. When present, the titer of live SV40 in IPV that had escaped inactivation was probably on the order of 10^2–10^3 infectious units per ml [1]. In contrast, live SV40 would have been present in each OPV preparation as seed stocks were contaminated and SV40 titers in OPV lots were higher, ranging from ~10^4–10^6 infectious units per ml, as no inactivation step was involved in vaccine production [1]. A higher inoculum presumably would have increased the chances of successfully establishing an SV40 infection in a recipient. A second contributory factor was probably the route of exposure. Evidence suggests that polyomaviruses can be transmitted by the fecal/urine–oral route. SV40 and other polyomaviruses have been found in stool samples, in addition to urine [2–6], and human polyomaviruses are found in sewage and in human feces-contaminated environmental waters [7–10]. In addition, 19% of newborn children and 15% of infants 3- to 6-months-old at the time of receiving OPV were shown to excrete infectious SV40 in their stools for up to 5 weeks after vaccination [11]. Thus, oral administration of OPV likely reflected a more natural route for transmission of infection by SV40 than the intramuscular inoculation of IPV. Whereas exposure to IPV may have initiated some SV40 infections, it was in all likelihood less effective at doing so than OPV.

The dynamics and maintenance of SV40 human infections can be envisioned based on other infectious agents spread by the fecal–oral route. Well-characterized examples include poliomyelitis before vaccination, hepatitis A virus, and *Helicobacter pylori* [12–17]. As standards of living increase, infection rates for those agents decrease. In environments with lack of clean water, inadequate sewage disposal, poor household hygiene, and overcrowding, infections are common in infants and young children, leading to a relatively high frequency of seroprevalence. These conditions occur most often in developing countries, although similar pockets of poor hygiene or living conditions can be found in developed countries. As standards of living and sanitation levels improve, fewer individuals are exposed to the agent, resulting in lower prevalence rates. Thus, antibody prevalence to the agent in a population group will often reflect the level of hygiene in the living conditions of that population (Figure 1).

Polyomaviruses establish persistent infections in their hosts, in contrast to poliovirus and hepatitis A. This could result in sporadic shedding of SV40 in feces and/or urine over long periods of time.

History of use of SV40-contaminated vaccines

Potentially contaminated poliovaccines were used mainly from 1954 to 1963. Vaccines were supposed to be free from SV40 after mid-1961, but previous lots of vaccine were allowed to

be used until stores were exhausted. There is evidence that the Russian OPV was very likely contaminated until the late 1970s [18]. IPVs were widely used in the US and other countries starting in 1955. Large field trials with candidate live attenuated OPVs were carried out from 1958 to 1960 (Table 1). Major trials with OPV were not performed in the US because prior use of IPV had resulted in polio antibodies in many individuals. The Sabin candidate vaccine strains were tested at several sites in Mexico and very widely throughout the USSR. The Lederle candidate vaccine strains were tested in Central and South America and in Florida. The Koprowski candidate vaccine was tested in Poland, Croatia, and the Belgian Congo [19–23]. Other vaccine tests were conducted as well. The Sabin vaccine strains were concluded to be less virulent and were selected for licensing in the US in 1961 and 1962 and studies of the other candidate vaccines were discontinued. The Russian vaccine was shared on occasion with other countries, such as Japan and Egypt. A unique feature in Egypt was an antischistosomiasis campaign in place until the 1980s. Repeated intravenous injections of a compound to kill blood flukes were given on mass treatment days, providing a setting in which blood-borne pathogens could be transmitted if injection equipment was not adequately sterilized. This parenteral antischistosomal therapy is believed to be largely responsible for the spread of hepatitis C virus in Egypt [24] and could theoretically have contributed to the spread of SV40. Some countries did not use any contaminated OPV, while the status of OPVs used in other countries is uncertain.

The US military used SV40-contaminated adenovirus vaccines to protect recruits against acute respiratory disease. This provided another source of human exposure to SV40 [25]. Several hundred thousand military recruits were vaccinated between 1957 and 1961 with those contaminated vaccines before their use was discontinued [1,26].

Predictions of the model

This model predicts that in developed countries, such as the US, prevalence rates for SV40 infections will be very low. Even if SV40 infections were seeded by contaminated poliovaccines 50 years ago, most virus transmission would have been interrupted by good sanitation conditions. Based on the model and the property of persistent infections by polyomaviruses, it is possible that immigrants from high-prevalence regions could take SV40 infections with them to low-prevalence areas and might transmit the infection to family members there. The model also predicts that SV40 infections and virus-positive malignancies will be restricted both geographically and demographically and will not be evenly distributed worldwide. Those with detectable infections will often have links to specific populations and locations. This model articulates the difference in expected patterns of findings between studies of SV40 and those of a cancer virus that is distributed worldwide, such as human papillomavirus. It highlights the importance of selection of study populations for investigations of SV40–human infections.

Evidence of SV40 infections in humans

Many reports in the literature over the last two decades have detected SV40 markers in noncancer samples from healthy children and adults (Box 1), including in urine, stool, blood, and lymphoid tissues [23]. Studies have included subjects from the US, Europe, Japan, Egypt, and Russia. The prevalence of SV40 infections appears to be low in randomly collected human samples. It is noteworthy that individuals born long after the use of contaminated vaccines have displayed evidence of infection, showing that the virus is transmissible among humans.

Box 1

Evidence of SV40 infections in humans

Evidence that SV40 is causing human infections includes the detection of infectious virus excreted in the stool by infants fed contaminated poliovaccine and the detection of SV40 DNA in urine and stool samples from children, in stool and blood samples from healthy adults, in lymphoid specimens from healthy children, and in transplanted kidneys in children. Serological surveys have found SV40 antibodies in both children and adults. Evidence of infection is found in individuals too young to have been exposed to contaminated vaccines, indicating on-going cycles of infections in humans. Evidence linking SV40 to human cancer includes detection of SV40 DNA in human tumors (predominantly brain, bone, non-Hodgkin lymphoma, and mesothelioma tumor types), T-antigen expression in tumors, and the isolation of infectious virus from a pediatric brain tumor. However, the observed prevalence of SV40 has varied widely among reported studies and the associations detected with tumors do not prove causality. (See Butel [23,34] for original references.)

Serological findings

Serological assays are frequently used to determine the prevalence of viral infections. Estimates of SV40 prevalences have been from 2% to greater than 10% in different groups [23,27,28]. Neutralization assays are highly specific, but are too labor-intensive and time-consuming to apply to large population surveys for SV40. Enzyme immunoassays based on virus-like particles (VLPs) lend themselves to testing large numbers of serum samples. However, those assays detect all binding antibodies, including nonneutralizing antibodies and those that recognize cross-reactive epitopes on polyomaviruses BKV and JCV. Absorption of sera with BKV or JCV VLPs often removes much of the SV40 reactivity. A new immunoassay based on peptides specific for SV40 VP1 and VP2/3 detected antibodies in healthy blood donors in Italy [29]. These antibodies appeared to be specific as they reacted with two different SV40 peptides. SV40 antibodies in humans are usually low-titered, perhaps reflecting low-grade viral replication or a weak specific immune response. The majority of reported serological studies have involved populations from countries with high standards of living (US, UK). The model predicts that those populations would be expected to have a low frequency of SV40 antibodies.

We have recently analyzed archival sera collected in the 1990s in Houston, TX, from women visiting the public hospital. The goal was to compare SV40 seroprevalence in different ethnic groups. Caucasians and African-Americans displayed similar low rates of neutralizing antibody (5%, 6%), whereas Hispanics showed a significantly higher prevalence of SV40 antibodies (23%) (unpublished). There are many immigrants in Houston from Mexico and Central America and they often use the public hospital to access medical care. A possible explanation of the results is that the Hispanic group included immigrants or their parents from higher prevalence areas in Latin America who had been infected with SV40 in their previous environment. The study provides evidence that SV40 seroprevalence can vary among population groups. Seroprevalence studies need to be carried out in other populations predicted to be at higher risk of SV40 infections to more clearly establish the frequency of human infections [30].

Association of SV40 with human cancer

A number of studies have found evidence linking SV40 with human tumors, with the most commonly associated tumor types being brain tumors, mesotheliomas, osteosarcomas, and

lymphomas [23,31–34]. Studies involving lymphomas are summarized in Table 2. The listed studies all investigated primary cancer samples (not cell lines), used PCR-based assays to detect viral DNA, and analyzed control tissue specimens (not cell lines) in parallel. The table reveals inconsistency in findings. Overall, SV40 was detected significantly more often in cancer than in controls, but the percent viral positivity of cancers ranged from 56% to 0% in different studies. In the studies that reported SV40-positive findings, the percentage of positive lymphoma samples was much higher than for the control samples, ruling out contamination as an explanation for the results. Based on the proposed model, the variable results reported could reflect, at least in part, the geographic origin of specimens analyzed. For example, the study from Egypt reported a prevalence of SV40 positivity of over 50%; the Russian OPV had been used in Egypt [35] that also provided parenteral antischistosomal therapy. Although the US had limited exposure to contaminated OPV, the positive US reports (19–43%) described studies carried out in Texas and California, states with significant numbers of immigrants from Mexico and Central America. Archival samples analyzed in those studies may have included persons originally from high-prevalence areas. Studies from Japan found a low prevalence of SV40 DNA in lymphomas (2%, 11%). The Russian vaccine had been used in Japan approximately 40 years earlier, but the relatively good standard of living in that country probably reduced transmission and maintenance of SV40 infections over time. Negative findings have been reported from the UK and Tasmania; as far as is known, no contaminated OPV was used in those countries. The status of poliovaccines used in some of the other countries is unclear.

A recent study tested the hypothesis that the frequency of SV40 association with lymphomas varies among different populations [36]. We obtained archival samples from two hospitals in Houston, TX — the veterans hospital (for military veterans) and the public hospital (for people with no insurance or limited ability to pay for care). Tumor pathologies were similar, but patient demographics differed significantly between the lymphoma patients from the two hospitals, with more Hispanics represented in the public hospital group. Lymphoma specimens from the public hospital were 23% SV40 positive, whereas those from the veterans hospital were only 3% virus positive ($p<0.0001$); control samples were negative. All the specimens were subjected to the same laboratory procedures, thereby ruling out technical variability as an explanation for the results. This study illustrated that, as predicted by the model, the prevalence of SV40 tumor positivity can vary significantly, depending on the sources of specimens.

We have also analyzed archival tissue samples from Costa Rica, a region known to have been exposed to contaminated OPV (Box 1; Table 1). In an analysis involving more than 200 specimens, lymphomas were found to be 20% SV40 positive whereas control tissues were negative [37]. SV40 T-antigen expression was detected in SV40 DNA-positive tumors. Thus, SV40-positive cancers can be found in a region previously exposed to SV40-contaminated OPV, compatible with the proposed model.

However, as with any cancer-associated virus, detection of the virus in human tumors does not prove that the virus caused those malignancies. Several different criteria need to be met before etiology is established [34].

Epidemiology

There is currently no epidemiological evidence supporting a link between SV40 infections and human cancers [30,38–42]. However, most reported studies have been based on data from countries with good sanitation and hygiene, predominantly the US, and designed to examine whether potential exposure to contaminated IPV resulted in an increased risk of cancer. No associations were found. Because of the focus on IPV and the analysis of data

obtained from developed countries, such negative associations are predicted by the model. It would be informative to carry out epidemiological studies on populations exposed to contaminated OPV in regions expected to maintain cycles of infections by SV40.

Conclusions

The model described here proposes that patterns of SV40 infections in humans reflect past exposure to SV40-contaminated oral poliovaccines and poor sanitation or living conditions that allow transmission of viral infections by a fecal/urine–oral route. This model is compatible with known SV40 biology and historical usage of contaminated vaccines. It can explain apparent inconsistencies in published findings and can be tested using appropriately designed studies.

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Highlights

- The model proposes that human infections by polyomavirus SV40 were established primarily by the use of contaminated oral poliovaccines and that infections persist today in regions where conditions allow transmission of virus by a fecal/urine–oral route.
- SV40 infections will be restricted geographically and demographically and prevalence will be low in developed countries.
- This model can explain many of the inconsistencies in the published literature of human infections by SV40.

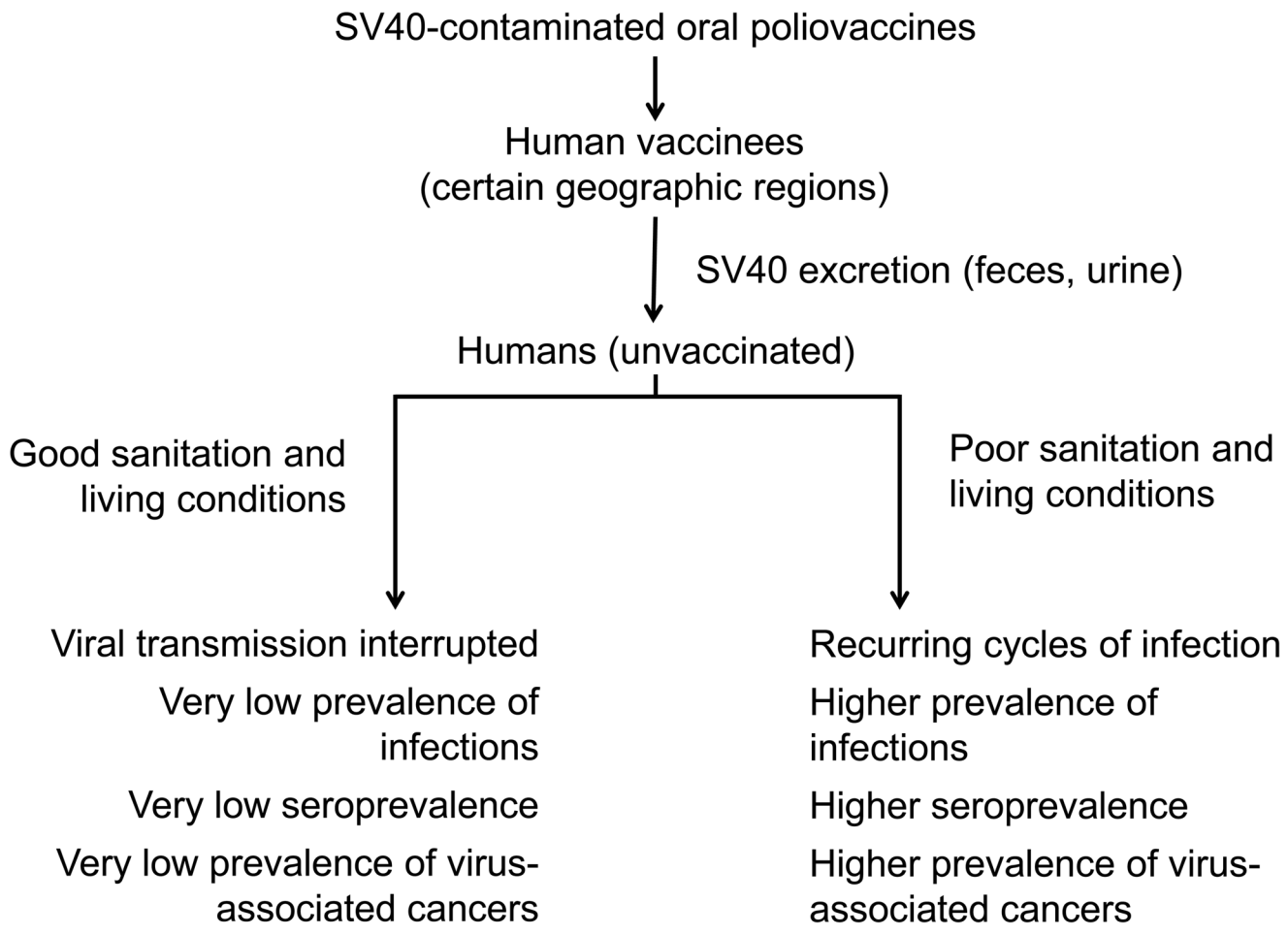

Figure 1.
Model of contemporary SV40 infections and association with cancer in humans. The diagram illustrates the proposal that SV40 infections were established in humans primarily by exposure to contaminated oral poliovaccines and that infections persist today in geographic regions where poor sanitation or living conditions allow maintenance of cycles of infections transmitted by a fecal/urine–oral route. Predictions related to the prevalence of SV40 infections in different locations are listed.

Table 1

Examples of estimated usage of SV40-contaminated oral poliovaccines[a,b]

Country	Source of OPV[c]	Date of usage	Estimated no. of vaccinees
Belgian Congo	CHAT	1958	240,000
Colombia	Lederle	1958–1959	140,000
Costa Rica	Lederle	1959–1960	272,000
Croatia	CHAT	1960	1.3 million
Czechoslovakia	Sabin	1958–1959	143,000
Egypt[d]	Russian	NA[d]	NA
Hungary	Russian	1960–1978 (est.)	2.5 million (1960)
Japan	Russian	1961–1963	~15 million
Mexico	Sabin	1958–1959	308,000
Nicaragua	Lederle	1958–1959	42,000
Poland	CHAT	1959	9 million
Uruguay	Lederle	1958–1959	218,000
USA, Cincinnati	Sabin	1960	181,000
USA, Miami	Lederle	1959	410,000
USSR	Russian	1959–1978 (est.)	Many millions

[a] See Butel [23,34] for original references. The list is not comprehensive.

[b] Mainly children were vaccinated.

[c] OPV, oral poliovaccine; CHAT, Koprowski candidate vaccine that was based on the same poliovirus strains as Lederle Laboratories' candidate vaccine; Russian OPV was based on Sabin vaccine virus strains.

[d] NA, not available. Parenteral antischistosomal therapy was provided in Egypt until the 1980s.

Table 2

Detection of SV40 DNA by PCR in Lymphomas[a]

Author, year	Country	SV40 DNA by PCR [no. positive/no. tested (%)]	
		Lymphoma	Control
Amara et al., 2007	Tunisia	63/108 (56)	4/60 (6)[b]
Zekri et al., 2007	Egypt	85/158 (54)	4/34 (12)[b]
Shivapurkar et al., 2002	US	29/68 (43)	5/120 (4.2)
Vilchez et al., 2002	US	64/154 (42)	0/240 (0)
Shivapurkar et al., 2004	US	33/90 (36)	1/56 (1.2)
Meneses et al., 2005	Costa Rica	30/125 (24)	0/91 (0)
Vilchez et al., 2005	US	12/55 (22)	0/19 (0)
David et al., 2001	US	15/79 (19)	19/187 (10)[b]
Martini et al., 1998	Italy	11/79 (14)	3/50 (6)[b]
Chen et al., 2006	Taiwan	13/91 (14)	0/106 (0)
Nakatsuka et al., 2003	Japan	14/122 (11)	3/64 (4.7)[b]
Capello et al., 2003	Spain, Italy	17/500 (3)	0/15 (0)
Daibata et al., 2003	Japan	3/125 (2)	0/31 (0)
MacKenzie et al., 2003	UK	0/152 (0)	0/45 (0)
Sui et al., 2005	Tasmania	0/50 (0)	0/50 (0)
Schüler et al., 2006	Germany	0/77 (0)	0/61 (0)
TOTAL		389/2033 (19.1)[c]	39/1207 (3.2)[b,c]

[a] See Butel [34] for original references.

[b] Among control samples positive for SV40 were 28 blood samples from noncancer patients or healthy individuals.

[c] $p<0.001$ (Z test of proportions).