Cytokeratin 7 and Cytokeratin 20 Expression in Epithelial Neoplasms: A Survey of 435 Cases

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Cytokeratin 7 (CK 7) and cytokeratin 20 (CK 20) are low molecular weight cytokeratins. Their anatomic distribution is generally restricted to epithelia and their neoplasms. We surveyed 435 epithelial neoplasms from various organ systems by immunohistochemistry using CK 7 and CK 20 monoclonal antibodies. Expression of CK 7 was seen in the majority of cases of carcinoma, with the exception of those carcinomas arising from the colon, prostate, kidney, and thymus; carcinoid tumors of the lung and gastrointestinal tract origin; and Merkel cell tumor of the skin. The majority of cases of squamous cell carcinoma of various origins were negative for CK 7, except cervical squamous cell carcinoma, in which 87% of cases were positive. Approximately two thirds of cases of malignant mesothelioma were CK 7-positive. CK 20 positivity was seen in virtually all cases of colorectal carcinomas and Merkel cell tumors. CK 20-positive staining was also observed in cases of pancreatic carcinomas (62%), gastric carcinoma (50%), cholangiocarcinomas (43%), and transitional cell carcinomas (29%). The expression of CK 20 was virtually absent in carcinomas from other organ systems and in malignant mesothelioma. CK 7- and CK 20-negative epithelial neoplasms included adrenal cortical carcinoma, germ cell tumor, prostate carcinoma, renal cell carcinoma, and hepatocellular carcinoma.

KEY WORDS: Carcinoma, Cytokeratin 7, Cytokeratin 20.

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The most common malignancies are derived from simple epithelia of the breast, lung, colon, prostate, ovaries, and endometrium. Carcinomas from these sites usually metastasize to regional lymph nodes and other organs, such as lung, brain, liver, and bone. The diagnosis of the metastatic carcinoma of unknown origin can be very difficult. The determination of the primary site of the metastasis is a challenge to both oncologists and pathologists, having potentially important clinical and therapeutic consequences.

Many tumor markers have been developed in the past two decades as immunohistochemical aids to the diagnosis of carcinoma. Some of these tumor markers, such as prostate specific antigen (PSA), are very organ specific. Others, such as carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA), although widely used, lack organ specificity. Although the expression of cytokeratins (CKs) is generally confined to epithelia and their neoplasms (1–6), they are not specific tumor markers. However, the highly diverse expression patterns of CKs have been correlated with different pathways of epithelial differentiation, and thereby allow the accurate and sophisticated classification of epithelial cells into different subtypes (1, 7, 8). During cell transformation and tumor development, this cell type specificity of cytokeratins is largely conserved (4, 9).

The diverse and unique expression of CK 7 and CK 20 in carcinomas has been found to be useful in the differential diagnosis of some carcinomas of epithelial origin (10, 11). Studies have shown that the different expression patterns of CK 7 and CK 20 are among the most discriminant markers in: (1) the differential diagnosis between metastatic colon and ovarian adenocarcinomas (7, 10, 12–17); (2) the differential diagnosis between Merkel cell tumor of skin and small cell carcinomas of other origins (7, 11, 18–21); and (3) the differential diagnosis between lung, endometrial, and breast adenocarcinomas and colon adenocarcinoma (20, 22). Studies of CK 7 and CK 20 expression in other epithelial carcinomas have also been explored in the past ten years (11, 20–22). However, most of these studies have either involved few cases or studied limited organ systems. One relatively comprehensive study has been reported, but the reproductivity of these findings has not been confirmed in other laborato-

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ries, and even a previous large study only studied a limited number of organ systems (16).

MATERIALS AND METHODS

Cases

Four hundred thirty-five cases of carcinomas from different organs were selected from our surgical pathology files. Of 26 cases of breast adenocarcinomas, 20 cases were ductal and six were lobular carcinomas. Of 24 cases of ovarian adenocarcinomas, 12 were serous papillary, four were clear cell, and eight were endometrioid. Of 55 cases of thyroid tumors, 24 were adenomas, 16 were medullary carcinomas, five were follicular carcinomas, and 10 were papillary carcinomas. Of 10 cases of salivary gland tumors, five were mixed tumors, two were Warthin's tumors, and two were mucoepidermoid carcinomas. Of 14 cases of germ cell tumors, six were embryonal carcinomas, four were seminomas, three were teratomas, and one was a yolk sac tumor. The diagnoses were reconfirmed; only cases of primary carcinoma were used. All tissues had been fixed in 10% neutral formalin and embedded in paraffin. The organ origins of carcinomas are listed in Tables 1 and 2.

Immunohistochemistry

Commercially available CK 7 (clone OV-TL-12/30) and CK 20 (clone IT-Ks 20.8) antibodies were purchased from DAKO (DAKO Corporation, Carpinteria, CA) and ARP (American Research Products, Inc., Belmont, MA), respectively. These two clones were selected because they have been used in our immunohistochemistry lab with better results in comparison to other commercially available keratin 7 and keratin 20 clones. Serial 5-μm sections were cut from each case. The sections were deparaffinized and rehydrated in graded alcohol. For heat-induced epitope retrieval (HIER), the sections were subjected into 100-mM EDTA buffer (pH 8.0) in a Steamer (Black & Decker, Shelton, CT) at 100° C for 20 min. The sections were then brought to an automated stainer (TechMate, Tucson, AZ), following the vendor's protocol. Two sections were stained with CK 7 (1:200) and 20 (prediluted by vendor). Avidin-biotin complex (ABC) and peroxidase methods were used.

Cytoplasmic immunoreactivity was assessed. Only those cases showing greater than 5% tumor cell positivity were regarded as positive.

RESULTS

CK 7 in Epithelial Neoplasms

The frequency of CK 7 expression is summarized in Table 1. CK 7 positivity was generally diffuse and cytoplasmic. The vast majority of cases of adenocarcinomas were positive for CK 7, including lung (100%), ovary (100%), uterus (100%), breast (96%)

TABLE 1. CK 7 in Epithelial Neoplasms

Organs	Tumor Types	Total Cases	Positive Cases	%
Lung	Adenocarcinoma	10	10	100
Ovary	Adenocarcinoma	24	24	100
Salivary gland	All tumors	9	9	100
Uterus	Endometrial carcinoma	10	10	100
Thyroid	All tumors	55	54	98
Breast	Ductal and lobular carcinoma	26	25	96
Liver	Cholangiocarcinoma	14	13	93
Pancreas	Adenocarcinoma	13	12	92
Bladder	Transitional cell carcinoma	24	21	88
Cervix	Squamous cell carcinoma	15	13	87
Mesothelium	Malignant mesothelioma	17	11	65
Lung, liver, small bowel	Neuroendocrine carcinoma	9	5	56
Lung	Small cell carcinoma	7	3	43
Stomach	Adenocarcinoma	8	3	38
Head & neck	Squamous cell carcinoma	30	8	27
Lung	Carcinoid tumor	9	2	22
Esophagus	Squamous cell carcinoma	14	3	21
GI tract	Carcinoid tumor	15	2	13
Kidney	Carcinoma	19	2	11
Liver	Hepatoma	11	1	9
Germ cell	Germ cell tumor	14	1	7
Colon	Adenocarcinoma	20	1	5
Adrenal	Cortical carcinoma	10	0	0
Lung	Squamous cell carcinoma	15	0	0
Prostate	Adenocarcinoma	18	0	0
Skin	Merkel cell tumor	9	0	0
Thymus	Thymoma	8	0	0
Soft tissue	Epithelioid sarcoma	12	0	0

GI, gastrointestinal.

TABLE 2. CK 20 in Epithelial Carcinomas

Organs	Tumor Types	Total Cases	Positive Cases	%
Colon	Adenocarcinoma	20	20	100
Skin	Merkel cell tumor	9	7	78
Pancreas	Adenocarcinoma	13	8	62
Stomach	Adenocarcinoma	8	4	50
Liver	Cholangiocarcinoma	14	6	43
Bladder	Transitional cell carcinoma	24	7	29
Lung	Adenocarcinoma	10	1	10
Liver	Hepatocellular carcinoma	11	1	9
GI tract	Carcinoid tumor	15	1	7
Head & neck	Squamous cell carcinoma	30	2	6
Ovary	Adenocarcinoma	24	1	4
Adrenal	Cortical carcinoma	10	0	0
Breast	Lobular and ductal carcinoma	26	0	0
Cervix	Squamous cell carcinoma	15	0	0
Esophagus	Squamous cell carcinoma	14	0	0
Germ cell	Germ cell tumor	14	0	0
Kidney	Carcinoma	19	0	0
Lung, liver, small bowel	Neuroendocrine carcinoma	9	0	0
Lung	Carcinoid tumor	9	0	0
Lung	Small cell carcinoma	7	0	0
Lung	Squamous cell carcinoma	15	0	0
Mesothelium	Malignant mesothelioma	17	0	0
Prostate	Adenocarcinoma	18	0	0
Salivary gland	All tumors	9	0	0
Soft tissue	Epithelioid sarcoma	12	0	0
Thyroid	All tumors	55	0	0
Thymus	Thymoma	8	0	0
Uterus	Endometrial carcinoma	10	0	0

GI, gastrointestinal.

(Fig. 1A), salivary gland (100%), thyroid neoplasms (100%), cholangiocarcinoma (93%), pancreas (92%), and transitional cell carcinoma (88%). In contrast, only a small percentage of cases of adenocarcinoma of colon (5%), stomach (28%), and kidney (11%) were CK 7-positive. Squamous cell carcinoma of the cervix was positive in 87% of cases (Fig. 1B). In contrast, squamous cell carcinoma of the head and neck (27%) and esophagus (21%) were positive in a minority of cases; and squamous cell carcinoma of the lung (0%) was negative in all cases. Malignant mesothelioma was positive in 65% of cases. Of neuroendocrine neoplasms, about one-half of cases of small cell carcinoma of the lung (56%) and neuroendocrine carcinomas from a variety of sites (43%) were positive for CK 7, a minority of cases of carcinoid tumor (22%) were positive, and Merkel cell tumor of skin (0%) was entirely negative. Other neoplasms that were rarely or never CK 7-positive included hepatocellular carcinoma (9%), germ cell tumor (7%), adrenal cortical carcinoma (0%), prostate adenocarcinoma (0%), thymoma (0%), and epithelioid sarcoma (0%).

CK 20 in Epithelial Neoplasms

The frequency of CK 20 expression is summarized in Table 2. In Merkel cell tumor, CK 20 positivity was dot-like cytoplasmic, whereas in other neoplasms, CK 20 positivity was diffuse cytoplasmic. Unlike CK 7, CK 20 expression was restricted to a few organ systems. All cases of colon carcinoma were positive for CK 20 as were most cases of Merkel cell tumor of skin (78%) and adenocarcinoma of the pancreas (62%). One-half of cases of adenocarcinoma of the stomach were CK 20-positive, as were a subset of cases of cholangiocarcinoma of the liver (43%) and transitional cell carcinoma of the bladder (29%). All other neoplasms studied were rarely or never positive for CK 20.

Correlation of CK 7 and CK 20 Expression Patterns in Different Epithelial Neoplasms

The correlation of CK 7 and CK 20 expression in epithelial neoplasms is summarized in Table 3.

CK 7^+/CK 20^+ epithelial neoplasms

The majority of cases in this category were carcinomas from the gastrointestinal and genitourinary tracts. Sixty-two percent of cases of pancreatic carcinoma (Fig. 2,A-B), 43% of cases of cholangiocarcinoma (Fig. 2, C-D), 25% of cases of bladder transitional cell carcinoma (Fig. 2, E-F), and 13% of cases of gastric carcinoma were CK 7^+/CK 20^+. The positive cells in CK 7^+/CK 20^+ tumors were often overlapping (Fig. 2).

CK 7^+/CK 20^- carcinomas

Virtually all cases of breast (96%) (Fig. 3, A-B), ovarian adenocarcinoma (96%) (endometrioid, serous papillary and clear cell subtypes) (Fig. 3, C-D); lung (90%) (Fig. 3, E-F), endometrial (100%) (Fig. 3, G-H), and thyroid tumors (98%) (follicular, papil-

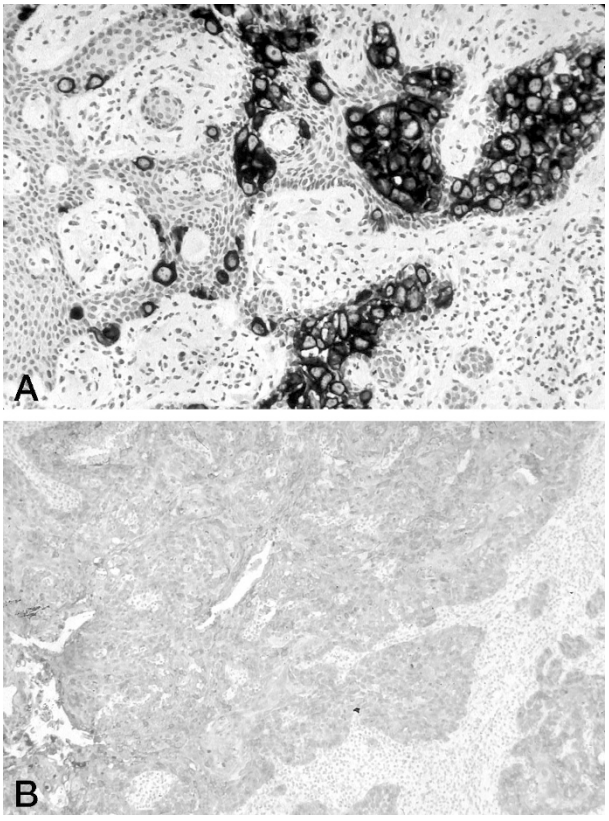

FIGURE 1. Pagetoid cells in breast nipple (**A**) and a case of moderately differentiated cervical squamous cell carcinoma (**B**) are strongly cytoplasmic positive for CK 7. Note the negative staining in the non-neoplastic epithelium (**A**).

lary, and medullary subtypes); and salivary gland tumors (100%) were CK 7^+/CK 20^-. In addition, approximately two-thirds (65%) of cases of malignant mesothelioma were also CK 7^+/CK 20^-.

CK 7^-/CK 20^+ carcinomas

Virtually all cases (95%) of colorectal carcinoma (Fig. 4, A-B), 78% of cases of Merkel cell tumor of skin (Fig. 4, C-D), and 37% of cases of gastric adenocarcinoma were CK 7/CK 20^+. The CK 20-positive staining pattern in Merkel cell carcinoma was cytoplasmic dot-like, which was different from that seen in cases of CK 20-positive gastric and colorectal carcinoma (diffuse cytoplasmic staining).

CK 7^-/CK 20^- carcinomas

All cases of adrenal cortical carcinomas, prostatic carcinomas, thymomas, and epithelial sarcomas were CK 7/CK 20^-. In addition, the majority of cases of hepatocellular carcinomas (9/11), carcinoid tumors of lung (7/9) and gastrointestinal tract (12/15), and renal cell carcinomas (17/19) were also CK 7^-/CK 20^-.

DISCUSSION

It is often important to determine the site of origin of a metastatic carcinoma of unknown primary site, particularly because this may affect the choice of the treatment. Determination of the primary site may take several steps. Clinical features, such as age, sex, and site of metastases may give a first indication. The histologic assessment is often very helpful, but may not differentiate adequately between various primary tumors. Immunohistochemical staining may provide a third level of data.

Intermediate filaments (7 to 11 nm) are major cytoskeletal proteins in eukaryotic cells. Unlike actin-biding microfilaments and tubulin-containing microtubules of the cytoskeleton family, the five types of intermediate filaments show some specificity in both normal tissue (4) as well as their neoplasms (23, 24). Therefore, immunohistochemistry of intermediate filaments is widely used in surgical pathology for differential diagnosis of sarcomas (vimentin), including rhabdomyosarcomas (desmin), carcinomas (cytokeratins), nervous tissue tumors (neurofilament), and gliomas (glial fibrillary acid protein). Carcinomas are a diverse group of neoplasms, and so are the cytokeratins found in these carcinomas. In the past 20 years, we have gained tremendous knowledge, both in cytokeratin biology and their distribution in normal tissue, as well as in applications in diagnostic surgical pathology. CK 7 and 20 are two of the most commonly used CKs in surgical pathology (12, 16, 17).

For comparison, the results of the current study and that of Wang, *et al.* (16) are summarized in Table 3. One must note that the cut-off percentage of staining for a positive result is different between the current study (5%) and that used by Wang *et al.* (1%), which in part may contribute to differences in the results in some groups of carcinomas between the two studies. We concur with others (17) that a 5% cut-off percentage for positivity may eliminate more "false positive" results than a 1% cut-off. In addition, the CK 20 monoclonal antibody used in the current study (American Research Products [APR], Inc., Belmont, MA) was different from that used by Wang *et al.* (16) (DAKO). We did a pilot comparison study of several different commercially available CK 20 antibodies, and found that the CK 20 antibody from ARP gave the best results in our laboratory. Nonetheless, our results are similar to that of Wang *et al.* for most major categories of carcinomas. One notable difference, however, was a much lower incidence of CK 20 positivity in transitional cell carcinoma of the bladder, 29% *versus* 89% in the series of Wang *et al.* We found that well differentiated transitional cell carcinomas were more likely to be CK 20 positive than poorly differentiated transitional cell carcinomas; thus, the difference in CK 20 expression in the present study and that of Wang *et al.* may be due to the

TABLE 3. Histologic Distribution of CK 7 and CK 20 in Epithelial Neoplasms

Tumor Subtypes	CK 7/CK 20 Profile	Percentage of Cases Positive (%)	
		Current Study	Wang *et al.*
Adrenal, adrenal cortical tumor	$CK7^+/CK20^+$	0/10 (0%)	—
	$CK7^+/CK20^-$	0/10 (0%)	—
	$CK7^-/CK20^+$	0/10 (0%)	—
	$CK7^-/CK20^-$	10/10 (100%)	—
Bladder, transitional cell carcinoma	$CK7^+/CK20^+$	6/24 (25%)	17/19 (89%)
	$CK7^+/CK20^-$	15/24 (63%)	2/19 (11%)
	$CK7^-/CK20^+$	1/24 (4%)	0/19 (0%)
	$CK7^-/CK20^-$	2/24 (8%)	0/10 (0%)
Breast, infiltrating ductal carcinoma	$CK7^+/CK20^+$	0/20 (0%)	6/38 (16%)
	$CK7^+/CK20^-$	19/20 (95%)	31/38 (82%)
	$CK7^-/CK20^+$	0/20 (0%)	1/38 (3%)
	$CK7^-/CK20^-$	1/20 (5%)	0/38 (0%)
Breast, infiltrating lobular carcinoma	$CK7^+/CK20^+$	0/6 (0%)	1/11 (9%)
	$CK7^+/CK20^-$	6/6 (100%)	10/11 (91%)
	$CK7^-/CK20^+$	0/6 (0%)	0/11 (0%)
	$CK7^-/CK20^-$	0/6 (0%)	0/11 (0%)
Colon, colorectal adenocarcinoma	$CK7^+/CK20^+$	1/20 (5%)	4/40 (10%)
	$CK7^+/CK20^-$	0/20 (0%)	0/40 (0%)
	$CK7^-/CK20^+$	19/20 (95%)	30/40 (75%)
	$CK7^-/CK20^-$	0/20 (0%)	6/40 (15%)
Esophagus, squamous cell carcinoma	$CK7^+/CK20^+$	0/14 (0%)	—
	$CK7^+/CK20^-$	3/14 (21%)	—
	$CK7^-/CK20^+$	0/14 (0%)	—
	$CK7^-/CK20^-$	11/14 (79%)	—
Gastrointestinal tract, carcinoid tumor	$CK7^+/CK20^+$	0/15 (0%)	—
	$CK7^+/CK20^-$	2/15 (13%)	—
	$CK7^-/CK20^+$	1/15 (7%)	—
	$CK7^-/CK20^-$	12/15 (80%)	—
Germ cell tumor	$CK7^+/CK20^+$	0/14 (0%)	—
	$CK7^+/CK20^-$	1/14 (7%)	—
	$CK7^-/CK20^+$	0/14 (0%)	—
	$CK7^-/CK20^-$	13/14 (93%)	—
Head and neck, squamous cell carcinoma	$CK7^+/CK20^+$	0/30 (0%)	—
	$CK7^+/CK20^-$	8/30 (27%)	—
	$CK7^-/CK20^+$	2/30 (6%)	—
	$CK7^-/CK20^-$	20/30 (67%)	—
Kidney, renal cell carcinoma	$CK7^+/CK20^+$	0/19 (0%)	0/17 (0%)
	$CK7^+/CK20^-$	2/19 (11%)	4/17 (24%)
	$CK7^-/CK20^+$	0/19 (0%)	1/17 (6%)
	$CK7^-/CK20^-$	17/19 (89%)	12/17 (71%)
Liver, hepatocellular carcinoma	$CK7^+/CK20^+$	0/11 (0%)	2/30 (7%)
	$CK7^+/CK20^-$	1/11 (9%)	5/30 (17%)
	$CK7^-/CK20^+$	1/11 (9%)	0/30 (0%)
	$CK7^-/CK20^-$	9/11 (82%)	23/30 (77%)
Liver, cholangiocarcinoma	$CK7^+/CK20^+$	6/14 (43%)	—
	$CK7^+/CK20^-$	7/14 (50%)	—
	$CK7^-/CK20^+$	0/14 (0%)	—
	$CK7^-/CK20^-$	1/14 (7%)	—
Lung, carcinoid tumor	$CK7^+/CK20^+$	0/9 (0%)	—
	$CK7^+/CK20^-$	2/9 (22%)	—
	$CK7^-/CK20^+$	0/9 (0%)	—
	$CK7^-/CK20^-$	7/9 (78%)	—
Lung, liver, and small bowel neuroendocrine carcinoma	$CK7^+/CK20^+$	0/9 (0%)	—
	$CK7^+/CK20^-$	5/9 (56%)	—
	$CK7^-/CK20^+$	0/9 (0%)	—
	$CK7^-/CK20^-$	4/9 (44%)	—
Lung, squamous cell carcinoma	$CK7^+/CK20^+$	0/15 (0%)	0/12 (0%)
	$CK7^+/CK20^-$	7/15 (47%)	0/12 (0%)
	$CK7^-/CK20^+$	0/15 (0%)	1/12 (8%)
	$CK7^-/CK20^-$	8/15 (53%)	11/12 (89%)
Lung, adenocarcinoma	$CK7^+/CK20^+$	1/10 (10%)	—
	$CK7^+/CK20^-$	9/10 (90%)	—
	$CK7^-/CK20^+$	0/10 (0%)	—
	$CK7^-/CK20^-$	0/10 (0%)	—
Lung, small cell carcinoma	$CK7^+/CK20^+$	0/7 (0%)	0/11 (0%)
	$CK7^+/CK20^-$	3/7 (43%)	2/11 (18%)
	$CK7^-/CK20^+$	0/7 (0%)	0/11 (0%)
	$CK7^-/CK20^-$	4/7 (57%)	9/11 (82%)

TABLE 3. *—continue*

Tumor Subtypes	CK 7/CK 20 Profile	Percentage of Cases Positive (%)	
		Current Study	Wang *et al.*
Mesothelioma	$CK7^+/CK20^+$	0/17 (0%)	0/16 (0%)
	$CK7^+/CK20^-$	11/17 (65%)	11/16 (69%)
	$CK7^-/CK20^+$	0/17 (0%)	0/16 (0%)
	$CK7^-/CK20^-$	6/17 (35%)	5/16 (31%)
Ovary, adenocarcinoma	$CK7^+/CK20^+$	1/24 (4%)	0/19 (0%)
	$CK7^+/CK20^-$	23/24 (96%)	19/19 (100%)
	$CK7^-/CK20^+$	0/24 (0%)	0/19 (0%)
	$CK7^-/CK20^-$	0/24 (0%)	0/19 (0%)
Pancreas, adenocarcinoma	$CK7^+/CK20^+$	8/13 (62%)	15/23 (65%)
	$CK7^+/CK20^-$	4/13 (30%)	6/23 (26%)
	$CK7^-/CK20^+$	0/13 (0%)	2/23 (9%)
	$CK7^-/CK20^-$	1/13 (8%)	0/23 (0%)
Prostate, adenocarcinoma	$CK7^+/CK20^+$	0/18 (0%)	1/13 (8%)
	$CK7^+/CK20^-$	0/18 (0%)	1/13 (8%)
	$CK7^-/CK20^+$	0/18 (0%)	3/13 (23%)
	$CK7^-/CK20^-$	18/18 (100%)	8/13 (62%)
Salivary gland tumor	$CK7^+/CK20^+$	0 /9 (0%)	—
	$CK7^+/CK20^-$	9 /9 (100%)	—
	$K7^-/CK20^+$	0 /9 (0%)	—
	$CK7^-/CK20^-$	0 /9 (0%)	—
Skin, Merkel cell tumor	$CK7^+/CK20^+$	0 /9 (0%)	—
	$CK7^+/CK20^-$	0 /9 (0%)	—
	$CK7^-/CK20^+$	7 /9 (78%)	—
	$CK7^-/CK20^-$	2 /9 (12%)	—
Soft tissue, epithelioid sarcoma	$CK7^+/CK20^+$	0/12 (0%)	—
	$CK7^+/CK20^-$	0/12 (0%)	—
	$CK7^-/CK20^+$	0/12 (0%)	—
	$CK7^-/CK20^-$	12/12 (100%)	—
Stomach, gastric adenocarcinoma	$CK7^+/CK20^+$	1 /8 (13%)	11/29 (38%)
	$CK7^+/CK20^-$	2 /8 (25%)	5/29 (17%)
	$CK7^-/CK20^+$	3 /8 (37%)	10/29 (35%)
	$CK7^-/CK20^-$	2 /8 (25%)	3/29 (10%)
Thyroid, follicular, papillary and medullary carcinoma	$CK7^+/CK20^+$	0/55 (0%)	—
	$CK7^+/CK20^-$	54/55 (98%)	—
	$CK7^-/CK20^+$	0/55 (0%)	—
	$CK7^-/CK20^-$	1/55 (2%)	—
Thymus, thymoma	$CK7^+/CK20^+$	0 /8 (0%)	—
	$CK7^+/CK20^-$	0 /8 (0%)	—
	$CK7^-/CK20^+$	0 /8 (0%)	—
	$CK7^-/CK20^-$	8 /8 (100%)	—
Uterus, endometrial adenocarcinoma	$CK7^+/CK20^+$	0/10 (0%)	3/25 (12%)
	$CK7^+/CK20^-$	10/10 (100%)	20/25 (80%)
	$CK7^-/CK20^+$	0/10 (0%)	0/25 (0%)
	$CK7^-/CK20^-$	0/10 (0%)	2/25 (8%)
Uterus, cervical squamous cell carcinoma	$CK7^+/CK20^+$	0/15 (0%)	—
	$CK7^+/CK20^-$	13/15 (87%)	—
	$CK7^-/CK20^+$	0/15 (0%)	—
	$CK7^-/CK20^-$	2/15 (13%)	—

selection of cases of different degrees of differentiation.

In the absence of results of other markers, the demonstration of CK 7 positivity alone has limited value in differential diagnosis of metastatic carcinoma (11). Its expression is often seen in the major categories of adenocarcinoma, including adenocarcinoma of the breast, lung, ovary, endometrium, thyroid, salivary gland, pancreas, and bile duct (21, 25, 26). However, there are circumstances in which the determination of CK 7 positivity is useful. We agree with Ramaekers *et al.* (11) that CK 7 immunostaining can be extremely useful when the differential diagnosis between a prostatic carcinoma and a transitional cell carcinoma of prostate or other genitourinary organs is an issue. In the current study, all cases (0/18) of prostatic carcinoma were CK 7-negative, whereas the majority of cases (21/24) of transitional cell carcinoma were CK 7-positive. CK 7 has been regarded as "bile duct keratin" because it only stains bile ducts in normal liver (27, 28). The current study showed that the majority of cases of cholangiocarcinoma (13/14) were CK-7 positive; whereas majority cases of hepatocellular carcinoma (1/11) were CK 7-negative. These results are similar to those of Maeda *et al.* (29) who found that over 97% of cholangiocarcinoma, whereas only 7% of hepatocellular carcinomas, were CK 7-positive. Therefore, the expression of CK 7 also can be useful in the differential diagnosis of a cholangiocarcinoma *versus* hepatocellular carcinoma. The further demonstration of CK 20 positivity may provide additional evidence favoring a cholangiocarcinoma, as 43% of

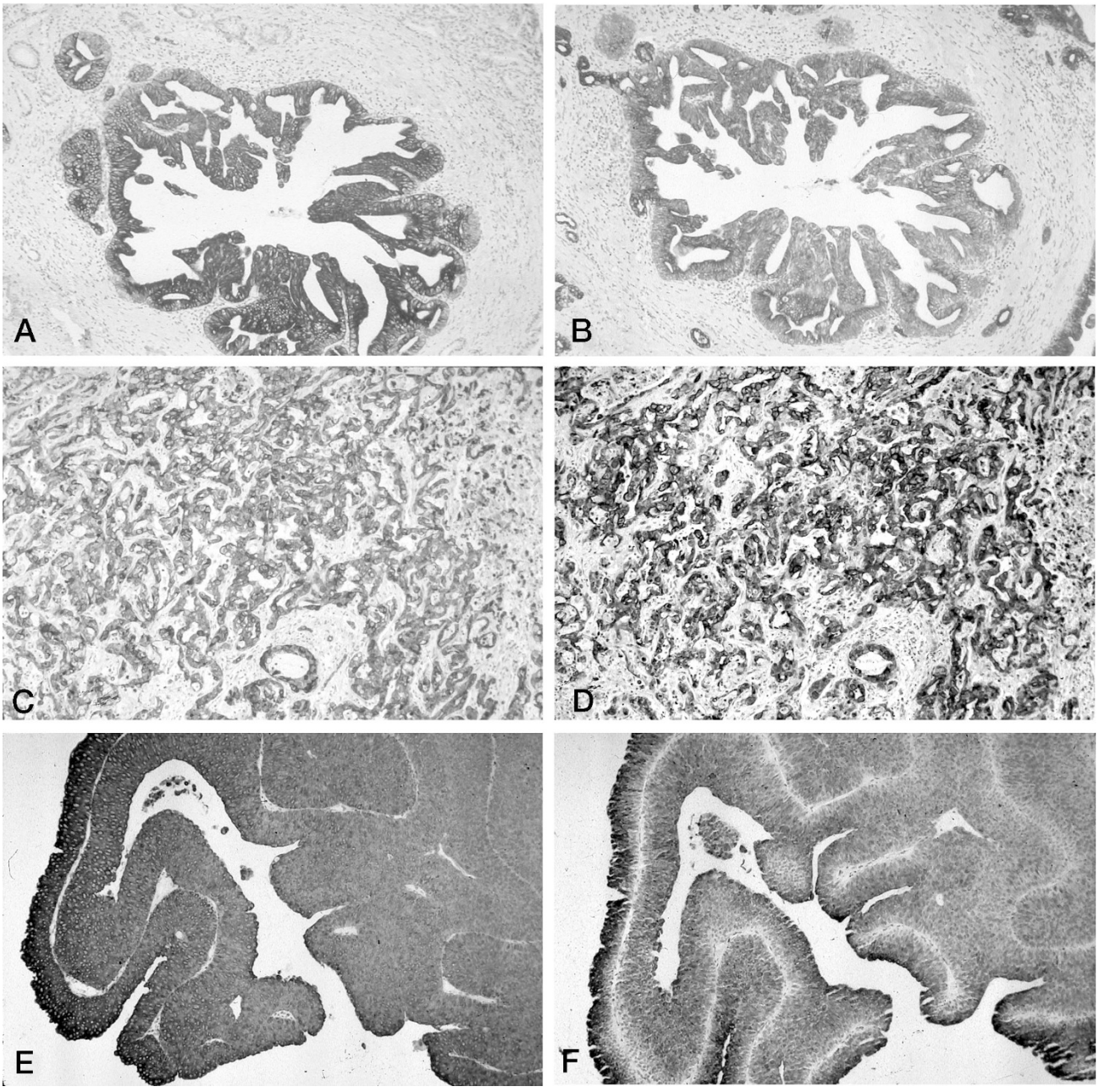

FIGURE 2. CK 7+/CK 20+ coexpression in a case of pancreatic carcinoma (**A**, **B**, respectively), a case of cholangiocarcinoma (**C**, **D**, respectively) and a case of transitional cell carcinoma (**E**, **F**, respectively). The CK 7 and CK 20 cytoplasmic positive immunostaining results were taken from the same field.

these cases are positive for CK 20 *versus* 9% of cases of hepatocellular carcinoma.

CK 7 is also a very specific marker for mammary and extramammary Paget's disease (30, 31). After comparing various markers (CK 7, CAM 5.2, CK 20, CEA, Ber-EP4), Smith *et al.* (32) concluded that CK 7 is the only marker exhibiting strong and specific staining within the epidermis in all cases of breast Paget's disease. The current study further supports the conclusion made by Smith *et al.* (32). However, in some cases of perianal Paget's disease associated with colorectal adenocarcinoma, the pagetoid cells are often CK 7+/CK 20+ or CK 7-/CK 20+ (33, 34).

The finding of CK 7 negativity has greater diagnostic value (11). When a carcinoma is CK 7-negative, the differential diagnosis should include prostate, renal cell, neuroendocrine, hepatocellular, and adrenal carcinomas, carcinoid tumors, germ cell tumors, and squamous cell carcinomas of various origins with exception of cervical squamous cell carcinoma. These tumors may be distinguished by adding other markers, such as prostate specific antigen (prostate carci-

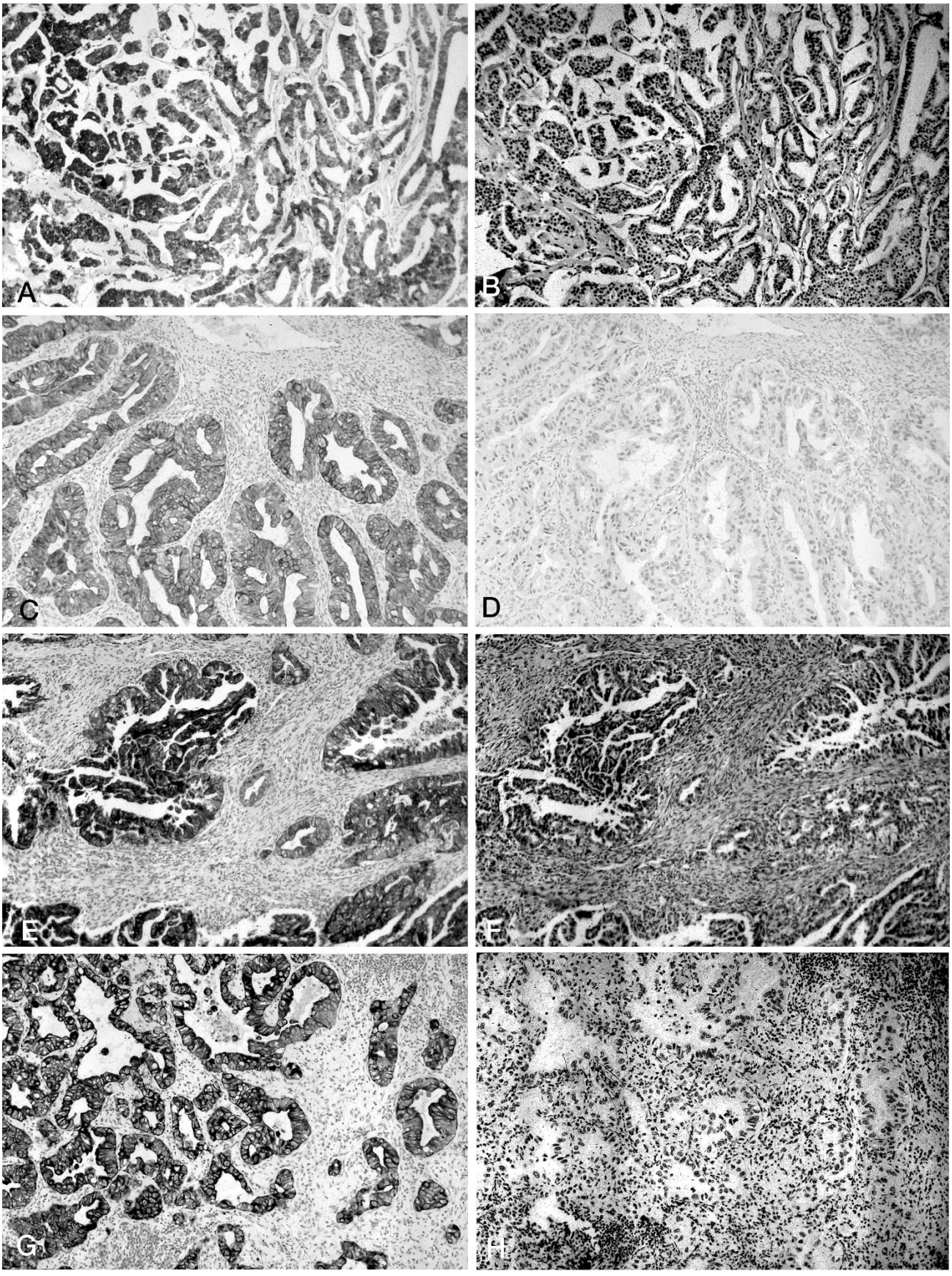

FIGURE 3. CK 7+/CK 20- immunostain in a case of breast ductal carcinoma (**A**, **B**, respectively), a case of ovarian carcinoma (**C**, **D**, respectively), a case of lung adenocarcinoma (**E**, **F**, respectively), and a case endometrial adenocarcinoma (**G**, **H**, respectively). The CK 7 and CK 20 immunostaining results were taken from the same field.

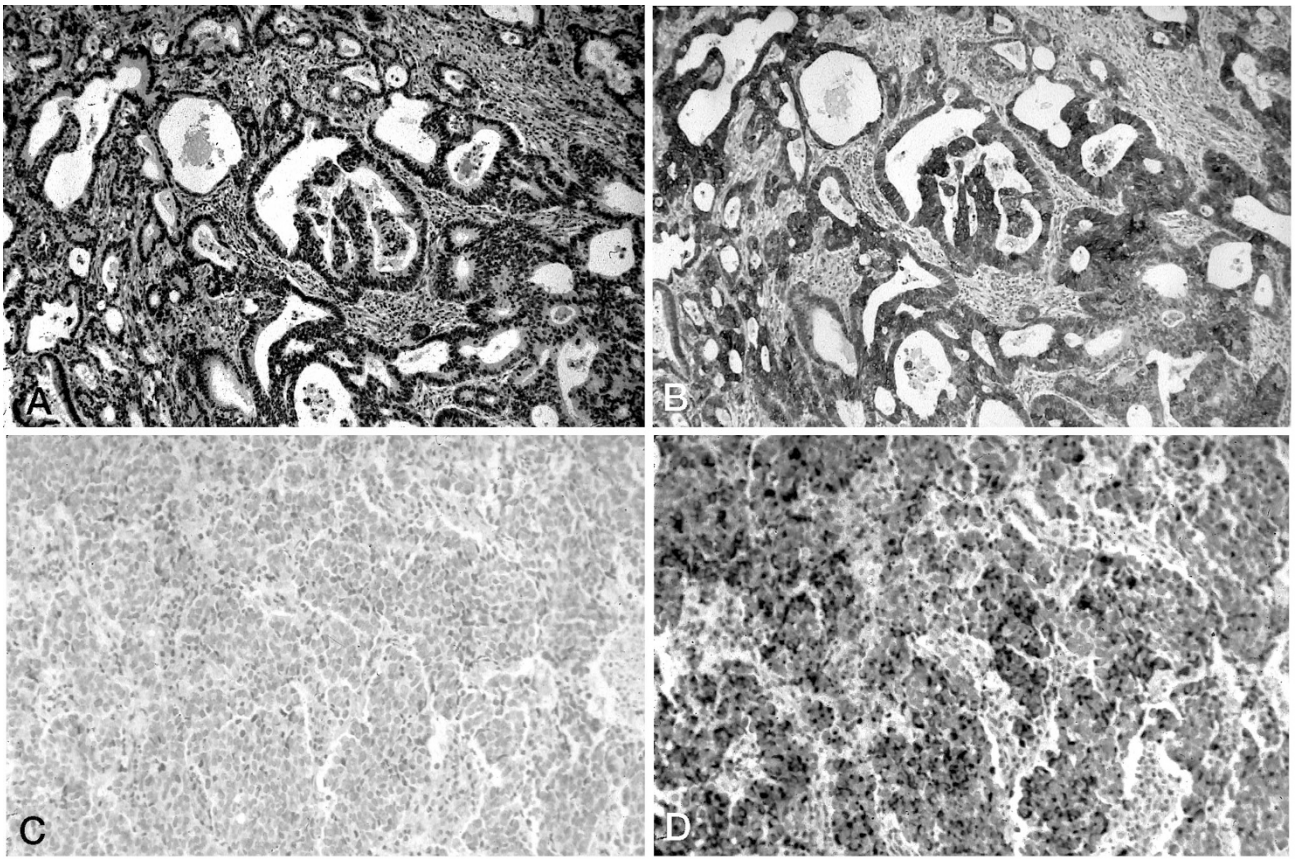

FIGURE 4. CK 7-/CK 20+ in a case of colon adenocarcinoma (**A**, **B**, respectively), and a case of Merkel cell tumor of skin (**C**, **D**, respectively). The CK 7 and CK 20 immunostaining results were taken from the same field. Note the CK 20 cytoplasmic dot-like staining pattern (**D**).

noma), chromogranin (neuroendocrine carcinoma), bile-duct specific CEA or alpha-fetoprotein (hepatocellular carcinoma) and keratin AE-1 (negative in adrenocortical carcinoma), or vimentin (renal cell carcinoma).

The majority of cases of squamous cell carcinoma of various origins are CK 7-/CK 20-. However, when a squamous cell carcinoma is CK 7-positive, squamous cell carcinoma of the uterine cervix should be considered. Normal ectocervical squamous mucosa lacks CK 7 positivity (35). However, dysplastic cervical epithelium and squamous cell carcinoma *in situ* tends to express CK 7. We found that the majority of cases of cervical squamous cell carcinomas (13/15) were CK 7-positive, whereas the CK 7-positive rate of squamous cell carcinoma of other origins was much lower (20 to 30%).

CK 20 positivity is seen in the majority of cases of colorectal adenocarcinoma (5, 10, 17), and over one-third of cases of gastric adenocarcinoma. However, unlike regular colonic adenocarcinoma, rectal adenocarcinoma *de novo* is CK 7+/CK 20+ or CK 7+/CK 20- (33, 34). CK 20-positivity in carcinomas with neuroendocrine features is primarily seen in Merkel cell tumor (10, 18), as other small cell tumors, neuroendocrine carcinoma of various origins, and carcinoid tumors of gastrointestinal tract and lung are usually negative for CK 20 (Table 2). The cytoplasmic dot-like CK 20 positivity is very specific to Merkel cell tumor and is not seen in other common CK 20-positive carcinomas, such as colorectal adenocarcinoma.

CK 7 and CK 20 antibodies are best used together in the differential diagnosis of a poorly differentiated carcinoma (13, 17). When a carcinoma is CK 7+/CK 20+, the differential diagnosis should include pancreatic carcinoma, cholangiocarcinoma, transitional cell carcinoma, and intestinal-type sinonasal adenocarcinoma (36). However, not all these carcinomas are CK 20-positive. The current study, as well as several other studies, showed that approximately one-third of pancreatic adenocarcinoma are CK 20-negative (5, 16, 22). For a metastatic adenocarcinoma in which the differential diagnosis is colorectal *versus* ovarian (12, 14, 17, 20), breast (22), endometrial (37), or lung (20) adenocarcinoma, CK 7 and CK 20 are the most useful markers. Over 90% of colonic adenocarcinomas are CK 7-/CK 20+ (Table 4), whereas over 90% of ovarian adenocarcinomas, and over 80% of endometrial, breast, and lung adenocarcinomas are CK 7+/CK 20-. However, it should be kept in mind that ovarian mucinous tumors have a high CK 20-positive rate (14, 16, 17). Mucinous tumors of ovar-

TABLE 4. CK 7 and CK 20 in Differential Diagnosis of Colonic *Versus* Ovarian, Breast, and Lung Adenocarcinomas[a] and Differential Diagnosis Between Merkel Cell Carcinomas and Lung Small Cell Carcinomas[b]

	Colonic Adeno CA		Ovarian Adeno CA[c]		Lung Adeno CA		Breast Adeno CA		Merkel Cell CA		Lung Small Cell CA	
	CK 7$^+$	CK 20$^+$	CK 7$^+$	CK 20$^+$	CK 7$^+$	CK 20$^+$	CK 7$^+$	CK 20$^+$	CK 7$^+$	CK 20$^+$	CK 7$^+$	CK 20
Baars *et al.* (25)	0/9	/	11/11	/	4/4	/	9/9	/	/	/	0/2	/
Berezowski *et al.* (12)	1/21	21/21	24/24	6/24	/	/	/	/	/	/	/	/
Brinkachmidt *et al.* (38)	/	/	/	/	/	/	/	/	/	17/18	/	/
Chan *et al.* (18)	/	/	/	/	/	/	/	/	/	33/34	/	1/37
Kaufmann *et al.* (22)	/	21/25	/	0/29	/	3/35	/	5/129	/	/	/	/
Loy and Calaluce (20)	16/77	75/77	70/74	4/74	/	/	/	/	/	/	/	/
Loy *et al.* (14)	6/16	16/16	106/109	33/109	/	/	/	/	/	/	/	/
Miettinen (10)	/	98/102	/	/	/	4/69	/	1/9	/	5/5	/	/
Moll *et al.* (7)	/	89/93	/	0/34	/	0/33	/	1/146	/	15/15	/	0/15
Ven de Molengraft *et al.* (21)	/	/	/	/	20/20	/	/	/	/	/	1/10	/
Wang *et al.* (16)	4/40	34/40	19/19	0/19	3/3	0/3	48/49	8/49	/	/	2/11	0/11
Wauters *et al.* (17)	11/32	28/32	10/10	0/10	/	/	/	/	/	/	/	/
Current	1/20	19/20	26/26	1/26	10/10	0/10	25/26	1/26	0/9	7/9	3/7	0/7
Total	39/215 (16%)	401/426 (94%)	266/273 (97%)	44/325 (13%)	37/37 (100%)	7/150 (4%)	82/84 (97%)	16/259 (6%)	0/9 (0%)	77/81 (95%)	6/30 (20%)	1/70 (1%)

[a] Includes primary and metastatic adenocarcinomas.
[b] All cases in this table have >5% positive tumor cells.
[c] Excludes mucinous ovarian carcinomas.

ian, pancreatic, or gastrointestinal tract origins were not specifically examined in the current study.

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Book Review

Corrin B: Pathology of the Lungs, 676 pp, London, Churchill and Livingstone, 2000 ($295.00).

Although this book represents the revised and updated version of a previous edition published approximately 10 years ago as Volume 5 of the series on systemic pathology edited by Symmers, it is still a major tour de force. Books of this size and significance are simply not written anymore by a single author. One must admire the effort and dedication of Professor Corrin, his meticulous perfectionism, and his devotion to beauty that pathologists periodically discover in their specimens, as long as they are willing to spend the necessary time to search for the fleeting moment to be captured with their cameras.

First of all, this is a beautiful book. It is printed on heavy paper, nicely bound, illustrated with high-quality color-balanced pictures and quite a number of line drawings. Overall, it is a pleasure to hold in one's hands and even greater pleasure to peruse. The text, written in awe-inspiring English, is comprehensive, informative, and authoritative. It is apparent that the author, who can explain the meaning and evolution of terms such as *endogenous pneumoconiosis* , must have been around for some time. Discussion of topics such as catamenial hemothorax and the reasons why it is almost always on the right side or micronodular hyperplasia of pneumocytes type II in tuberous sclerosis may sound esoteric, but this shows that the author is not only informed but also a true scholar. In an era when scholarship is somewhat out-of-fashion, such an approach is reassuring, at least for some of us old-timers.

I have used the book for almost a month and have not yet found a topic that is not adequately explained. Professor Corrin is an excellent teacher and when he says something, you believe him. On the other hand when he writes "such claims must be regarded as somewhat tenuous," you know that he is politely, but firmly, disagreeing with the particular view expressed by some authors. Practicing pathologists will appreciate this kind of honesty, in the best tradition of Maimonides ("Teach thy tongue to say I do not know"), and I hope that many of you will include it among the essential books of your library.

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