Clinical Significance of Serum Mesothelin in Patients with Mesothelioma and Lung Cancer

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Abstract

Purpose: High levels of serum-soluble mesothelin family proteins (SMRP) have been found to be associated with malignant mesothelioma (MM), but not lung cancer (LC). To verify the clinical role of this marker for both these tumors, we tested serum SMRP in the largest population of thoracic cancers ever assembled.

Experimental Design: SMRP blood concentrations were measured in 107 patients with MM, 215 patients with LC, 130 patients with benign respiratory diseases (BRD), and 262 controls. Statistical comparison between mean serum SMRP levels in all groups was done and receiver operating characteristic curves were constructed to evaluate the performance of this marker.

Results: SMRP levels were significantly higher in patients with MM and LC than in patients with benign respiratory diseases and controls ($P < 0.001$). The area under the receiver operating characteristic curve for serum SMRP discriminating MM and controls was 0.77 (95% confidence interval, 0.71-0.83), with a best cutoff of 1.00 nmol/L (sensitivity, 68.2%; specificity, 80.5%). In both MM and LC, serum SMRP levels did not differ significantly between early and late stages. High SMRP levels proved to be an independent negative prognostic factor in patients with MM.

Conclusions: Our data confirm that serum SMRP is a promising marker for the diagnosis, prognosis, and clinical monitoring of MM. We found that serum SMRP dosage may prove helpful in LC diagnosis as well. These data may also have positive repercussions on secondary preventive medical strategies for workers previously exposed to asbestos.

Pleural malignant mesothelioma (MM) is a highly aggressive tumor with a poor survival rate whose incidence in Western Europe is expected to increase dramatically in the next 10 to 15 years (1). Several etiologic cofactors other than asbestos, such as genetic susceptibility or viral oncogenes (SV40), have been recently hypothesized (2–5). In particular, SV40 is a DNA tumor virus which contaminated polio vaccines from 1955 until 1978, although exposure to this virus varied in different countries, and this may account for the reported geographic differences in the incidence of SV40-positive tumors (6). However, by far, most cases of MM and a significant portion of lung cancers (LC; refs. 7, 8) can be directly attributed to the inhalation of asbestos fibers. Moreover, asbestos also acts as a cocarcinogen of LC in association with a smoking habit.

Because of the widely exposed population, a secondary prevention strategy exclusively based on radiological examinations for MM is not very feasible from either an ethical or an economical point of view, whereas the advisability of radiological screening for LC is still a matter of debate. In fact, although it is indisputable that spiral CT screening can detect early stage LC, its effectiveness in reducing LC-related mortality has not yet been shown (9). Therefore, the investigation of biological markers as "risk factors" or "markers of early diagnosis" is strongly recommended by the scientific community (10, 11).

Recently, several authors have proposed mesothelin as a promising predictive marker for early evidence of MM (12–17). The human mesothelin gene codes for several proteins and is consistently expressed in normal mesothelial cells and even more in mesotheliomas, ovarian cancers, and pancreatic adenocarcinomas. The primary product of the gene is a 71-kDa precursor protein which undergoes physiologic cleavage by a furin-like protease resulting in two main proteins. One is the 31-kDa NH_2-terminal megakaryocyte potentiation factor, which is normally secreted into the blood. The COOH-terminal product of the cleavage, a 40-kDa

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Received 3/19/07; revised 6/15/07; accepted 6/22/07.

Grant support: Nonprofit "Buzzi Unicem Foundation for Pleural Mesothelioma Research".

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doi:10.1158/1078-0432.CCR-07-0629

glycosylated phosphatidylinositol-linked glycoprotein, remains bound to the cell membrane and provides epitopes for immunohistochemistry. Some authors have suggested that after further subsequent cleavages, this cell surface protein releases soluble mesothelin-related peptides (SMRP), which are the principal mesothelin family proteins tested thus far (12–15). In order to evaluate its clinical (prognostic/diagnostic) significance, we assessed the level of serum SMRP in patients with MM and LC and in patients with benign pleural or lung diseases (benign respiratory diseases—BRD) and controls with or without a history of asbestos exposure.

Materials and Methods

Study population. Enrolled subjects came from two Italian regions (Tuscany and Liguria) where relevant asbestos exposure due to industrial activity is currently causing a high incidence of MM. Serum samples were collected (before treatment in tumor patients) from all the subjects (see Table 1 for a detailed description of the study population).

Both MM and LC diagnoses were done with the aid of histologic and cytologic analyses of biopsies or surgical samples. Diagnoses were reviewed and validated by a panel of expert pathologists and clinicians.

A questionnaire, elaborated by the Italian National Institute of Occupational Safety and Prevention, and aimed at assessing asbestos exposure level (classified as "ascertained", "probable", and "possible") as well as providing data regarding the history of previous diseases and dwellings, was administered by trained personnel either directly to each participant or to their relatives. Approval from the ethical boards and written informed consent was obtained from all participants.

SMRP dosage. Serum mesothelin concentrations were determined using Mesomark (by Cisbio International), following the manufacturer's instructions. SMRP assays were all done in a single laboratory ("Santa Chiara", Pisa University Hospital) by investigators who were unaware of the patients' diagnoses. All serum samples were analyzed in duplicate.

Statistics. SMRP levels were transformed into natural logarithms. Differences in the values between the groups studied were checked using independent samples test and ANOVA procedures. The univariate relation of each independent variable to the groups was examined using the χ^2 test. Pearson's correlation method was used to correlate the SMRP level with age.

In order to evaluate the performance of SMRP, receiver operating characteristic curves (18), areas under the receiver operating characteristic curves (AUC), and their 95% confidence intervals (95% CI) were calculated using standard techniques.

Logistic regression models were established to evaluate the power of the five cut-points considered to discriminate between cases and controls. Age, gender, and asbestos exposure were included in the models to adjust for the possible confounding effects. Akaike information criteria (19) was used to compare the goodness-of-fit of each model. The "optimal" cut-point was estimated through an "ad hoc" developed STATA routine (20, 21), and its 95% CI was computed by means of a bootstrap procedure (22). All other statistical tests were done by using SPSS for Windows.

Predictive values were estimated on the basis of the number of MM expected among the asbestos-exposed population according to the incidence rate in our geographic areas (two cases/10,000 person-years in the 55-65 years old age groups) increased 5-fold due to asbestos exposure (10 cases/10^4 person-years).

In order to evaluate the SMRP prognostic significance on survival of patients with MM, Cox's proportional hazards regression analysis (21) was carried out as multivariate analysis, adjusting for age, sex, histology, platelet count, treatments (chemotherapy, radiotherapy, or surgery), and clinical stage (according to the International Mesothelioma Interest Group staging system). Survival time was calculated from the date the serum sample was obtained. Survival curves were determined using the Kaplan-Meier method. The log-rank test allowed us to evaluate the differences between survival curves.

Results

Serum SMRP levels in patients with cancer, BRD, and controls are shown in Table 2 and Fig. 1. No correlation was found between SMRP levels and age or asbestos exposure in any of the groups under investigation (Table 1).

SMRP levels in MM. The log of the SMRP mean values was significantly higher in patients with MM than in patients with BRD or controls ($P < 0.001$). Furthermore, a statistically higher concentration was observed in MM compared with LC ($P < 0.001$).

SMRP was higher in epithelioid than in sarcomatous mesothelioma ($P = 0.01$), whereas the desmoplastic type showed the lowest levels in comparison with other groups ($P = 0.04$ versus epithelioid and $P = 0.05$ versus mixed tumors; Table 2). Differences in SMRP levels between the early and late stages of MM were evident, although not statistically significant (Table 2).

The receiver operating characteristic curves showing the performance of SMRP in discriminating between either thoracic

Table 1. Characteristics of the study subjects

	MM (n = 107)	LC (n = 215)	BRD (n = 130)	Controls (n = 262)*
Age (mean ± SD)	69.1 ± 9.9	65.4 ± 8.7	61.9 ± 10.5	53.9 ± 12.9
Sex				
Male	89 (83.2%)	181 (84.2%)	114 (87.7%)	208 (79.4%)
Female	18 (16.8%)	34 (15.8%)	16 (12.3%)	54 (20.6%)
Asbestos exposure				
No exposure	19 (17.8%)	125 (58.1%)	19 (14.6%)	54 (20.6%)
Possible	5 (4.7%)	21 (9.8%)	2 (1.5%)	5 (1.9%)
Probable	5 (4.7%)	9 (4,2%)	3 (2.3%)	—
Ascertained	77 (72%)	52 (24.2%)	105 (80.8%)	203 (77.5%)
NOS †	1 (0.8%)	8 (3.7%)	1 (0.8%)	—

* Two hundred and three out of these 262 patients were workers previously exposed to asbestos (for at least a decade). The remaining patients were either blood donors or patients hospitalized for orthopedic traumatic injury or eye disease.
† Not otherwise specified.

Table 2. Serum SMRP concentration (nmol/L) according to tumor morphology and stage

	n (%)	Mean ± SD	Median (range)
Mesothelioma	107	3.05 ± 5.6	1.42 (0.21-40.84)
Histology			
Epithelioid	72 (67.3)	3.72 ± 6.6	1.64 (0.21-40.84)
Mixed	7 (6.5)	1.69 ± 0.7	1.79 (0.48-2.74)
Sarcomatous	10 (9.4)	0.99 ± 0.6	1.02 (0.25-2.16)
Desmoplastic	3 (2.8)	0.5 ± 0.3	0.49 (0.23-0.77)
NOS*	15 (14.0)	2.37 ± 2.7	1.42 (0.42-10.32)
Stage			
I-II	43 (40.2)	2.24 ± 3.8	1.25 (0.23-25.10)
III-IV	45 (42.0)	3.93 ± 7.4	1.51 (0.21-40.84)
NOS*	19 (17.8)	2.83 ± 3.4	1.06 (0.35-10.32)
Lung cancer	215	1.05 ± 1.1	0.82 (0.10-11.84)
Histology			
SCLC	5 (2.3)	0.96 ± 0.5	0.88 (0.44-1.65)
Adenocarcinomas	104 (48.4)	1.14 ± 1.4	0.84 (0.10-11.84)
Squamous	62 (28.8)	0.81 ± 0.5	0.70 (0.10-2.15)
NSCLC	26 (12.1)	0.97 ± 1.0	0.70 (0.16-5.37)
NOS*	18 (8.4)	1.44 ± 1.0	0.99 (0.53-3.61)
Stage			
I-II	43 (20.0)	1.04 ± 0.8	0.85 (0.22-3.91)
III-IV	145 (67.4)	1.06 ± 1.2	0.88 (0.10-11.84)
NOS*	27 (12.6)	1.01 ± 0.7	0.79 (0.22-3.41)
BRD	130	0.76 ± 0.4	0.68 (0.12-2.47)
Asbestosis	12 (9.2)	0.70 ± 0.4	0.69 (0.15-1.74)
BRD, asbestos †	46 (35.4)	0.75 ± 0.3	0.69 (0.20-1.58)
BRD, no asbestos ‡	31 (23.9)	0.72 ± 0.5	0.61 (0.20-2.17)
COPD§	25 (19.2)	0.87 ± 0.5	0.70 (0.33-2.48)
Others‖	16 (12.3)	0.81 ± 0.6	0.68 (0.12-1.83)
Controls	262	0.76 ± 0.4	0.66 (0.16-2.36)
Healthy exposed	203 (77.5)	0.75 ± 0.4	0.64 (0.16-2.36)
Other controls¶	59 (22.5)	0.81 ± 0.4	0.72 (0.20-2.18)

* Not otherwise specified.
† Pleural plaques, asbestos-related pleural thickening.
‡ Interstitial lung diseases, chronic pleuritis.
§ Chronic obstructive pulmonary disease.
‖ Pneumonia, tuberculosis, sarcoidosis, empyema, other benign non–asbestos-related lung and pleural disorders.
¶ Blood donors or patients hospitalized for orthopedic traumatic injury or eye disease.

cancers and BRD or controls were comparable, so comparisons were made between MM (Fig. 2A) or LC and the latter group. The AUC value was 0.77 for both groups of MM regardless of the stage (95% CI, 0.71-0.83) and for patients with stage I to II disease (95% CI, 0.68-0.89; Fig. 2B). In patients with stage III to IV MM, the AUC value was 0.81 (95% CI, 0.72-0.90). AUC was 0.81 (95% CI, 0.75-0.88) in epithelioid or mixed MM and 0.62 (95% CI, 0.40-2.85) in the sarcomatous type.

The best diagnostic efficacy at the 77% level (combination of sensitivity and specificity), was observed with a cutoff of 1.00 nmol/L, with a sensitivity of 68.2%, and a specificity of 80.5% (Table 3). With this cutoff, the probability of a false-negative result (low SMRP values in the presence of MM) was 13.9% and the probability of a false-positive result was 41.1%. Predictive positive value was 0.35% and predictive negative value was 99.96%. Excluding the sarcomatous type, with the same cutoff of 1.00 nmol/L (best diagnostic efficacy, 79%), sensitivity and specificity were 75% and 80.5%, respectively. False-negative results decreased to 8.7%, whereas false-positive results increased to 46.4%. When considering the comparison between MM and LC, the AUC was 0.70 (95% CI, 0.63-0.77). With the same cut-point, the specificity was 68.0%. False-negative results were 32.0%, and false-positive results were 33.5%.

The resulting cutoff points, for both MM and LC, were supported by Akaike information criterion indicating that with an age-, sex-, and asbestos exposure–adjusted model, the best fit observed was with a SMRP value of >1 nmol/L.

SMRP and survival in MM. Most of the patients with MM (101) were followed up. During the study period, 69 patients (68.3%) died. Median follow-up time was 6 months (range, 0.30-57.6 months) and 9.4 months (range, 0.4-51.7 months) for censored and deceased patients, respectively. In agreement with the literature (23), median survival time for the entire group was 13 months. Median survival of patients was 21.5 months (for patients with MM) and 9.8 months (for patients with SMRP), lower and higher than the assumed cutoff of 1 nmol/L, respectively ($P < 0.001$; Fig. 3).

Cox's regression analysis was done on 52 patients for whom data on age, sex, histology, stage, platelet count, chemotherapy, radiotherapy, or surgery were available. A statistically significant prognostic effect on the survival of stage (III-IV versus I-II; HR, 2.06; 95% CI, 1.36-3.11; $P = 0.001$), platelet count (>400 versus ≤400 $10^3/\mu L$; HR, 2.32; 95% CI, 1.47-3.67; $P < 0.001$), age (≥68 versus <68 years; HR, 1.50; 95% CI, 1.04-2.18; $P = 0.03$) was found. Interestingly, SMRP levels above the assumed cutoff of 1 nmol/L were found to be independent predictors of poor survival (HR, 1.62; 95% CI, 1.10-2.39; $P = 0.02$).

SMRP levels in LC. The log of the SMRP mean values were also significantly higher in patients with LC than in patients with BRD ($P = 0.001$) or controls ($P < 0.001$).

Contrary to what was observed in patients with MM, SMRP dosage in LC was not related to histology. No significant difference in SMRP levels was found among different stages of LC (Table 2).

The efficacy of SMRP in discriminating between LC and BRD was 52%. AUC was 0.58 (95% CI, 0.52-0.64). Although associated with a high specificity (79.0%), the sensitivity was

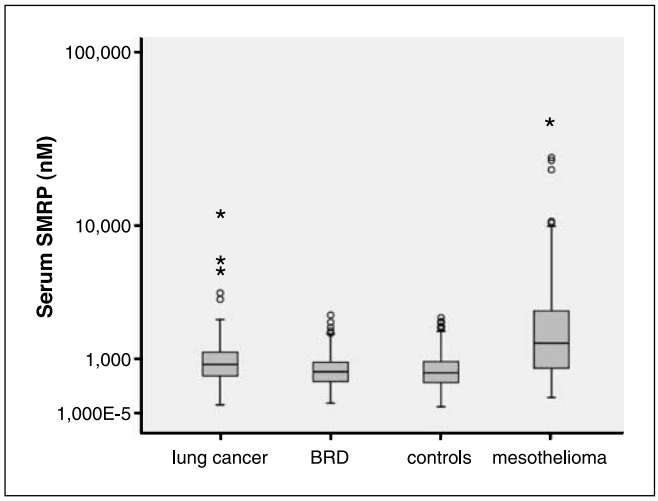

Fig. 1. Serum SMRP concentrations in the population under investigation.

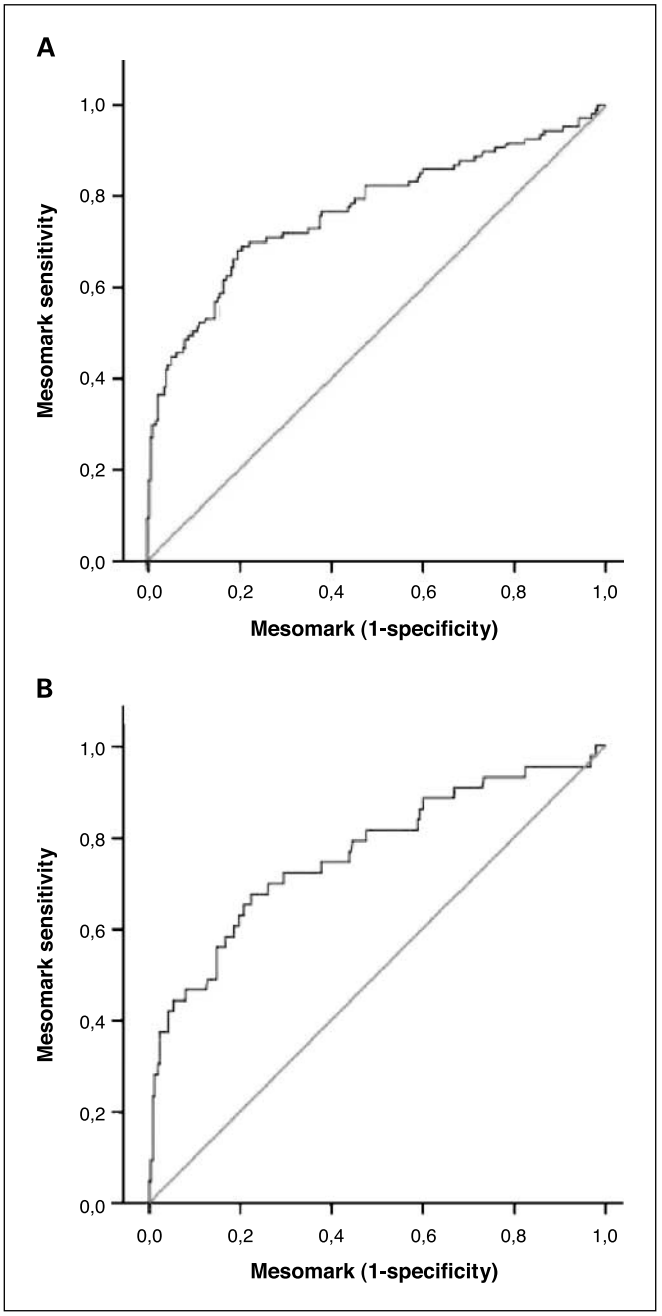

Fig. 2. *A,* Mesomark performance in differentiating between mesotheliomas and controls. *B,* Mesomark performance in differentiating between mesothelioma cases stage I to II and controls.

low (33.0%).The efficacy of SMRP in discriminating between LC and controls was 59.0%. AUC was 0.62 (95% CI, 0.56-0.68), the specificity was 80.2% and the sensitivity was 33.5%.

Discussion

Our study included the largest number of patients with thoracic cancers (107 MM and 215 LC), as well as previously exposed healthy controls (203 individuals), ever tested for SMRP, which is the main target of the clinical application of this test. SMRP levels were significantly higher in patients with MM (mean ± SD, 3.0 ± 5.6) than in patients with LC (1.1 ± 1.3), BRD (0.8 ± 0.4), or controls (0.8 ± 0.4). The difference between LC and BRD or controls were statistically significant as well. Thus, the SMRP levels seemed to be related to MM and, to a lesser extent, to LC. In agreement with previous publications, high SMRP concentrations were detected only in the epithelioid and mixed MM. Moreover, with a multivariate analysis (age-, gender-, and exposure-adjusted) we also found that 1 nmol/L was the best cutoff point for discriminating between MM and controls or BRD and (although with less specificity) between LC and controls or BRD.

With regard to the comparison between patients with MM and controls, we found that the cutoff of 1 nmol/L is associated with a sensitivity of 68.2% and a specificity of 80.5%. Comparing MM and BRD, the specificity was very similar (80.8%).

Robinson et al. (15), comparing 48 patients with MM with 40 asbestos-exposed healthy controls, found a sensitivity of 83% (40 out of 48 patients) and a specificity of 82.5% (33 of 40). Hassan et al. (13), using a different method, observed higher SMRP levels with respect to 24 healthy volunteers and 95 random hospital patients, in 40 out of 56 patients with MM (sensitivity, 71%; specificity, 88% versus hospital patients). Recently, in 74 patients with MM versus 28 patients with benign pleural lesions associated with asbestos exposure, Scherpereel et al. (14) identified a cutoff of 0.93 nmol/L, which allowed the differentiation of MM from benign pleural diseases, with a sensitivity of 80% and a specificity of 82.6%. To date, the difference in mesothelin sensitivity and specificity observed in different studies may reflect differences in methods used or in the size of the populations studied. Both Robinson's and Hassan's groups data were obtained by a self-arranged method of analyzing mesothelin, whereas Scherpereel et al. used the same kit that we did (Mesomark).

In our study, no asbestos exposure effect was observed on SMRP levels in all the categories of patients considered. Furthermore, our results suggest that the presence of very high levels of SMRP (>2.4 nmol/L) may be an additional useful tool for MM diagnosis in those difficult cases with lung

Table 3. Efficacy of SMRP in differentiating between MM or LC and controls

	Mesothelioma						Lung cancer					
Cutoff	TP	FN	FP	TN	Se	Sp	TP	FN	FP	TN	Se	Sp
0.500	94	13	185	77	87.9	29.4	174	41	188	74	80.9	28.2
0.600	91	16	155	107	85.1	40.8	148	67	159	103	68.8	31.2
0.700	83	24	115	147	77.6	56.1	120	95	117	145	55.8	55.3
0.800	77	30	91	171	72.0	65.3	108	107	92	170	50.2	64.9
0.900	76	31	69	193	71.0	73.7	86	129	70	192	40.0	73.3
1.000	73	34	51	211	68.2	80.5	72	143	52	210	33.5	80.2
1.200	60	47	37	225	56.1	85.9	50	165	37	225	23.3	85.9
1.400	54	53	26	236	50.5	90.1	37	178	26	236	17.2	90.1
1.600	49	58	15	247	45.8	94.2	28	187	15	247	13.0	94.3
1.800	43	64	9	253	40.2	96.6	18	197	9	253	8.4	96.6
2.400	29	78	0	262	27.1	100.0	10	205	0	262	4.7	100.0

Abbreviations: TP, true positives; FN, false-negatives; FP, false-positives; TN, true negatives; Se, sensitivity; Sp, specificity.

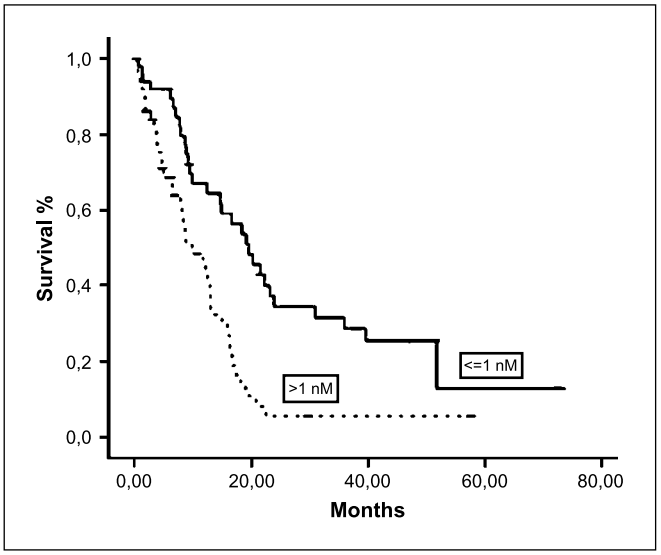

Fig. 3. Survival of mesothelioma patients according to serum SMRP levels.

abnormalities and previous asbestos exposure, when in clinical experience, the advisability of thoracoscopy is often doubtful. Of the 392 patients included in the study who did not suffer from any kind of tumor, neither controls nor patients with BRD presented SMRP levels higher than 2.4 nmol/L. It was observed (12, 13) that SMRP decreases after a surgical debulking procedure, whereas it tends to remain stable in patients who did not respond to chemotherapy, this suggests that SMRP may be a useful marker for monitoring response to treatment, although no previous publications have described a correlation with patient survival. Interestingly, in our study, the results of the Cox's regression analysis indicated that the SMRP concentration is also a significant independent prognostic factor. In fact, median survival of patients with MM was 11.7 months longer for patients with SMRP levels lower than the assumed cutoff of 1 nmol/L compared to those with higher SMRP levels. This is the first evidence that SMRP levels can play this prognostic role in patients with MM. This provides clinicians with an opportunity to consider this test a novel tool for achieving better prediction of tumor aggressiveness in patients with previously histologically demonstrated MM, regardless of its stage.

Mesothelioma is characterized by a long latency period in spite of its rapid, aggressive clinical outcome. Therefore, effective preventive protocols may include very frequent instrumental diagnostic tests done over a long period of time, i.e., decades, which may be neither economical nor ethical. Consequently, the use of early high-sensitivity/high-specificity diagnostic markers is strongly recommended.

In agreement with data previously obtained by other authors (12–17), our findings indicate that SMRP may be a useful marker in the periodic surveillance of individuals previously exposed to asbestos.

The choice of the best cutoff level for clinical practice as well as for surveillance of exposed workers is a crucial point. A highly sensitive cutoff would be responsible for a high number of false-positives, and consequently, a high number of unnecessary potentially harmful radiological tests. On the contrary, a more specific cutoff would reduce the sensitivity. In addition, even with very high levels of sensitivity and specificity, none of these markers could reach a satisfactory positive predictive value for a rare tumor such as mesothelioma. As far as the clinical use of mesothelin dosage in LC is concerned, a few considerations are worth noting. Mesothelin showed a good performance in discriminating between LC and controls or BRD (80.2% and 79.0% of specificity), as well as between MM and LC (68% of specificity). These data suggest that serum mesothelin, together with other exams, may prove helpful in some difficult differential diagnoses (i.e., involving LC versus MM). On the other hand, the ability of the test to detect LC at a cutoff of 1 nmol/L was relatively poor (33% sensitivity) so the feasibility of serum mesothelin dosages in LC screening cannot be proposed. Nevertheless, we believe that among individuals previously exposed to asbestos, those with higher levels of serum SMRP might represent a subgroup at higher risk for either LC or even more so, MM. Therefore, this subgroup at higher risk may need a dedicated medical follow-up (i.e., more frequent diagnostic exams). Currently, further ongoing studies on a larger population are attempting to determine the most appropriate SMRP cutoff to be applied when screening subjects who have been exposed to asbestos.

On the whole, our findings provide evidence that high SMRP dosages can be considered an independent negative prognostic tool for patients with MM. Moreover, they suggest that this test could be helpful for both clinical and preventive purposes.

Acknowledgments

We thank the staff of the "Sezione di Medicina del Lavoro-AOUP" for their assistance in the management of the cases, the Gruppo Italiano Mesotelioma for logistics support, and Cisbio International for the mesothelin measurement kits.

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Clin Cancer Res 2007;13:5076-5081.