A Molecular Epidemiology Case Control Study on Pleural Malignant Mesothelioma

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Abstract

Pleural malignant mesothelioma is an uncommon neoplasm usually associated with asbestos exposure. The increasing incidence of malignant mesothelioma cases involving individuals with low levels of asbestos exposure suggests a complex carcinogenic process with the involvement of other cofactors. Cytogenetic studies revealed the complexity of the genetic changes involved in this neoplasm reflecting the accumulation of genomic damage. One of the most used methodologies for assessing genomic damage is the cytokinesis-blocked micronucleus test applied in peripheral blood lymphocytes (PBL). This approach allows the detection of chromosomal alterations expressed in binucleated cells after nuclear division in vitro. This marker could provide a tool for assessing genetically determined constitutional differences in chromosomal instability. A biomonitoring study was carried out to evaluate the micronuclei frequency in PBLs of patients with pleural malignant mesothelioma with respect to lung cancer, healthy, and risk controls as a marker of cancer susceptibility in correlation with the presence of SV40. A significant increased micronuclei frequency was observed in patients with malignant mesothelioma in comparison with all the other groups, the mean micronuclei frequency was double in patients with malignant mesothelioma compared with healthy controls, risk controls, and patients with lung adenocarcinoma (median 11.4 binucleated cells with micronuclei/1,000 binucleated cells versus 6.2, 6.1, and 5.1, respectively). Our data indicate that human T lymphocyte samples carry DNA sequences coding for SV40 large T antigen at low prevalence, both in cancer cases and controls. Evidence of cytogenetic damage revealed as micronuclei frequency in mesothelioma cancer patients could be related to exogenous and endogenous cofactors besides asbestos exposure. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1741–6)

Introduction

Pleural malignant mesothelioma is a rare, highly aggressive neoplasm arising primarily from the surface serosal cells of the pleural cavity. The incidence is rising sharply in the U.S. and Western Europe, where ~250,000 deaths due to malignant mesothelioma are predicted for the next 30 to 35 years (1, 2). Diffuse pleural malignant mesothelioma could be difficult to diagnose (3), it has a poor survival rate, and death usually occurs within 4 to 12 months after diagnosis (4).

Although it is well-established that asbestos exposure is the major causative agent in the development of mesothelioma, accounting for about 80% of cases (5, 6), the incidence of cases involving individuals with low levels of asbestos exposure is increasing. The molecular steps in the process of malignant mesothelioma carcinogenesis remain unknown. Recently, sequences belonging to SV40, a DNA tumor virus, have been associated with malignant mesothelioma as a probable cofactor in producing this malignancy (7-11).

Malignant mesothelioma is characterized by a long latency period from the time of asbestos exposure to clinical diagnosis, suggesting that multiple somatic genetic changes may be required for the tumorigenic conversion of a mesothelial cell. Early evidence in support of this hypothesis was provided by karyotypic analyses, which revealed multiple clonal cytogenetic alterations in most human malignant mesotheliomas (9).

Several common cytogenetic aberrations in malignant mesothelioma are deletions involving discrete regions in chromosome arms 1p, 3p, 4q, 6q, 9p, 13q, 14q, 15q, and 22q gains of chromosome 5, 7, and 20 (9, 12-18) or alterations of tumor-related genes, such as neurofibromatosis type 2 (NF2) and p16 (19-21) genes.

The high frequency of specific chromosome region losses is consistent with a recessive mechanism of oncogenesis and can be considered as an indicator of the locations of putative tumor suppressor genes responsible for the development and progression of malignant mesothelioma. The evidence of a complex heterogeneity of the structural chromosomal aberrations in malignant mesothelioma seems to reflect an intrinsic predisposition of the cells to accumulate genomic damage. Autosomal dominant transmission of malignant mesothelioma in the Cappadocian region of Turkey (22, 23), and clustering of malignant mesothelioma in families (24, 25), support the hypothesis that genetic susceptibility might play a relevant role as a contributing factor in the etiology of this neoplasm. The role of genetic polymorphisms involving critical metabolic genes, such as GSTM1 and NAT2, as risk modifiers in asbestos-related malignant mesothelioma, has been recently shown in asbestos-exposed populations (26, 27). Other heritable differences in hosts resistant to genetic changes may be identified at different phases of the carcinogenic process, such as DNA repair competency and chromosome stability. In this context, a biomarker for genetic instability could be helpful in...
identifying people who are at high risk for malignant mesothelioma.

Chromosomal alterations have also been shown in different kinds of neoplastic diseases as predictors of risk or as a prognostic specific factor (28, 29). Human neoplasms exhibit chromosomal aberrations in tumor tissue samples, as well as in peripheral blood lymphocytes (PBL). PBLs offer the advantage of noninvasive sample collection and provide a large quantity of cells for analysis. Cytogenetic damage, measured as chromosomal aberrations in PBL, is a reliable biomarker for human cancer risk independently of the exposure to carcinogens (30).

The micronucleus test in PBLs has been applied as a simple and reliable method for the detection of cytogenetic damage. This assay could be used to assess chromosomal damage as chromosomal fragments or whole chromosome that are excluded from the nucleus at mitosis. Micronucleus test in PBLs seems to be a useful method for monitoring individuals with genetic instability (31) and as a screening test for carriers of specific mutations in evaluating cancer susceptibility (32, 33).

Elevated levels of micronuclei frequency in PBLs of cancer patients prior to chemotherapy or radiotherapy have been reported in a number of papers (34-37). Ad hoc biomonitoring studies dealing with specific types of cancer could help to understand the importance of this biomarker in terms of individual genetic cancer susceptibility.

Polyomaviruses such as SV40 and JC virus (JCV) are oncogenic in animal models and transform animal and human cells of different types (38, 39). Moreover, SV40 and JCV are able to infect human PBLs inducing chromosomal instability (40, 41). The present study was carried out to evaluate the micronuclei frequency in PBLs of patients with pleural malignant mesothelioma with respect to lung cancer along with two control groups, as a marker of cancer risk and/or susceptibility, and in correlation with the presence of SV40 and JCV Tag sequences.

Materials and Methods

Study Population. Subjects in this study were enrolled from March 1996 to August 2000 in three areas in northwestern Italy (Genova, Casale, and La Spezia), characterized by asbestos exposure related to industrial activities.

The study includes 21 patients with malignant mesothelioma and 37 patients with lung cancer, admitted to the Surgery, Oncology, or Pneumology Departments. Sixty-two subjects as healthy controls, and 33 with benign respiratory diseases, as at-risk controls, were also studied. Benign diseases were mostly chronic obstructive pulmonary disease (27 patients). The other patients had asbestosis (1), silicosis (3), or emphysema (2).

The histologic examination and classification of tumors were done according to WHO criteria (42). Lung cancer stage was mostly chronic obstructive pulmonary disease (27 patients) with respect to lung cancer along with two control groups, as a marker of cancer risk and/or susceptibility, and in correlation with the presence of SV40 and JCV Tag sequences.

Samples and DNA Extraction. T lymphocytes, isolated from whole blood, were resuspended in acetone solution and kept at -80°C until the analysis. Cell pellets were digested with a lysis buffer containing 100 mmol/L Tris (pH 8.3), 1.25 mmol/L MgCl₂, 0.1% gelatin, 0.45% Tween 20, 0.45% Nonidet P40 and 10 mg/mL of Proteinase K at 55°C for 1 hour. Cell debris were collected by centrifugation and DNA recovered from the supernatant. In order to verify whether cross-contamination occurred during DNA extraction, each sample was purified simultaneously with a specimen of salmon sperm DNA and a mock specimen lacking DNA, and then subjected to PCR analysis.

DNA samples were analyzed for the conserved SV40 Tag NH₂-terminal coding sequences by oligonucleotide pairs which efficiently amplify these sequences (14, 18, 20). Briefly, in reconstruction experiments with serial dilution of high-purified SV40 DNA, from 100 ng to 1 ag, in a background of 500 ng of genomic DNA from human placenta, the NH₂-terminal Tag coding sequences of 543 bp, amplified by seminested PCR, was detected in gel stained by ethidium bromide till 10 fg, whereas these SV40 sequences were detected till 10 ag by filter hybridization with the SV probe. Viral DNA 100 ng each from SV40 776 strain, cloned in plasmid vectors, were used as positive control.

SV40 Tag NH₂-terminal coding sequences were investigated by seminested PCR using the primer sets SV.for2-SV.rev (5'-CTTTGGACGTCTCTGCAACT-3') and SV.for2-SV.rev (5'-GATGACTCTAAAAATTTAGCATTCC-3') nucleotides 4,945-4,921; SV.rev, 5'-GATGACTCTAAAAATTTAGCATTCC-3' nucleotides 4,372-4,399) and SV.for2-PV.rev (PV.rev, 5'-GAAAGCTTCTAGGCTTCTAC-3' nucleotides 4,403-4,425),
yielding amplification products of 575 and 543 bp, respectively. The SV40 specificity of PCR-amplified products was assessed by filter hybridization with the internal SV probe (5'-ATGTGAGTGTCAGCGATAGCC-3', nucleotides 4,452-4,473).

JCV T antigen sequences were investigated by PCR and seminested PCR with the primer set JCfor.2/JCrev (5'-GCTTGACTGAGGAATGCATGCAGATCT-3' and 5'-GAGTCAGCAGTAGCC-3') yielding amplification products of 575 and 545 bp, respectively. The seminested PCR product was further subjected to Southern blot hybridization with the specific internal JC probe (5'-GTTTGACTGAGGAATGCATGCAGATCT-3', nucleotides 4,303-4,323).

DNA was amplified in a total volume of 50 μL containing 10 mmol/L Tris-HCl (pH 8.3), 50 mmol/L KCl, 1.5 mmol/L MgCl2, 0.01% gelatin, 150 μmol/L of each deoxynucleotide triphosphate, 25 pmol of each primer and 1 unit of Taq polymerase linked to its specific antibody (Life Technologies). PCR products were run in 1% agarose gel, stained by ethidium bromide and transferred to a nylon membrane. DNA was cross-linked to filter hybridization with antifluorescin horseradish peroxidase–conjugate anti-IgG (Amersham). Film exposure with antifluorescin horseradish peroxidase–conjugate anti-IgG (Amersham, Milan, Italy). Detection of the fluorescent hybrid was carried out by UV irradiation for 2 minutes. Specific internal oligoprobes were 3' end-labeled with a tail of dUTP-fluorescein by terminal transferase, as recommended by the manufacturer (Amersham, Milan, Italy). Detection of the fluorescent hybrid was carried out with antifluorescin horseradish peroxidase–conjugate antibody, as indicated by the supplier (Amersham). Film exposure was at room temperature for 15 minutes to 1 hour.

**Statistical Analysis.** All reported micronuclei counts are the mean of duplicate determinations. Means, medians and SD were calculated for cancers and controls in terms of binucleated cells with micronuclei (BNMN/1,000 PBL) according to type, sex, age, smoking, and asbestos exposure.

**Differences in the values between the groups under study were checked using the Kruskal-Wallis test, whereas the Mann-Whitney U test was used for comparison of two groups. A x2 test was used to test relationships between categorical variables. Fisher’s exact test was applied when necessary. The Spearman correlation method was used to correlate the level of the micronuclei with other variables.**

**Results**

The characteristics of the study subjects are summarized in Table 1. Median age was 68 years (range 54-84) in malignant mesothelioma, 63.8 years (48-82) in lung cancer, 61.8 years (27-79) in at-risk controls, and 56.0 years (20-87) in healthy controls. A significant difference was present for age between neoplastic patients and healthy controls (P ≤ 0.04). Number of females was significantly lower in lung cancer with respect to healthy controls (P = 0.004).

Patients with malignant mesothelioma reported previous asbestos exposure significantly higher with respect to all other groups (P < 0.0001). Patients with lung cancer presented a higher number of smokers with respect to malignant mesothelioma (P = 0.01) and healthy controls (P < 0.0001), and had a higher cumulative smoking history (median 45 versus 35 pack years for all other groups).

Among patients with malignant mesothelioma, 43% were epithelial types and 29% were biphasic. Twenty four percent of patients with malignant mesotheliomas were not microscopically defined. Among patients with lung cancer, 49% were squamous, 27% adenocarcinomas, and 11% were microscopically defined as non–small cell lung cancer. Two cases were small cell carcinomas.

Data on micronuclei frequency by type, age, gender, smoking status, and asbestos exposure are reported on Table 2. No age-related increase in micronuclei frequency was observed in...
any group examined. An increase, although not statistically significant, was evident in females. No correlation between micronuclei frequency and smoking status was observed. No difference in micronuclei frequency was observed with the number of cigarettes, cigarette pack/years, length of smoking or time from cessation.

In each group, micronuclei distribution was not different in subjects with a previous asbestos exposure with respect to nonexposed subjects. No combined effect between smoking and asbestos exposure on micronuclei frequency was observed in any group.

A significantly higher median frequency was recorded for patients with malignant mesothelioma (11.4 BNMN/1,000 BN) with respect to lung cancer (5.1, P < 0.0001), at-risk controls (6.1, P = 0.002) or healthy controls (6.2, P < 0.0001; Fig. 1). Significant differences (P < 0.001) also persisted when considering only histologically confirmed malignant mesothelioma (median 12.1). The patient with asbestosis in the at-risk controls group showed a micronuclei value of 5.7 BNMN/1,000 BN, not different from the nonmalignant mesothelioma groups.

Characteristics of malignant mesothelioma patients are reported on Table 3. The length of the exposure ranges from 8 to 46 years. Only 43 subjects are nonsmokers. Two malignant mesothelioma patients (females, ages 63 and 68 years, respectively) did not report asbestos exposure. Micronuclei frequency in these subjects was 13.6 and 14.5 BNMN/1,000 BN, respectively. Also, the third (out of four) female affected by mesothelioma despite a low level of exposure to asbestos fibers, as a wife of a dockyard worker, showed a very high frequency of micronuclei (21.4 BNMN/1,000 BN).

Assuming the corresponding mean ± 2 SD of micronuclei in healthy controls as the cutoff value (14.2 BNMN/1,000 BN), 8 out of 21 malignant mesothelioma patients (38%) were positive versus 0 of 37 (0%) of lung cancer, 3 of 33 (9%) of at-risk controls, and 4 of 62 (6%) of healthy controls.

No significant differences were found between malignant mesothelioma and lung cancer histologic types or lung cancer stages. No association between micronuclei frequency and presence of familiarity for any type of tumor in cancer cases or controls was observed.

The prevalence of SV40 Tag NH2-terminal region in T lymphocyte samples was 4 of 59 (6.8%; two patients with malignant mesothelioma and two patients with lung cancer). A sample from controls showed a weak positive signal and was considered SV40-negative (Table 4). None of the T lymphocyte samples was JCV-positive.

### Discussion

A significant increase in micronucleated binucleated lymphocytes were observed in patients with malignant mesothelioma in comparison with all other subjects. The most consistent demographic variables influencing the micronuclei frequency in human lymphocytes were considered. The effect of aging on this biomarker is well-established: age was associated with significantly increased micronuclei levels in most of the largest studies that specifically evaluated this issue, including two reanalyses of data pooled from thousands of data (45-47).

### Table 3. Characteristics of malignant mesothelioma patients

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Job/type of activity</th>
<th>Asbestos exposure (y)</th>
<th>Smoking</th>
<th>Histology</th>
<th>MN/1,000 binucleated cells</th>
<th>SV40</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>54</td>
<td>coach-repairer, turner</td>
<td>12</td>
<td>former</td>
<td>sarcomatous</td>
<td>4.8</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>58</td>
<td>carpenter</td>
<td>36</td>
<td>never</td>
<td>epithelioid</td>
<td>5.5</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>60</td>
<td>carpenter on ships</td>
<td>31</td>
<td>former</td>
<td>malignant mesothelioma*</td>
<td>6.4</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>61</td>
<td>dockers</td>
<td>32</td>
<td>former</td>
<td>epithelioid</td>
<td>17.5</td>
<td>+</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>insulator</td>
<td>46</td>
<td>former</td>
<td>malignant mesothelioma*</td>
<td>28.0</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>insulator</td>
<td>26</td>
<td>current</td>
<td>biphasic</td>
<td>14.5</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>dockers</td>
<td>34</td>
<td>current</td>
<td>biphasic</td>
<td>11.0</td>
<td>+</td>
</tr>
<tr>
<td>M</td>
<td>67</td>
<td>carpenter</td>
<td>37</td>
<td>current</td>
<td>malignant mesothelioma*</td>
<td>4.2</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>67</td>
<td>dockers</td>
<td>33</td>
<td>never</td>
<td>epithelioid</td>
<td>20.5</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>68</td>
<td>building</td>
<td>26</td>
<td>current</td>
<td>malignant mesothelioma*</td>
<td>15.4</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>69</td>
<td>carpenter on ships</td>
<td>41</td>
<td>current</td>
<td>epithelioid</td>
<td>15.5</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>73</td>
<td>foundry worker</td>
<td>15</td>
<td>former</td>
<td>biphasic</td>
<td>10.2</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>75</td>
<td>forwarding agent, asphalter</td>
<td>ND</td>
<td>former</td>
<td>biphasic</td>
<td>8.7</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>76</td>
<td>metallurgic</td>
<td>29</td>
<td>former</td>
<td>biphasic</td>
<td>11.0</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>79</td>
<td>metallurgic, ships</td>
<td>8</td>
<td>former</td>
<td>malignant mesothelioma*</td>
<td>11.4</td>
<td>–</td>
</tr>
<tr>
<td>M</td>
<td>79</td>
<td>metallurgic, ships</td>
<td>40</td>
<td>former</td>
<td>biphasic</td>
<td>6.5</td>
<td>–</td>
</tr>
<tr>
<td>F</td>
<td>63</td>
<td>shipping agent</td>
<td>40</td>
<td>current</td>
<td>epithelioid</td>
<td>13.3</td>
<td>–</td>
</tr>
<tr>
<td>F</td>
<td>68</td>
<td>housewife</td>
<td>–</td>
<td>never</td>
<td>epithelioid</td>
<td>13.6</td>
<td>–</td>
</tr>
<tr>
<td>F</td>
<td>68</td>
<td>housewife</td>
<td>–</td>
<td>current</td>
<td>epithelioid</td>
<td>21.4</td>
<td>–</td>
</tr>
<tr>
<td>F</td>
<td>73</td>
<td>agent, husband docker</td>
<td>ND</td>
<td>current</td>
<td>epithelioid</td>
<td>14.5</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Not otherwise specified.
Table 4. Prevalence of SV40 Tag NH2-terminal region according to type

<table>
<thead>
<tr>
<th>SV40</th>
<th>Malignant mesothelioma</th>
<th>Lung cancer</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>17 (89.5%)</td>
<td>16 (88.9%)</td>
<td>22 (100%)</td>
</tr>
<tr>
<td>+</td>
<td>2 (10.5%)</td>
<td>2 (11.1%)</td>
<td>—</td>
</tr>
</tbody>
</table>

In the present study, a significant age-related increase in the micronuclei frequencies was not observed as this effect is fully evident only when considering wide age ranges. The large majority of the subjects recruited in this study were instead comprised in a relatively narrow age interval.

A gender effect was evident in agreement with previous reports (46-48): females had higher micronuclei frequency than males, although no significant difference could be shown, probably due to the low number of women recruited.

With regards to cigarette consumption, never smokers showed slightly higher micronuclei frequency than ever smokers, whereas no association was observed with specific cigarette smoking indices (duration, intensity, pack/years, time from cessation). These results are in agreement with a recent reanalysis of pooled databases. The authors established that smokers experience a small decrease of micronuclei frequencies in current as well as in former smokers with respect to never smokers (49). Micronuclei frequencies were significantly higher only in very heavy smokers not occupationally exposed to genotoxic agents, a subgroup that was extremely poorly represented in our population.

An analysis of our data according to asbestos exposure was also carried out. A slight increase in micronucleus frequency in asbestos-exposed subjects, with respect to unexposed subjects, was observed only in mean values but not in median values. In addition, 4 out of 21 malignant mesothelioma patients in our study did not refer a history of asbestos exposure, although 2 of them were probably exposed at extremely low concentrations as housewives of dockers.

Asbestos has long been known to induce lung cancer and mesothelioma. Although the link between asbestos and mesothelioma was clarified, ~20% of cases occur in individuals without a known history of asbestos exposure. The mechanism responsible for the cytotoxicity and carcinogenicity of asbestos is not yet classified: asbestos fibers have been considered nongenotoxic carcinogens because of their failure to induce gene mutation in most short-term assays (50). Although more recently, revision of the scientific literature has revealed that asbestos fibers clearly induce DNA damage and structural and numerical chromosomal aberrations in different mammalian cell systems (51-53).

Various types of asbestos fibers show their capability to induce micronuclei using different modifications of the micronucleus test. The results of kinetochore analysis provides evidence that the loss of whole chromosomes as well as clastogenic events are involved in the induction of micronuclei by asbestos fibers (54, 55). Two major mechanisms have recently been proposed for asbestos-induced genotoxicity: one involves the physical effects of fibers on chromosome and on spindle apparatus; the second involves the production of reactive oxygen species or reactive nitrogen species directly or indirectly generated by the fibers (56-58).

Oxidative stress and oxidative DNA damage have been observed in workers highly exposed to asbestos fibers in the past, confirming the hypothesis of an oxidative mechanism (59). The individual antioxidant defense capacity may be a potential explanation for the variability in individual risk for asbestos-exposed individuals. The evidence of cytogenetic damage revealed as micronuclei frequency in mesothelioma cancer patients could be related to exogenous and endogenous cofactors besides asbestos exposure.

Genetic metabolic polymorphisms and the efficiency of the DNA repair enzymes have been considered as susceptibility factors responsible for the high extent of cytogenetic damage in restricted groups of subjects. The identification of the cofactors that render certain individuals more susceptible to asbestos or that could cause mesothelioma in people not exposed to asbestos has been an important matter of investigation in many laboratories worldwide.

Expression of virus interferes with protective cellular mechanisms with a significant increase of micronuclei in cells (60, 61) and viruses have been recently considered as a potential cause of mesothelioma. In particular, attention has been focused on the role of SV40 Tag sequences which have been found to be frequently present and overexpressed in mesothelioma tissues. It has been suggested that the SV40 large T antigen expression in mesothelial cells might impair the control of DNA integrity and enhance apoptosis. It may act as a cocarcinogen in association with asbestos exposure, playing an important role in the mesothelioma induction (62-64). Data on the prevalence of SV40 Tag sequences in cancer cases indicate that, in our conditions of DNA extraction and PCR assay, human T lymphocyte samples carry SV40 DNA at low prevalence (~ 10%).

In conclusion, our findings reveal that malignant mesothelioma is associated with a statistically significant increase of micronuclei frequency. No relationship is evident between micronuclei and the other explanatory variables such as intensity of asbestos exposure, smoking habits, and polyoma virus. The amount of cytogenetic damage measured by means of micronuclei frequency might be related to individual susceptibility. These results have to be confirmed in a larger population of cancer patients by evaluating other biomarkers and essaying for the presence of SV40 virus.

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