The PRAME (preferentially expressed antigen of melanoma) gene was previously shown to be overexpressed in ovarian/primary peritoneal serous carcinoma compared with malignant mesothelioma using gene expression arrays. The objective of this study was to validate this finding at the messenger RNA (mRNA) and protein levels. Quantitative real-time polymerase chain reaction analysis of 126 müllerian carcinomas and 23 malignant mesotheliomas showed significantly higher PRAME mRNA expression in the former tumor (< .001; test sensitivity and specificity, 89% and 91%, respectively). PRAME protein was expressed in 41 of 50 müllerian carcinomas and 0 of 30 mesotheliomas using Western blotting (< .001; test sensitivity and specificity, 82% and 100%, respectively). PRAME levels in müllerian carcinoma were unrelated to survival; however, PRAME protein expression was up-regulated in solid metastases compared with primary carcinoma and effusions (< .001). Our data confirm that PRAME effectively differentiates müllerian mesothelioma at the mRNA and protein levels, suggesting a role in the diagnostic workup of serosal cancers.

The serosal cavities, including the peritoneal, pleural, and pericardial spaces, are frequently affected by cancer. The presence of cancer cells in effusions at these anatomic sites is evidence of advanced-stage disease with metastatic spread and, regardless of the tumor site of origin, marks disease progression and is generally associated with poor survival. One of the most challenging differential diagnoses at this anatomic site is between müllerian serous carcinoma and malignant mesothelioma (MM), tumors that are closely related in terms of clinical manifestations, morphologic features, and immunohistochemical phenotype.

We recently reported on the differential expression of 189 genes in ovarian/primary peritoneal serous carcinoma and diffuse malignant peritoneal mesothelioma (DMPM) effusions studied by using complementary DNA microarray technology. Among the differentially expressed genes, PRAME was identified as a gene that is significantly overexpressed in ovarian/primary peritoneal serous carcinoma effusions compared with DMPM.

Preferentially expressed antigen of melanoma (PRAME) is a 509-amino-acid protein originally identified as an antigen recognized by cytotoxic T lymphocytes from a patient with melanoma. The tumor antigen PRAME is a nonmutated gene whose expression is mostly restricted to tumor cells, as most normal tissues do not express PRAME, the exceptions being testis and, to an even lesser extent, the endometrium, ovary, and adrenal gland. In addition, miniscule amounts of PRAME were found in some samples originating from the kidney, brain, and skin.

The function of PRAME was unknown before the discovery of its acting as repressor of retinoic acid receptor signaling.
Retinoic acid receptor signaling is essential in development, cell fate determination, and tissue homeostasis. By binding to its receptor and subsequent activation, retinoic acid initiates transcription of genes involved in proliferation arrest, differentiation, and apoptosis in a wide variety of cell types. In the context of retinoic acid, PRAME was recently implicated as a regulator of stem cell differentiation. The repressing action of PRAME on retinoic acid receptor signaling is therefore beneficial to cancer cells and tumor development.

PRAME is expressed in a wide range of malignancies, including melanoma, hematologic cancers (reviewed by Greiner et al and Wadelin et al), small blue round cell tumors, including neuroblastoma, medulloblastoma, and Wilms tumor; testicular germ cell tumors; and carcinomas of the breast, lung, kidney, cervix, and head and neck. Hypomethylation of the PRAME gene was found in cell lines from different tumors and in clinical acute myeloid leukemia specimens and suggested to be a mechanism mediating its overexpression in cancer.

Data about the expression and clinical role of PRAME in müllerian carcinoma is limited to reports from one group of investigators. Partheen and coworkers identified PRAME as a gene that is overexpressed in tumors from patients with worse outcome in gene expression analysis of 54 primary ovarian serous carcinomas diagnosed at International Federation of Gynecology and Obstetrics (FIGO) stage III and validated this finding using quantitative real-time PCR (qPCR), but this finding was not reproduced in a subsequent series analyzed using qPCR and Western blotting. The expression and clinical role of PRAME in metastatic müllerian carcinoma is unknown, as is its performance as a diagnostic marker of serosal cancers.

The present study evaluated the diagnostic value of PRAME messenger RNA (mRNA) and protein expression levels in differentiating müllerian carcinoma from MM and the clinical role of PRAME mRNA in the former tumor.

Materials and Methods

Cases and Material

Effusions

The 149 samples analyzed in the present study using qPCR consisted of 118 fresh frozen effusions and 31 surgical specimens.

Effusions consisted of 98 müllerian carcinomas and 20 MMs submitted for routine diagnostic purposes to the Department of Pathology, Norwegian Radium Hospital, Oslo, during the 1998-2011 period. Müllnerian carcinoma effusions (74 peritoneal, 24 pleural) were obtained from 93 patients (5 patients with 2 effusions each) diagnosed with FIGO stage II through IV ovarian carcinoma (n = 77), primary peritoneal carcinoma (n = 11), or carcinoma of the fallopian tube (n = 5). The majority of specimens (82/98 [84%]) were of the serous type. Clinicopathologic data for patients with müllerian carcinoma effusions were obtained from the Department of Gynecologic Oncology, Norwegian Radium Hospital, and are summarized in Table II. The majority of patients (83/93 [89%]) received platinum-based chemotherapy at diagnosis.

The 20 MM effusions consisted of 15 pleural and 5 peritoneal specimens. All were from patients diagnosed with MM of the epithelioid or biphasic type in biopsy specimens.

Effusion specimens were centrifuged immediately after tapping, and cell pellets were frozen at –70°C in equal amounts of RPMI 1640 medium containing 50% fetal calf serum and 20% dimethylsulfoxide. Smears and H&E-stained cell-block sections were reviewed by a surgical pathologist experienced in cytopathology (B.D.). Diagnoses were based on morphologic and immunohistochemical studies. The antibody panel used for differentiating müllerian carcinoma from MM and for establishing the malignant character of the mesothelial cell proliferations included Ber-EP4, B72.3, calretinin, desmin, and epithelial membrane antigen. BG-8 was added as a body panel used for differentiating müllerian carcinoma from MM and for establishing the malignant character of the mesothelial cell proliferations included Ber-EP4, B72.3, calretinin, desmin, and epithelial membrane antigen. BG-8 was added as

<table>
<thead>
<tr>
<th>Table II</th>
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<tr>
<td>Clinicopathologic Data for the Müllerian Carcinoma Effusion Cohort (n = 93)</td>
</tr>
<tr>
<td>Parameter</td>
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<td>---</td>
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<tr>
<td>Age range (mean), y</td>
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<tr>
<td>International Federation of Gynecology and Obstetrics stage</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
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<tr>
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</tr>
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<tr>
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<td>&gt;1 cm</td>
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<td>Complete</td>
</tr>
<tr>
<td>Incomplete§</td>
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<td>ND §</td>
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</table>

NA, not available.

* Unless otherwise indicated.
† Including clear cell, endometrioid, undifferentiated, and mixed histologic types of carcinomas.
‡ Patients with histologically diagnosed müllerian carcinoma for which the primary tumor could not be assessed for assessment of tumor type.
§ Includes effusions from patients with inoperable tumors in cases in which the biopsy specimen was too small for grading and patients who underwent operations in other hospitals for whom the primary tumor could not be assessed for assessment of grade.
|| Includes 9 patients with inoperable tumors and 5 patients with no record.
§ Partial response, stable disease, progression, or allergic or adverse reaction.
|| Includes patients who received no chemotherapy and patients who died before chemoresponse could be assessed.
a carcinoma marker in some cases, whereas WT-1 was used as a marker of serous differentiation in müllerian carcinoma specimens. The tumor cell population was more than 50% in all specimens analyzed in this study.

Surgical Specimens
In addition to the aforementioned effusions, 28 primary ovarian carcinomas, all of the serous type, and 3 DMPM specimens were examined. The histologic grade of the studied ovarian carcinomas was as follows: low, 5 tumors; and high, 23 tumors. The FIGO stage was as follows: I, 1 case; II, 1 case; III, 20 cases; and IV, 6 cases. Residual disease volume was available for 24 cases, of which 16 were debulked to 1 cm or less and 8 to more than 1 cm.

Surgical specimens were snap-frozen and kept at –70°C with no medium. Frozen sections from all tumors were evaluated for the presence of a more than 50% tumor component and absence of necrosis. H&E-stained sections from these tumors were reviewed to establish tumor type and histologic grade.

Quantitative Real-Time PCR
Total RNA was extracted using the automated sample preparation instrument QiaCube and the RNaseasy Mini Kit (Qiagen, Hilden, Germany). mRNA was reverse transcribed into complementary DNA using Superscript III Reverse Transcriptase (Invitrogen, Carlsbad, CA). The PRAME (NM_206953.1) assay covered exon junction 4-5. Primer specificity was validated by gel electrophoresis. The assay was controlled for primer dimers using the NetPrimer software by PREMIER Biosoft, Palo Alto, CA, as well as for single nucleotide polymorphisms through the National Center for Biotechnology Information database. Primer efficiency was tested using Power SYBR Green (Applied Biosystems, Foster City, CA) with a dilution series of synthetic oligonucleotides as template. The qPCR reaction was run using the Platinum qPCR SuperMix-UDG with ROX solution (Invitrogen) and quantified on the Applied Biosystems 7900HT Sequence Detection System.

Primer and probe sequences were as follows: Forward primer, 5'-CTGGGATCCATGTGGCTCAGGCA-3'; reverse primer, 5'-CATCACATCCCCCTCAGGAAG-3'; and probe Fam 5'-TGTGAGACCCCTTGGAAACCCCTCTCAATAC- AAATGCCC-3' nonfluorescent quencher.

An array of 12 reference genes (TaqMan low-density array human endogenous control panel, Applied Biosystems) was tested to identify the most uniformly expressed transcript in effusion specimens. Based on these results, the expression levels of PRAME were normalized against the housekeeping gene β-glucuronidase (GUS). The GUS primer and probe sequences have been published elsewhere. Standard curves for the GUS assay were commercially produced and purchased from Ipsogen (Marseille, France). Synthetic oligonucleotides were used as standard curve for PRAME. Standard curves were used to obtain copy numbers of PRAME and GUS. The copy number for PRAME was divided by the copy number for GUS to obtain normalized values for PRAME mRNA levels. These normalized values were used for the statistics.

Western Blotting
The material analyzed using Western blotting consisted of 50 müllerian carcinomas (23 effusions, 18 primary ovarian carcinomas, and 9 solid metastases, the majority omental) and 30 MM effusions (26 pleural, and 4 peritoneal). In addition, 6 benign reactive effusions containing a large number of mesothelial cells were analyzed. All müllerian carcinoma specimens were from the Norwegian Radium Hospital. The MM effusions were from the Norwegian Radium Hospital and Aalborg University Hospital, Aalborg, Denmark, and specimens from Aalborg were used with permission from Søren Nielsen. Specimens analyzed using qPCR included 11 müllerian carcinoma effusions, 6 primary ovarian carcinomas, and 12 MM effusions. Specimens were diagnosed as described.

Cells were lysed in 1% NP-40, 20 mmol/L tris (hydroxymethyl)aminomethane (Tris) hydrochloride (pH 7.5), 137 mmol/L sodium chloride, 0.5 mmol/L EDTA, 10% glycerol, 1% protease inhibitor cocktail (Sigma-Aldrich, St Louis, MO), and 0.1% sodium dodecyl sulfate (SDS). Following centrifugation, the supernatant was collected, and protein content was evaluated by the Bradford assay. Thirty micrograms from each sample under reducing conditions were loaded into each lane and separated by electrophoresis on a 12% SDS polyacrylamide gel. Following electrophoresis, proteins were transferred to Immobilon transfer membranes (Millipore, Billerica, MA). Nonspecific binding was blocked by incubation with TBST (10 mmol/L Tris-HCl [pH 8.0], 150 mmol/L sodium chloride, and 0.1% polysorbate-20) containing 5% skim milk for 1 hour at room temperature. Membranes were subsequently incubated with a mouse polyclonal antibody against PRAME (catalog No. H00023532-B01P; Novus Biologicals, Littleton, CO) and an α-tubulin antibody (Sigma-Aldrich) at dilutions of 1:1,000 and 1:5,000, respectively. Antibody was detected using peroxidase-conjugated AffiniPure goat antirabbit IgG (Jackson ImmunoResearch, West Grove, PA) and enhanced chemiluminescence Western blotting detection reagents (Thermo Fisher Scientific, Waltham, MA). Densitometer analysis of the Western blotting bands was performed using a computerized image analysis (NIH IMAGE 1.63) program, and the values for PRAME were divided by the α-tubulin band size to yield a final expression value. A ratio of less than 0.05 was considered negative.

Statistical Analysis
Statistical analysis was performed using the SPSS-PC package (version 17.0, SPSS, Chicago, IL). Probability
of less than .05 was considered significant. The Mann-Whitney U test was used to analyze the differences in PRAME mRNA and protein expression between müllerian carcinoma and MM and to compare expression in primary ovarian carcinoma and müllerian carcinoma effusions by qPCR. The Kruskal-Wallis test was applied to a 3-tier analysis of PRAME protein expression in primary ovarian carcinoma, müllerian carcinoma effusions, and solid metastases.

The Mann-Whitney U test was also applied to analyses investigating the association between gene expression and clinicopathologic parameters (effusion site, age, histologic grade, FIGO stage, residual disease volume, previous chemotherapy, and response to chemotherapy at diagnosis) in müllerian carcinoma. For these analyses, clinicopathologic parameters were grouped as follows: age, 60 years of younger vs older than 60 years; histologic grade, low vs high; FIGO stage, III vs IV; residual disease volume, 1 cm or less vs more than 1 cm; previous chemotherapy, yes vs no; response to chemotherapy at diagnosis, complete vs partial response, stable disease, or progression.

Survival data were available for all patients with müllerian carcinoma. Univariate survival analyses of progression-free survival (PFS) and overall survival (OS) were executed using the Kaplan-Meier method and groups compared with the log-rank test. For this analysis, expression levels were grouped as low or high based on median values. For patients with more than 1 effusion, expression in the first specimen was analyzed.

Results

PRAME Is Overexpressed in Müllerian Carcinoma Compared With MM at the mRNA and Protein Levels

PRAME mRNA expression analysis using qPCR showed pronounced differences between müllerian carcinoma (n = 97; 1 failed test) and MM (n = 18; 2 failed tests) effusions with respect to PRAME copy number, with a müllerian carcinoma effusion expression range of 0 to 2,733 (median, 310) vs a range of 0 to 59 (median, 0) for MM (P < .001). With the exception of 2 effusions from a patient with pleomorphic

![Image 1](https://example.com/image1.png)

Image 1: Preferentially expressed antigen of melanoma (PRAME; A and B) and β-glucuronidase (GUS; C and D) messenger RNA (mRNA) expression in müllerian carcinoma (A and C) and malignant mesothelioma (MM; B and D) effusions. Quantitative real-time polymerase chain reaction amplification plots for PRAME and GUS mRNA in müllerian carcinoma and MM effusions. Cases were run in triplicate. PRAME mRNA expression is much higher in müllerian carcinoma compared with MM effusions, whereas the reference gene GUS is uniformly expressed.

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MM, in which expression of 38 and 59 copies was found, all MM effusions had levels of 7 copies or fewer. At a cutoff at 10 copies, test sensitivity and specificity were at 89% and 91%, respectively, whereas a cutoff at 100 copies resulted in test sensitivity and specificity of 76% and 100%, respectively. The 3 solid MM specimens had 0 or 1 copy.

Primary ovarian serous carcinomas had a PRAME expression range of 0 to 2,894 (median, 499). In statistical analysis, the difference between müllerian carcinoma effusions and primary ovarian carcinomas was not significant ($P > .05$). Values of the reference gene GUS showed little variation across different samples, irrespective of tumor type or anatomic site (Image 1).

Testing of the PRAME mouse polyclonal antibody for performance in immunohistochemistry applied to formalin-fixed, paraffin-embedded tissue showed unsatisfactory results (data not shown). We consequently performed Western blotting analysis of fresh frozen effusions and surgical specimens. By Western blotting, PRAME protein was detected in 41 (82%) of 50 müllerian carcinomas and 0 (0%) of 30 MMs ($P < .001$), with test sensitivity and specificity at 82% and 100%, respectively Image 2. All 27 surgical ovarian carcinoma specimens were PRAME+; the 9 negative specimens were effusions. PRAME protein was additionally absent in 6 reactive effusions. Comparative analysis of müllerian carcinoma specimens of different anatomic sites showed highest PRAME expression in solid metastases, followed by primary ovarian carcinoma, with the lowest levels in effusions ($P < .001$).

**PRAME Expression in Müllerian Carcinoma Is Unrelated to Disease Outcome**

Analysis of the clinical role of PRAME was performed exclusively for the qPCR data owing to the small number of specimens from each anatomic site analyzed by Western blotting. PRAME mRNA expression in effusions was unrelated to any of the clinicopathologic parameters of this cohort, including age, histologic grade, FIGO stage, residual disease volume, and response to chemotherapy at diagnosis. Expression was similarly unrelated to previous exposure to chemotherapy ($P > .05$). In primary ovarian carcinoma, higher PRAME mRNA expression was found in high-grade compared with low-grade tumors ($P = .008$), with no association with the remaining clinicopathologic parameters ($P > .05$).

The follow-up period for the 93 patients with müllerian carcinoma with effusions analyzed using qPCR ranged from 1 to 120 months (median, 25 months). PFS ranged from 0 to 66 months (median, 4 months), with 38 patients never achieving a disease-free period. At the last follow-up, 1 patient was alive with no evidence of disease, 4 patients were alive without disease, and 87 patients had died of disease. One patient died of an unrelated cause.

**Image 2** Preferentially expressed antigen of melanoma (PRAME) protein is selectively expressed in müllerian carcinoma. Western blotting for the PRAME protein shows high expression in primary ovarian carcinoma (A) and solid metastases (B), with lower expression in müllerian carcinoma effusions (C). Malignant mesothelioma effusions are uniformly negative (D). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as the loading control.
In univariate survival analysis of the entire müllerian carcinoma effusion cohort, \textit{PRAME} mRNA expression (grouped as low or high based on median value) was unrelated to PFS or OS ($P > .05$; data not shown). Residual disease volume and chemoresponse at diagnosis were the clinicopathologic parameters that were significantly associated with OS ($P = .037$ and $P < .001$ for residual disease volume and chemoresponse, respectively) and PFS ($P = .021$ and $P < .001$, respectively) in univariate analysis.

\textit{PRAME} mRNA expression levels were similarly unrelated to OS or PFS in separate analyses of the data for patients with prechemotherapy and postchemotherapy effusions or in analysis of primary ovarian carcinoma ($P > .05$; data not shown).

\textbf{Discussion}

\textit{PRAME} has been documented to be expressed in multiple cancer types, in many of which it is overexpressed compared with the corresponding normal tissue. Its role in differentiating between various cancer types has, nevertheless, not been explored to date.

The differentiation of müllerian carcinoma from MM may pose difficulties because these tumors morphologically resemble each other and coexpress many of the diagnostic markers used in surgical pathology and effusion diagnosis. In recent years, several specific markers that differentiate the majority of serous müllerian carcinomas from MMs have been identified. In a recent comprehensive review by Husain et al,\textsuperscript{33} calretinin and D2-40 were recommended as MM markers in this differential diagnosis, whereas MOC-31, Ber-EP4, BG8, and estrogen receptor were found to be useful serous müllerian carcinoma markers.

Despite improvements in this area, it is still important to identify and validate new high-throughput markers that can aid in differentiating these 2 cancer types in cases with equivocal immunohistochemical profiles. In agreement with the Affymetrix gene expression microarray analysis previously done by Davidson et al,\textsuperscript{3} the present study validated the finding of significantly higher \textit{PRAME} mRNA levels in müllerian carcinoma compared with MM using qPCR. Previous work by our group has shown that the folate receptor genes \textit{FOLR1} and \textit{FOLR3}, \textit{SCARA3} (scavenger receptor class A, member 3), and \textit{EHF} (Ets homologous factor) are overexpressed in müllerian carcinoma compared with MM, while \textit{TNXB} (tenascin-X) and \textit{PINCH-2} (particularly interesting new cysteine-histidine-rich) are overexpressed in MM compared with müllerian carcinoma.\textsuperscript{34-38} \textit{PRAME} mRNA expression data revealed cutoff copy numbers that could be used as a means of excluding MM when müllerian carcinoma has equivocal effusion cytology. Furthermore, despite the small number of MM biopsy specimens analyzed in the present study, our findings suggest that the diagnostic role of \textit{PRAME} may apply to surgical specimens as well because levels of this gene were high in primary ovarian carcinoma and very low in MM specimens. Based on these studies and additional studies that are currently submitted for publication or in preparation, we are in the process of developing a diagnostic qPCR panel for effusion diagnosis.

The translation of mRNA to protein is affected by posttranscriptional modifications, microRNAs, and epigenetic regulation, which may result in poor correlation between mRNA concentrations and the amount of protein produced. The excellent agreement between the mRNA and protein expression of \textit{PRAME} in the present study indicates that protein expression faithfully reflects the quantity of mRNA in the cancers studied and suggests that Western blotting is another method by which müllerian carcinoma and MM may be differentiated. It is interesting that \textit{PRAME} protein seems to be absent in benign reactive mesothelial cells, another entity that may be difficult to distinguish from well-differentiated müllerian carcinoma, adding to the power of this assay.

Soikkeli et al\textsuperscript{11} identified \textit{PRAME} as a useful gene for detecting melanoma micrometastasis. However, data regarding the differential expression of \textit{PRAME} at different anatomic sites within a given tumor entity are largely unavailable. In the present study, \textit{PRAME} transcript levels did not differ between müllerian carcinoma effusions and primary ovarian carcinomas. In contrast, \textit{PRAME} protein expression levels significantly differed at various anatomic sites of müllerian carcinoma, with highest levels in solid metastases, followed by primary ovarian carcinoma, and lowest levels in effusions. The fact that \textit{PRAME} is differentially expressed at the protein level at these anatomic sites suggests that its biologic function is modulated along tumor progression in this cancer. This increase in protein expression level may reflect the profound changes that tumor cells undergo as they spread from the primary tumor to distant sites, which may include altered phenotype due to cross-talk with cells in the new microenvironment, and new or altered survival cues within the cancer cell. The decreased \textit{PRAME} protein expression levels in effusions are especially likely to result from a change in the tumor microenvironment. Within solid organs, tumor cells are able to induce leaky vessels and obtain nutrients and oxygen, in addition to gaining access to the circulation. When present in effusions, however, tumor cells are in a unique microenvironment with reduced direct access to oxygen and nutrients and no longer in interaction with stromal myofibroblasts and endothelial cells, resulting in altered mRNA and protein expression.\textsuperscript{39} The molecular partners of müllerian carcinoma cells at each of these anatomic sites are yet to be identified.
The clinical role of PRAME in cancer seems to be related to the type of cancer studied. Whereas several studies have identified a predictive and/or prognostic role for PRAME in breast carcinoma,

19-21 and in neuroblastoma,

14 no such role was found in head and neck carcinoma.

27 Partheen et al reported on the prognostic role of PRAME levels in primary serous advanced-stage ovarian carcinoma but were unable to reproduce this finding in an independent ovarian carcinoma cohort. Our analysis of the clinical role of PRAME in metastatic müllerian carcinoma suggests that its mRNA levels in effusion specimens are unrelated to any clinicopathologic parameters, including PFS and OS. In our limited series of primary serous ovarian carcinoma, higher PRAME mRNA expression levels were detected in high-grade compared with low-grade tumors, indicating increased activity of PRAME in less differentiated tumors. However, as with effusions, no association was found with survival. The number of specimens from each anatomic site analyzed for PRAME protein expression was too small to enable us to perform survival analysis. However, in view of the high PRAME protein levels in solid metastases, analyzing the prognostic role of this protein in these lesions in the future may be of interest.

qPCR analysis and Western blotting confirmed that PRAME effectively differentiates müllerian carcinoma from MM at the mRNA and protein levels, suggesting PRAME to be a novel marker in the diagnostic panel of serosal tumors. Western blotting additionally identified high PRAME protein levels in solid metastatic ovarian carcinoma, suggesting a role for this protein in disease progression, although not as a prognosticator. The biologic interactions involved in these tumor type–specific and anatomic site–related differences are yet to be established.

References


