NY-BR-1 and PAX8 Immunoreactivity in Breast, Gynecologic Tract, and Other CK7+ Carcinomas

Potential Use for Determining Site of Origin

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Key Words: NY-BR-1; PAX8; Breast; Gynecologic tract; Upper gastrointestinal tract; Pancreatic carcinoma; Cholangiocarcinoma

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Abstract

The distinction between breast and müllerian carcinomas from each other and from tumors with a similar cytokeratin profile can be difficult. We tested the usefulness of 2 new markers, NY-BR-1 and PAX8, by staining a variety of breast and gynecologic carcinomas, along with tumors of pancreas, bile ducts, stomach, and gastroesophageal junction. NY-BR-1 expression (ie, H score >10) was seen in 58.4% of breast carcinomas (111/190), 5.6% of müllerian carcinomas (8/142), 7% of pancreatic tumors (1/15), 0% of cholangiocarcinomas (0/22), 0% of gastric tumors (0/36), and 0% of gastroesophageal carcinomas (0/25). All 188 breast carcinomas were negative for PAX8. PAX8 expression was seen in 72.4% of müllerian tumors (105/145). All pancreatic tumors (n = 15), cholangiocarcinomas (n = 23), and gastric (n = 35) and gastroesophageal junction (n = 25) carcinomas were negative for PAX8. Addition of NY-BR-1 and PAX8 in a panel would be useful in distinguishing breast cancer, gynecologic tumors, and tumors of the upper gastrointestinal tract.

Synchronous and metasynchronous breast and gynecologic tumors can present a diagnostic problem to clinicians and pathologists. Breast cancer metastasis to the ovary has been reported in 10% to 30% of autopsy cases and in a substantial number of prophylactic oophorectomy specimens. Women with BRCA1 or BRCA2 mutations are at an increased risk for primary breast and ovarian carcinomas, with breast cancer usually occurring first and ovarian cancer diagnosed later in life. Breast and gynecologic carcinomas can share morphologic features and often have similar immunohistochemical profiles. An accurate diagnosis is of the utmost importance in these cases because the decision to undergo a specific surgical procedure and chemotherapeutic agents will differ for each diagnosis. We tested the usefulness of 2 recently described markers, PAX8 and NY-BR-1.

PAX8 is a member of the PAX gene family and has a crucial role in the development of the kidneys, thyroid, and müllerian system. Gene expression analysis using DNA microarrays showed that PAX8 was more highly expressed in ovarian carcinomas than in breast carcinomas. Bowen et al demonstrated PAX8 expression in the majority of nonmucinous epithelial ovarian carcinomas and in benign nonciliated secretory epithelium of the oviduct. A recent study comparing immunohistochemical staining of PAX8 and WT1 in breast and ovarian carcinomas suggests that PAX8 is more sensitive and specific for ovarian nonmucinous surface epithelial carcinomas than WT1.

NY-BR-1 is a mammary differentiation antigen that is expressed in normal breast tissue and its malignant counterpart...
but is not expressed in other tissues. It was first identified by Jager et al.\textsuperscript{11} using the serologic analysis of recombinant complementary DNA expression library (SEREX) in 2001. Reverse transcription–polymerase chain reaction revealed that messenger RNA expression of NY-BR-1 in benign tissues was limited to mammary glands, testis, and placental tissues. Messenger RNA expression in mammary and nonmammary tumors was predominantly limited to breast cancer samples.\textsuperscript{12}

Messenger RNA expression in mammary and nonmammary tumors was limited to mammary glands, testis, and placental tissues. Reverse transcription–polymerase chain reaction revealed that complementary DNA expression library (SEREX) in 2001.

The aim of this study was to compare the immunohistochemical staining patterns of PAX8 and NY-BR-1 in several morphologic types of primary gynecologic malignancies, including ovarian, endometrial, and cervical carcinomas, with the expression in primary breast carcinomas. Furthermore, we also examined NY-BR-1 and PAX8 expression in other carcinomas that can have a cytokeratin (CK)7+/CK20– profile but lack specific markers and are sometimes difficult to distinguish from breast and müllerian tumors.

Materials and Methods

Case Selection and Construction of Tissue Microarray

Breast cancer cases included consecutive invasive breast carcinomas represented on tissue microarrays (TMAs) with 3-fold redundancy. Four TMAs were constructed using 0.6-mm cores on a manual microarrayer, MTA1 (Beecher Instruments, Sun Prairie, WI). Initially, the TMAs were constructed from 198 cases consisting of 181 ductal (91.4%), 14 lobular (7.1%), and 3 mixed ductal and lobular (1.5%) carcinomas. However, owing to tissue loss, NY-BR-1 results were available for 190 cases (176 ductal, 12 lobular, and 2 mixed) and PAX8 results were available for 188 cases (174 ductal, 12 lobular, and 2 mixed).

The breast carcinomas were previously examined (at diagnosis) for Nottingham grade, pathologic stage, hormone receptor (HR) status, and HER2 status. Breast cancers were further classified into 4 categories as HR+/HER2–, HR+/HER2+, HR–/HER2+, or HR–/HER2– to study the correlation between the new markers and the most well-known prognostic/predictive markers of breast cancer. At our institution, HR staining is scored using a semiquantitative H score–like method that details the percentage of cells showing no, weak, moderate, or strong staining. The score is given as the sum of the percentage of staining multiplied by an ordinal value corresponding to the intensity level (0, none; 1, weak; 2, moderate; 3, strong). With 4 intensity levels, the resulting score ranges from 0 (no staining in the tumor) to 300 (diffuse strong staining of the tumor). In this study, a tumor was considered HR+ if it showed an H score of more than 10 for estrogen or progesterone receptor. The tumor was considered HER2+ if it showed 3+ immunohistochemical expression or an HER2/CEP17 ratio of more than 2.2 by fluorescence in situ hybridization.

The TMAs of 148 randomly selected gynecologic tumors were similarly constructed and included endometrioid endometrioid carcinoma (n = 39), endometrial nonendometrioid carcinoma (n = 16), endocervical carcinoma (n = 38), ovarian clear cell carcinoma (n = 34), ovarian endometrioid tumor (n = 5), and ovarian serous carcinoma (n = 16). The nonendometrioid endometrioid tumors included 8 serous, 3 clear cell, 3 undifferentiated, 1 mixed serous and clear cell, and 1 carcinosarcoma. The endocervical tumors included 20 typical endocervical type, 9 endometrioid, 4 adenoid basal, 3 serous papillary, and 2 mesoneoplastic carcinoma.

In addition to breast and müllerian tumors, TMAs of pancreatic tumors, cholangiocarcinomas, gastric tumors, and gastroesophageal junction adenocarcinomas were also examined for NY-BR-1 and PAX8. These tumors were selected because they can have a CK7+/CK20– immunoprofile and lack specific markers (unlike lung and thyroid adenocarcinomas).

The pancreatic tumor TMA consisted of 15 tumors, 12 ductal adenocarcinomas, and 3 intraductal pancreatic mucinous neoplasms. NY-BR-1 and PAX8 results were available for all cases.

The cholangiocarcinoma array consisted of 34 cholangiocarcinomas, 20 extrahepatic and 14 intrahepatic. However, owing to significant tissue loss, NY-BR-1 results were available for 22 cases (15 extrahepatic and 7 intrahepatic) and PAX8 results for 23 cases (16 extrahepatic and 7 intrahepatic).

The gastroesophageal junction tumor TMA consisted of 26 adenocarcinomas. NY-BR-1 and PAX8 results were available for 25 cases. In addition, this TMA also contained several cases of Barrett esophagus and high-grade dysplasia. NY-BR-1 and PAX8 results were available for 12 cases of Barrett esophagus and 17 cases of high-grade dysplasia.

Stomach TMA ST801 slides containing 38 stomach tumors and 40 normal stomach mucosae were purchased from US Biomax, Rockville, MD. According to the company, the tumors consisted of 36 carcinomas and 2 carcinoid tumors. NY-BR-1 results were available for 36 tumors and 39 normal cases. PAX8 results were available for 35 tumors and 38 normal cases.

Immunohistochemical Staining and Scoring

Each TMA section (4 μm thick) was stained with NY-BR-1 mouse monoclonal antibody (clone NY-BR-1 No.
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2, Labvision product, Thermo Fisher Scientific, Fremont, CA). The protocol consisted of pretreatment with CC1 cell conditioning (Ventana Medical Systems, Tucson, AZ) at pH 8.0. The antigen-antibody complexes were detected by using iView DAB (Ventana) detection on a Ventana BenchMark XT. The protocol also included biotin blockage to block endogenous biotin. Only cytoplasmic staining was used for scoring. The tumors were semiquantitatively scored using the H score method as described with the score ranging from 0 (negative) to 300 (diffuse strong reactivity).

For PAX8, each TMA section was stained with rabbit polyclonal antibody (dilution 1:50; Protein Tech Group, Chicago, IL). The pretreatment was performed with citrate (pH 6.0) microwave, and the detection was performed with Universal ImmPRESS (Vector Laboratories, Burlingame, CA). Only nuclear staining was used for scoring. All tumors were semiquantitatively scored using the H score method. Although, an H score method was used for NY-BR-1 and PAX8 scoring, cases were subsequently divided into positive and negative for statistical analysis. The cases showing an H score of more than 10 were considered positive.

Statistical Analysis
Statistical analysis was performed using SPSS software, version 16.0 (SPSS, Chicago, IL). Univariate analysis was performed by using χ² and Fisher exact tests to compare the differences in percentages between groups. A P value of less than .05 was considered significant.

Results
NY-BR-1 Staining in Primary Breast Carcinomas
Benign ductal epithelium present adjacent to tumors and in initial validation slides showed moderate-intensity staining Image 1. Among the carcinomas, the staining intensity in our series ranged from negative to diffuse strongly positive (Image 1). The staining was mainly cytoplasmic; however, in moderate to strongly positive tumors, nuclear staining was also observed (Image 1). NY-BR-1 was positive in 58.4% of all tumors (111/190). If only HR+ tumors are considered, the sensitivity would be slightly higher (68%). NY-BR-1 expression was strongly associated with estrogen receptor expression (P < .0001) and progesterone receptor expression (P < .0001). The mean and median H scores for NY-BR-1 staining with respect to HRs and HER2 expression are shown in Table 1. As a vast majority of HR+ tumors are well-differentiated, NY-BR-1 expression was also related to Nottingham grade (P < .0001). NY-BR-1 was positive in 42 (82%) of 51 grade I tumors, 53 (63%) of 84 grade II tumors, and only 16 (29%) of 55 grade III tumors. There was no statistically significant association between NY-BR-1 expression with respect to HER2 status, tumor size, lymph node status, or overall tumor stage.

NY-BR-1 Staining in Gynecologic Tumors
Endometrial, endocervical, and ovarian tumors were only rarely positive for NY-BR-1 expression. However, among these 3 sites, the expression was slightly more common in endometrial tumors than in ovarian or endocervical tumors (P = .013). Unlike the primary breast carcinomas, none of the tumors showed strong staining. The maximum H score was only 60, seen in 1 endometrial endometrioid tumor and in 1 ovarian endometrioid tumor.

PAX8 Staining in Primary Breast Carcinomas
All 188 breast carcinomas were negative for PAX8 expression. Although an H score of more than 10 was a requirement for a positive result in this study, none of the tumors showed an H score of even 1.

PAX8 Staining in Gynecologic Tumors
PAX8 expression (albeit weak) was seen in all 6 benign endometrium samples present within the TMA Image 2. Among the gynecologic tract tumors, PAX8 was more often positive in endometrial and ovarian tumors (Image 2) compared with cervical tumors (P = .004). The mean and median PAX8 H scores on positive cases are shown in Table 3 for all gynecologic tumors. In endometrium, PAX8 expression was seen in 33 (85%) of 39 endometrioid tumors and in 14 (88%) of 16 nonendometrioid tumors. No statistical difference was identified between endometrioid and nonendometrioid tumors for PAX8 staining (P = .783). In endocervical tumors, PAX8 expression was seen in 12 (63%) of 19 typical endocervical tumors and in 8 (44%) of 18 variant endocervical tumors. No statistical difference was identified between typical endocervical and variant tumors for PAX8 staining (P = .330). Similarly, PAX8 was not differentially expressed in various morphologic subtypes (serous, endometrioid, and clear cell) within the ovary (P = .347).

NY-BR-1 and PAX8 Staining in Other Tumors
Tumors from 4 nonbreast, nonmüllerian sites, but with a similar CK profile (CK7+/CK20–) were also stained with NY-BR-1 and PAX8. Of the 15 pancreatic tumors, only 1 (ductal adenocarcinoma) was positive for NY-BR-1, with an H score of 150, ie, moderate reactivity. All 15 pancreatic tumors were negative for PAX8. All cholangiocarcinomas were negative for NY-BR-1 (n = 22) and PAX8 (n = 23). All cases had an H score of 0 except 1 case that showed an H score of 10 for NY-BR-1.
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Image 1  A. Moderate reactivity for NY-BR-1 in a normal breast lobule (×200). B-D. Breast carcinomas showed variable reactivity for NY-BR-1 that ranged from weak (B, ×200) to moderate (C, ×200) to strong (D, ×200). Although the majority of cases showed cytoplasmic reactivity, the entire cell is stained in a strongly positive case (D).

Table 1
NY-BR-1 Expression With Respect to HRs and HER2 Expression in Breast Carcinoma

<table>
<thead>
<tr>
<th>Tumor Group</th>
<th>No. Positive/ Total (%) for NY-BR-1</th>
<th>Mean (Median) H Score for Positive Cases</th>
<th>Maximum H Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2−</td>
<td>94/134 (70.1)</td>
<td>78 (65)</td>
<td>300</td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>16/18 (56)</td>
<td>34 (20)</td>
<td>120</td>
</tr>
<tr>
<td>HR−/HER2+</td>
<td>3/6 (50)</td>
<td>138 (100)</td>
<td>300</td>
</tr>
<tr>
<td>HR−/HER2−</td>
<td>4/30 (13)</td>
<td>96 (115)</td>
<td>135</td>
</tr>
</tbody>
</table>

HR, hormone receptor.

Table 2
NY-BR-1 Expression in Gynecologic Tumors

<table>
<thead>
<tr>
<th>Site and Tumor Type</th>
<th>No. Positive/ Total (%) for NY-BR-1</th>
<th>Mean (Median) H Score for Positive Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial endometrioid</td>
<td>4/39 (10)</td>
<td>31 (25)</td>
</tr>
<tr>
<td>Endometrial nonendometrioid</td>
<td>3/16 (19)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Endocervical carcinomas</td>
<td>0/34 (0)*</td>
<td>—</td>
</tr>
<tr>
<td>Ovarian serous</td>
<td>0/16 (0)*</td>
<td>—</td>
</tr>
<tr>
<td>Ovarian endometrioid</td>
<td>0/15 (0)*</td>
<td>—</td>
</tr>
<tr>
<td>Ovarian clear cell</td>
<td>0/32 (0)*</td>
<td>—</td>
</tr>
</tbody>
</table>

* Data not available for 4 cases.
† Data not available for 2 cases.
Discussion

Although they are not common, breast cancers can metastasize to the gynecologic tract, and gynecologic tract carcinomas can metastasize to the breast. In either scenario, there is a significant potential for misdiagnosis if a high degree of suspicion is lacking. An even more difficult scenario is the presence of adenocarcinoma at a metastatic site in a patient with a high risk for developing breast and gynecologic tract carcinoma, such as carriers of BRCA1 and BRCA2 mutations and obese patients. A panel of immunohistochemical stains such as CK7 and CK20, WT1, HRs, CA-125, mammaglobin, and gross cystic disease fluid protein (GCDFP)-15 is useful in these difficult cases.
Pancreatic ductal carcinomas.4,23,24 GCDFP-15 is a specific marker of breast carcinoma, but it has very low sensitivity, too low to be helpful in small specimens. Although NY-BR-1 expression was identified in 10% of breast mucinous carcinomas25 and rare reactivity in breast micropapillary carcinomas,26 it still is a useful marker to distinguish ovarian serous carcinomas from other tumors. Even after the addition of these specific markers, the distinction between breast and müllerian tumors (particularly the nonserous type) remains challenging,2,4,23 especially in small core biopsy specimens.

For breast vs müllerian tract carcinomas, WT1 and MIB-1 are often the first step in immunohistochemical assessment of an adenocarcinoma of an unknown primary site is examination of its differential CK7 and CK20 profile. In a carcinoma with a CK7+/CK20− profile, the differential diagnosis for site of origin is broad and includes breast, müllerian (gynecologic tract), lung, thyroid, upper gastrointestinal tract, and pancreatobiliary tract carcinomas. Addition of specific markers such as thyroid transcription factor-1 for lung and thyroid, thyroglobulin for thyroid, HRs for breast and müllerian tumors, mammaglobin and GCDFP-15 for breast, and rare reactivity in breast micropapillary carcinomas,26 some additional value in distinguishing between breast and müllerian endometrioid tumors because both are CK7+/ CK20− and express HRs.

For breast vs müllerian tract carcinomas, WT1 and GCDFP-15 are most distinctive, and, to a certain extent, mammaglobin is distinctive. All morphologic types of ovarian, endometrial, cervical, and breast adenocarcinomas generally show a CK7+/CK20− immunoprofile. HRs are variably expressed in breast and gynecologic tumors, and the expression is strongest in well-differentiated carcinomas. Mammaglobin, a sensitive marker of breast carcinoma, is also expressed in approximately 40% of müllerian tumors with endometrioid morphologic features and, therefore, may not be very useful in this differential. Studies report up to 90% positivity of CA-125 in ovarian carcinomas, but, unfortunately, the rate of positivity in breast carcinomas ranges from 10% to 40%, and CA-125 expression has also been reported in a high number of cholangiocarcinomas and pancreatic ductal carcinomas.4,23,24 GCDFP-15 is a specific marker of breast carcinoma, but it has very low sensitivity, especially in small core biopsy specimens.

Table 3
PAX8 Expression in Gynecologic Tumors

<table>
<thead>
<tr>
<th>Site and Tumor Type</th>
<th>No. Positive/ Total (%) for PAX8</th>
<th>Mean (Median) H Score for Positive Cases</th>
<th>Maximum H Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>33/39 (85)</td>
<td>92 (90)</td>
<td>200</td>
</tr>
<tr>
<td>Serous</td>
<td>8/8 (100)</td>
<td>111 (105)</td>
<td>200</td>
</tr>
<tr>
<td>Clear cell</td>
<td>3/3 (100)</td>
<td>90 (100)</td>
<td>120</td>
</tr>
<tr>
<td>Mixed serous and clear cell</td>
<td>1/1 (100)</td>
<td>100 (100)</td>
<td>100</td>
</tr>
<tr>
<td>MMMT Undifferentiated</td>
<td>2/3 (67)</td>
<td>45 (45)</td>
<td>50</td>
</tr>
<tr>
<td>Endocervix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>12/19 (63)*</td>
<td>66 (60)</td>
<td>100</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>6/9 (67)</td>
<td>62 (60)</td>
<td>110</td>
</tr>
<tr>
<td>Mesonephric</td>
<td>0/2 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serous</td>
<td>2/3 (67)</td>
<td>80 (80)</td>
<td>120</td>
</tr>
<tr>
<td>Adenoid basal</td>
<td>0/4 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>12/15 (80)*</td>
<td>86 (75)</td>
<td>210</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>3/5 (60)</td>
<td>70 (90)</td>
<td>90</td>
</tr>
<tr>
<td>Clear cell</td>
<td>23/33 (70)*</td>
<td>94 (80)</td>
<td>250</td>
</tr>
</tbody>
</table>

Table 4
NY-BR-1 and PAX8 Staining in Nonbreast, Nonmüllerian Lesions and Tumors

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. Positive/ Total (%) for NY-BR-1</th>
<th>No. Positive/ Total (%) for PAX8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Pancreatic IPMN</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>0/3 (0)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>Gastric adenocarcinoma</td>
<td>0/3 (0)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>Gastric carcinoid</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>GE junction adenocarcinoma</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Barrett esophagus</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Gastric mucosa</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
</tbody>
</table>

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would strongly suggest a breast primary tumor. Although weak NY-BR-1 reactivity was identified in Barrett esophagus and benign mucosal glands in the stomach, all malignant upper gastrointestinal tract tumors were negative. The reason for this unexpected staining in normal gastric mucosa is poorly understood at present. Nevertheless, the lack of NY-BR-1 reactivity in gastroesophageal carcinomas, gastric adenocarcinomas, cholangiocarcinomas, and most pancreatic tumors (1 of 15 was positive) in this study further supports the usefulness of this antibody in workup of a CK7+/CK20– tumor of unknown origin.

Expression of the second marker, PAX8, was evaluated in a variety of gynecologic tumors and primary breast carcinomas. Previous studies have focused mainly on PAX8 expression in ovarian and breast carcinomas.5,6,9,10 PAX8 has been reported to be negative in primary breast carcinomas,5 and our study showed identical findings. The majority of ovarian carcinomas were positive for PAX8 expression. Our study, along with others, did not show any significant difference in the staining frequency among clear cell, endometrioid, and serous carcinomas.10 We did not include any primary ovarian mucinous carcinomas in our TMAs, but others have reported lack of PAX8 expression in the majority of mucinous carcinomas.10,14

Our study confirms that unlike WT1, which is more specific for ovarian serous adenocarcinoma,4,23 PAX8 expression does not seem to be specific to any morphologic type. In addition, we report PAX8 expression in a variety of endometrial and cervical adenocarcinomas. Our study showed a moderate level of PAX8 expression in more than 80% of endometrial carcinomas regardless of the histologic type. PAX8 expression was also identified in a significant number (>60%) of typical endocervical tumors and in more than 40% of endocervical variant tumors, indicating that PAX8 is a broad-spectrum müllerian marker. All pancreatic, bile duct, gastric, and gastroesophageal junction carcinomas in this study were negative for PAX8, further supporting an important role for PAX8 in determining site of origin of a CK7+/CK20– tumor of unknown origin.

Therefore, PAX8 nuclear expression (even weak) in a CK7+/estrogen receptor+/CK20– tumor supports a gynecologic primary tumor rather than a breast carcinoma. Our findings are in compete concordance with a recently published report by Ozcan et al35 on PAX8 expression in a variety of tissue types. The present study expands on the findings of Ozcan et al35 and provides convincing evidence for the use of PAX8 in the assessment of site of origin for carcinoma of unknown origin. Although it was not the focus of this study, it is important to know that apart from müllerian tumors, PAX8 is also expressed in the majority of renal and thyroid tumors and lymphomas and about one third of pancreatic islet cell tumors.7,8,35

In this study, we examined 2 markers, NY-BR-1 and PAX8, from which 4 different profiles are theoretically possible: NY-BR-1+/PAX8+, NY-BR-1+/PAX8–, NY-BR-1–/PAX8+, and NY-BR-1–/PAX8–. The majority of breast cancers are NY-BR-1+/PAX8–, and the majority of müllerian tumors are NY-BR-1–/PAX8+. However, a müllerian tumor with the breast cancer profile (ie, NY-BR-1+/PAX8–) may result in erroneous conclusions. We analyzed our data for 141 gynecologic tumors on which results for both NY-BR-1 and PAX8 were available and found that only 1 case showed such a profile. This was an undifferentiated carcinoma of the endometrium that was negative for PAX8 and showed very weak expression for NY-BR-1 (H score, 15). Therefore, we believe that combining these 2 markers in a panel would be most informative.

Apart from the diagnostic value of the 2 markers, recent studies suggest that NY-BR-1 is also a potential target for immunotherapy.36 Monoclonal antibodies that target tumor-specific antigens, such as trastuzumab, are becoming increasingly popular in combination chemotherapy.14,36,37 It is interesting that although NY-BR-1 expression seems to be lost with dedifferentiation, it seems to remain stable with disease progression. We did not evaluate metastatic disease in this study, but others have shown concordant expression in primary breast carcinomas and metastases.14,15,36 Theurillat et al14 compared lymph node and distant metastases and found no significant difference from the autologous primary tumors. Because therapeutic decisions are often made based on the expression profile of the primary tumor, the concordance of NY-BR-1 in lymph node and distant metastases is promising.15

Our study supports the inclusion of NY-BR-1 and PAX8 immunohistochemical staining in the differentiation of primary breast and gynecologic tumors from each other and from tumors that share a similar CK profile. Moderate to strong cytoplasmic staining with NY-BR-1 supports the diagnosis of a primary breast cancer, whereas nuclear staining with PAX8 supports the diagnosis of a gynecologic primary tumor in the appropriate clinical setting.

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Note: Since the acceptance of this paper, we have noticed patchy weak to moderate PAX8 reactivity on 1 primary invasive breast carcinoma (with unequivocal in situ component) in our clinical practice. We still stand by our results but caution readers for occasional unexpected reactivity and stress the usefulness of a panel and clinical information.
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