

SV40 Enhances the Risk of Malignant Mesothelioma among People Exposed to Asbestos: A Molecular Epidemiologic Case-Control Study

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Abstract

We conducted a case-control study on asbestos exposure and presence of SV40 in tumor samples of malignant mesotheliomas (MMs) and bladder urotheliomas (BUs). PCR analysis revealed the presence of SV40 DNA (SV40+) in eight (42.1%) MMs and 6 (33.3%) BUs. The odds ratio for MM Asb- and SV40+ was 0.4 [95% confidence interval (95% CI), 0.03-4.0], for Asb+ and SV40- was 3.6 (95% CI, 0.6-21.0), and for Asb+ and SV40+ was 12.6 (95% CI, 1.2-133.9). Our results suggest that SV40 increases the risk of MM among individuals exposed to asbestos. (Cancer Res 2005; 65(8): 3049-52)

Introduction

Asbestos is the major cause of malignant mesothelioma (MM) in the Western world. Only a relatively small percentage of people who have been exposed to asbestos during their lifetime will develop MM (1), suggesting that alternative carcinogenic agents could have a contributory role. SV40 is a DNA tumor virus encoding two proteins responsible for its oncogenic potential: the large T antigen (Tag) and the small t antigen (tag). SV40 Tag is directly mutagenic as it causes structural and numerical karyotype alterations (1). Tag binds and inhibits p53 and other Rb family proteins blocking the related apoptotic pathways (2). Tag stimulates the expression of key cellular growth regulators like hepatocyte growth factor, vascular endothelial growth factor (VEGF), and Notch 1, thus promoting cell growth. Small t antigen enhances Tag activities and inhibits protein phosphatase 2A, leading to activator protein-1 (AP-1) activation. Moreover, SV40 induces telomerase activity (3). If injected in hamsters' pleural cavity, SV40 induces MM in 100% of animals (4). This large number of biomolecular findings contrasts with a substantial lack of epidemiologic evidence. To date, not all major epidemiologic

studies have been able to attribute a causative role to SV40 in MM development (reviewed in ref. 5). Most were ecological studies with SV40-positive cohorts defined on the probability of being infected with SV40-contaminated polio vaccines. These studies did not take into consideration the possibility that SV40 could be transmitted among humans like other viruses. The possible mechanisms of transmission remain to be elucidated, but it is well known that humans infected with SV40 excreted infectious virus with the feces (6). Others were small-scale studies. In addition, the authors did not evaluate the possibility that the virus acts in combination with other agents, such as asbestos, and not as an ultimate carcinogen. Finally, the length of follow-up of most epidemiologic longitudinal surveys could not take into consideration the average natural latency of MM, which may range from three to five decades (7).

To test our hypothesis that SV40 contributes to mesothelioma pathogenesis only as a cofactor, among asbestos-exposed individuals, we conducted a molecular epidemiologic case-control study to retrospectively assess the risk of developing MM among people exposed to asbestos and infected with SV40.

Materials and Methods

The population under investigation comprised 19 MM and 18 bladder urotheliomas (BUs) patients who were diagnosed at the Pathology Unit of the Alessandria Hospital and at the Pathology Unit of Pisa "Santa Chiara Hospital", respectively. BUs were chosen as controls in this study because, to date, there were no data in the medical literature indicating that this kind of cancer is somehow linked to either SV40 or asbestos. In addition, BU is a very frequent tumor and, therefore, it makes sample collection and control recruitment relatively easy. The recruitment of both cases and controls was exclusively on a random basis. The pathologists who made the diagnoses and provided samples for laboratory experiments did not know whether the patients had been exposed to asbestos or their SV40 status. The year of diagnosis ranged from 2001 to 2004 for MM and from 2003 to 2004 for BU.

The histologic examination and classification of tumors were done according to WHO criteria (The New WHO/International Association for the Study of Lung Cancer Histologic Classification of Lung and Pleural Tumors, 1999). The diagnosis of MM was achieved through cytologic assessment of pleural effusion specimens or histologic examination of pleural biopsies obtained through thoracoscopy or thoracotomy. All MM biopsies studied contained a vast majority of malignant cells and minimal stromal/inflammatory or otherwise nonmalignant cells. Light microscopy examination was always supplemented by immunochemistry using a standard battery of primary antibodies (calretinin, cytokeratin, carcinoembryonic

Note: A. Cristaudo, R. Foddis, and A. Vivaldi designed, supervised, did all the experiments, and wrote the report; R. Buselli, V. Gattini, G. Guglielmi, F. Cosentino, F. Ottenga, M. Tognon, and L. Mutti were involved in the conceptualization and implementation of the work; E. Ciancia, P. Betta, and R. Libener were also involved in project conceptualization and management of samples; R. Filiberti, M. Neri, and R. Puntoni made statistical calculations; all the authors were involved in the design of the work.

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antigen, BerEP-a, and CD15). All final diagnoses of mesothelioma were supported by both clinical and pathologic evidence. Histologically, MM samples were composed of 16 epithelioid, 2 mixed, and 1 sarcomatoid histotype. The diagnosis of BU was done according to WHO criteria.

A written informed consent was obtained from all patients before enrollment and study protocol was approved by the ethics committee of the participating institution.

Personal interviews were done on all subjects by trained personnel using the questionnaire proposed by the Istituto Superiore per la Prevenzione e la Sicurezza del Lavoro (the Italian National Institute for Health and Safety in work places) and used by the National MM Registry (ReNaM), which is the result of implementation at a national level of European Community directive 83/477/EC. Interviewers were blinded to SV40 status and those interviewed were blinded to their case-control status. Data on the tumor, history of past illnesses, demographic status, smoking habits, diet, alcohol consumption, as well as a detailed work history, and any environmental source of asbestos exposure were gathered. The adopted definition of exposure is the one proposed by the ReNaM. According to ReNaM reference guidelines, we classified all cases and controls in patients with occupational or environmental exposure to asbestos, with no sufficient data for classification, or with no evidence at all of any asbestos exposure. Still, according to ReNaM criteria, the classification of occupational exposure set three levels of probability (ascertained, probable, possible). This made it feasible to classify also all those situations in which the interviewees had not explicitly declared to have been exposed because either the composition of materials or products used during their working life was not perfectly known or information was not substantiated by details useful to define the exposure.

DNA purification. Sections from formalin-fixed, paraffin-embedded tissues were extracted using a commercial kit (Qiagen, Milan, Italy) following the manufacturer's instructions.

PCR and filter hybridization. SV40 DNA from 776 (Sigma, Milan, Italy) strain was used as control in PCR amplification. Each DNA sample was first tested for suitability for PCR by amplification of *p53* gene sequences, exons 7 to 8 (Table 1). Only positive samples were further investigated for amplification of SV40 sequences. All experiments were carried out at the Department of Endocrinology and Occupational Medicine, University of Pisa. All available DNA was analyzed for the presence of SV40 DNA in triplicate, and the results were consistently reproduced. To avoid PCR contaminations, the following precautions were carefully taken. Pre- and post-PCR activities were done in separate rooms using dedicated lab tools and supplies. All reagents for both DNA extraction and PCR analysis were exclusively used for the experiments of this study. Only filter tips were used.

All samples were screened for the highly conserved SV40 Tag sequences of 172 bp, coding for the NH₂-terminal portion of the oncoprotein and for the regulatory region (Table 1). Primers sequence

homology with plasmids was assessed by computer search (<http://www.ncbi.nlm.nih.gov/BLAST>).

DNA was amplified for 45 cycles in a total volume of 100 μ L containing 10 mmol/L Tris-HCl (pH 8.3), 50 mmol/L KCl, 1.5 mmol/L MgCl₂, 200 μ mol/L deoxynucleotide triphosphate, 50 pmol of each primer, and 1 unit of Taq DNA Polymerase (Amersham Pharmacia Biotech, Milan, Italy). The amount of DNA included per reaction volume ranged from 100 to 350 ng. Primers, oligoprobes, annealing temperatures, and PCR product size are reported in Table 1. Ten microliters of each PCR reaction were loaded on 2% agarose gel and electrophoresed in 1 \times TAE buffer [40 mmol/L Tris acetate and 1 mmol/L EDTA (pH 8)], stained by ethidium bromide, and photographed. DNA was transferred to nylon membranes and cross-linked to filter by UV irradiation. All filters were hybridized to SV40-specific internal oligoprobes (Table 1) at 42°C in 5 \times SSC (20 \times SSC: 3 mol/L NaCl, 0.3 mol/L Na citrate), 0.1% SDS, block solution, and 0.5% dextran sulfate (Amersham Pharmacia Biotech). Oligoprobes were 3' end-labeled using the ECL labeling kit and revealed by a chemiluminescent reagent (Amersham Pharmacia Biotech). The stringency of the final wash was adjusted according to the melting temperature. Filters were exposed to X-ray films (Kodak, Rochester, NY) for 15 to 60 minutes.

The univariate relation of each independent variable to the groups under study was examined using the χ^2 test. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between MM and SV40 or asbestos were calculated.

Results

Eighteen BU and 19 MM samples, each one deriving from different patients, contained DNA suitable for PCR analysis. Case and control groups were similar with regards to sex distribution and age at diagnosis (Table 2). A previous asbestos exposure was shown in 13 of 19 patients with MM (68.4%). Exposure was assessed as of occupational origin in 10 of these 13 patients, whereas three were attributed to an environmental source of exposure (a fibrocement factory located very close to the houses where the patients had lived for decades). Previous exposure to asbestos was assessed only in 4 (22.2%) of the 18 patients with BU. Asbestos exposure in these four controls was of occupational origin.

Table 3 reports the association between SV40 regulatory region sequences (RReg) and/or asbestos and MM.

As expected, we found a statistically significant association between MM and a personal history of previous asbestos exposure (OR, 7.6; 95% CI, 1.7-33.1). Analysis of combined effect of RReg and asbestos showed a significant association between the MM and concurrent presence of both factors (OR, 12.6; 95% CI, 1.2-133.9) with respect to the absence of them (Table 3).

Table 1. Oligonucleotides used as primers in PCR and as probes in filter hybridization

SV40 DNA regions	Oligonucleotides*	Reference [†] position	T [°] ‡	Size (bp)
Tag NH ₂	PYV.for: 5'-TAGGTGCCAACCTATGGAACAGA-3'	nt 4,574-4,552	62	172
	PYV.rev: 5'-GAAAGTCTTTAGGGTCTTCTACC-3'	nt 4,403-4,425		
	SV probe: 5'-ATGTTGAGAGTCAGCAGTAGCC-3'	nt 4452-4473		
Regulatory	RA3: 5'-GCGTGACAGCCGGCGCAGCACC-3'	nt 358-336	64	483
	RA4: 5'-GTCCATTAGCTGCAAAGATTCCTC-3'	nt 5,118-5,142		
	R probe: 5'-AATGTGTGTCAGTTAGGGTGTG-3'	nt 264-244		
Human <i>p53</i> gene exons 7-8	For: 5'-ATCCTGAGTAGTGGTAATCT-3'	nt 14,441-14,460	55	151
	Rev: 5'-TACCTCGCTTAGTGCTCCCT-3'	nt 14,591-14,572		

*Oligonucleotides used as primers in PCR and as probes in filter hybridizations.

†Reference nucleotide positions in SV40 strain 776 and human *p53* gene as a control of DNA suitability (European Molecular Biology Laboratory/Genbank accession no. X54156).

‡PCR annealing temperature (°C).

Table 2. Characteristics of the study subjects

	Mesothelioma	Urothelioma
Sex		
Male	13 (68.42%)	15 (83.3%)
Female	6 (31.58%)	3 (16.7%)
Age (mean \pm SD)	65.6 \pm 10.9	71.3 \pm 9.2
Asbestos exposure		
No	6 (31.58%)	14 (77.8%)
Yes	13 (68.42%)	4 (22.2%)
Total no. of subjects	19	18

Assessing the association between MM and the different combination of SV40 Tag/asbestos, we observed a trend of ORs similar to the one analyzed using primers specific to RReg, although correspondent ORs were smaller. In any case, the association between MM and the concurrent presence of both SV40 Tag and asbestos was still positive (data not shown).

Discussion

Although limited in size, the present study gives the first epidemiologic support in favor of a possible cocarcinogenic effect between SV40 and asbestos in MM development through a molecular epidemiology approach. In a previous paper (8), SV40 was found to be associated with asbestos in a set of MM samples because SV40 sequences were detected in five asbestos-related MMs and not in another four nonasbestos-related ones. However, these data were not sufficient to quantify the risk of developing a MM attributable either to the two factors separately or to the combination of them both. Our data confirm the role of asbestos in the etiology of MM and support a role of SV40 in MM pathogenesis (9, 10). The percentage of RReg SV40 sequences in MM samples (42.1%), as well as the prevalence of MM with history of asbestos exposure (68.4%), are close to the average frequency previously observed by us and others. This suggests that the population of cases enrolled is representative of MM patients in the general population in the respective demographic region (11). As expected, a positive association was found between asbestos exposure and MM, regardless of SV40 sequence detection. Surprisingly, in this series, the strength of the association with asbestos was by far less strong within SV40-free patients, whereas in subjects exposed to both asbestos and positive for SV40-sequences the risk of MM was 12.6-fold higher than in subjects with no previous asbestos exposure and no SV40 DNA.

We found that 33.3% of BU samples contained SV40 RReg sequences. This is, to the best of our knowledge, the first time this type of cancer has been analyzed for the presence of SV40, and there is no immediate or simple explanation for this. We know that, thus far, SV40 DNA has been found in different kind of tumors with a prevalence of virus positivity ranging considerably among different cancers (12). Obviously, finding viral DNA in a minor portion of a limited number of tumor samples does not make it possible to substantiate a causal relationship. To date, there is too little information about this topic to speculate on the role of SV40 in this kind of tumor. However, this unexpected 33.3% of positivity for SV40 DNA among controls might have determined an underestimation of the association between SV40 alone and MM in the population under investigation.

In conclusion, our data suggest that SV40 alone may not be able to cause MM in humans, but that it strongly increases the carcinogenic effect of asbestos.

The same conclusions can be drawn considering results (not shown) obtained from the analysis of the association between MM and the different combination of SV40 Tag and asbestos. Once again, the presence of Tag in the absence of asbestos history is not associated with MM, whereas the presence of Tag increases the strength of the association between asbestos and MM. Nevertheless, considering the combinations with positive Tag sequences, ORs were smaller than the ones obtained using RReg sequences as marker of SV40 presence.

To date, no epidemiologic data have been provided supporting the observation that asbestos and SV40 are cocarcinogens *in vitro*. Recently, some authors (1, 12) have proposed an *in vitro* model of pathogenic interaction involving the two factors, which is schematically reported.

Asbestos fibers are reported to favor mesothelial cell transformation as a result of several important activities, such as extracellular signal-regulated kinase activity stimulation and epidermal growth factor receptor autophosphorylation, leading to subsequent expression of the proto-oncogenes and AP-1 family members, c-fos, and fra-1 activation (13). Besides, asbestos fibers can determine direct chromosomal breaking and, most important, can cause mononuclear phagocytes to release mutagenic reactive oxygen species resulting in DNA damage and DNA repair pathway activation (13). If DNA repair is not properly accomplished, damaged cells normally undergo apoptosis but occasionally may continue dividing with consequent accumulation of additional mutations. *In vitro*, the coexistence of other cofactors may allow these cells to overcome apoptotic pathways more efficiently. SV40 may block p53/pRb protein-related apoptotic pathways (14). SV40 also stimulates the expression of some cell growth regulators, such as insulin-like growth factor-I, hepatocyte growth factor, and VEGF, and induces the activation of AP-1, Notch-1, and telomerase (15, 16, 3). All these activities may extend the lifetime of damaged mesothelial cells that may divide and accumulate DNA mutations and chromosomal alterations. Consistently, with this hypothesis,

Table 3. Association between RReg sequences and/or asbestos and mesothelioma

SV40/asbestos status	Mesothelioma, n (%)	Urothelioma, n (%)	OR (95% CI)
Asbestos exposure			
No	6 (31.6)	14 (77.8)	1.0
Yes	13 (68.4)	4 (22.2)	7.6 (1.7-33.1)
Sv40- (RReg-)			
Asbestos exposure			
No	5 (45.5)	9 (75.0)	1.0
Yes	6 (54.5)	3 (25.0)	3.6 (0.6-21.1)
Sv40+ (RReg+)			
Asbestos exposure			
No	1 (12.5)	5 (83.3)	1.0
Yes	7 (87.5)	1 (16.7)	35 (1.7-703)
Asb/SV40			
Asb-/RReg-	5 (26.3)	9 (50.0)	1.0
Asb-/RReg+	1 (5.3)	5 (27.8)	0.4 (0.03-4.0)
Asb+/RReg-	6 (31.6)	3 (16.7)	3.6 (0.6-21.0)
Asb+/RReg+	7 (36.8)	1 (5.6)	12.6 (1.2-133.9)

Bocchetta et al. (17) reported that although focus formation was not observed in cultured mesothelial cells treated with either crocidolite fibers alone or transfected with plasmids containing only SV40 Tag, a high number of foci developed when mesothelial cells were at the same time treated with both asbestos and plasmid containing SV40 Tag.

Moreover, the well-known immunosuppressive effects of asbestos could allow SV40 to escape host immunologic defense, preventing immune lysis of Tag-positive cells (reviewed in ref. 1).

A recent report suggested that plasmid contamination may account for some of the positive results for SV40 reported in the literature (18). In fact, most sets of primers frequently used in previously published PCR-based studies amplify a region of the viral DNA coding for the Tag exon 2, which is within a 614 nucleotide portion of SV40 present in up to 80 common laboratory vectors. We tested our specimens with a set of primers that amplify a tract of the Sv40 RReg, which is included in two plasmids only, pSVL and pEUK-C1 (<http://www.ncbi.nlm.nih.gov/BLAST>). We chose these primers to reduce the risk of plasmid contamination, a concern supported by the recent findings of Lopez-Rios et al. (18), who also advised the use of "low-risk primers," such as ours, to test for SV40 sequences in human tumors. Moreover, the two plasmids indicated above were never used in our laboratory, further decreasing the risk of contamination. The fact that all of our negative controls that were handled in parallel with the mesothelioma biopsies at all steps of the procedure (from DNA extraction to the Southern blotting) tested repeatedly negative supported the reliability of our results and ruled out the possibility of laboratory artifacts, such as contamination. Concerning the broader issue of PCR-plasmid contamination raised by Lopez-Rios et al., this is an issue that must be considered by all researchers testing for SV40 in human tumors. Careful precautions and rigorous controls, such as those we used, should always be implemented. However, this risk should not be brought out of

proportion. There are over 70 publications from many different laboratories that have reported the presence of SV40 in human mesotheliomas and other cancers. PCR and many other technical approaches—electron microscopy, Western and Northern blotting, immunostaining and immunoprecipitation, *in situ* hybridization, viral rescue from human biopsies of SV40 strains never detected in laboratory, etc.—have been used to validate these findings. It is unlikely that so many laboratories using so many different techniques would be all wrong and that the results would always be error in detecting SV40. Moreover, the detection of SV40 in human cancers has undergone a very critical scrutiny by three independent review panels and all three concluded that SV40 was present in human cancers (12, 19, 20).

In conclusion, our data confirm the presence of SV40 in some mesotheliomas, confirm the reliability of PCR to detect SV40 when stringent precautions to prevent and detect contamination are taken, and provide, for the first time, epidemiologic evidence that support the notion that SV40 and asbestos are cocarcinogens in the pathogenesis of mesothelioma. Furthermore, our findings suggest that detection of SV40 among a cohort of individuals exposed to asbestos could represent a useful marker to identify those at higher risk for MM. This subgroup of high-risk individuals could be closely monitored for early detection and possibly curative surgical excision.

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