

Tissue-Specific Cadherin CDH17 Is a Useful Marker of Gastrointestinal Adenocarcinomas With Higher Sensitivity Than CDX2

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Abstract

Cadherin 17 (CDH17) is a cell adhesion molecule expressed in intestinal epithelium and transcriptionally regulated by CDX2. We compared the usefulness of CDH17 as an immunohistochemical intestinal marker to that of CDX2 in gastrointestinal and extragastrointestinal carcinomas and nonneoplastic tissues. Nonneoplastic intestinal and pancreatic duct epithelia were CDH17-positive. Most esophageal (79%), gastric (86%), and colonic (99%) adenocarcinomas were CDH17-positive/CDX2-positive, whereas 1% of colonic, 18% of esophageal, and 10% of gastric adenocarcinomas were CDH17-negative/CDX2-negative. Rare colonic, esophageal, and gastric adenocarcinomas were CDH17-positive/CDX2-negative (1%, 3%, and 4%, respectively), and none were CDH17-negative/CDX2-positive. Diffuse CDH17 was also observed in all metastatic colon carcinomas, 20% of which were only focally CDX2-positive. Of intestinal low-grade neuroendocrine tumors, 74% coexpressed CDX2 and CDH17. CDH17 was also positive in 12% of pancreatic and 24% of bronchial neuroendocrine tumors, all of which were CDX2-negative. Pancreatic adenocarcinomas and cholangiocarcinomas were more frequently CDH17-positive than CDX2-positive (50% vs 27%, 53% vs 27%). One (2%) hepatocellular carcinoma was CDH17-positive/CDX2-negative. Nine percent of non-small cell lung cancers and 7% of endometrial carcinomas were CDH17-positive, whereas 3% of lung, 5% of endometrial, 3% of ovarian, and 2% of breast carcinomas were CDX2-positive. Thus, CDH17 is slightly more sensitive than CDX2 when detecting gastrointestinal adenocarcinomas.

Metastatic tumors of unknown origin account for approximately 2.3% to 4.2% of all human malignancies, 90% of which prove to be carcinomas.¹ Pathologists are often called upon to suggest a site of origin in patients with metastasis and an unapparent primary tumor because some specific tumor types may respond well to targeted molecular therapies. Most tumors of unknown primary site are evaluated with immunohistochemical analysis in combination with morphologic assessment. Advanced imaging modalities and serum tumor markers are increasingly used to identify the site of tumor origin, and these clinical data also guide pathologists in choosing immunohistochemical antibody panels. Some markers, such as thyroid transcription factor-1 and prostate specific antigen, are tissue specific and have enhanced pathologists' ability to distinguish among adenocarcinomas in different organs. CDX2 is expressed in cells with an intestinal phenotype and commonly labels gastrointestinal carcinomas, but its expression may also be seen in tumors of the endometrium, ovary, uterine cervix, urinary bladder, and lung.²⁻⁶ Thus, there is a need for other diagnostic markers to facilitate tumor classification, particularly when a metastasis from the gastrointestinal tract is suspected.

Cadherins are cell-cell adhesion molecules characterized by several calcium-binding motifs in the extracellular domain, a single transmembrane region, and a carboxyl intracellular domain.⁷ This family of proteins plays an important role in maintaining tissue structure and morphology in the normal state, whereas loss of cadherin expression correlates with more aggressive behavior in some carcinomas.^{8,9} Cadherin 17 (CDH17) is a member of the cadherin superfamily that shows unique structural features.^{7,10} It has 7 extracellular cadherin repeats, compared with 5 in classic cadherins. Cadherin 17 also has an 18- to 20-residue intracellular domain, which is

shorter than the 150- to 160-amino acid domain of other cadherins.¹⁰ CDH17 expression was restricted to rat liver and intestine in animal studies, and thus it was originally designated as liver-intestine cadherin.¹⁰ Its expression is postulated to be regulated by CDX2, an intestine-specific caudal-related homeobox transcription factor.¹⁰⁻¹² Hixson and McEntire reported high levels of CDH17 in human fetal liver, but expressed sequence tags (ESTs) for CDH17 messenger RNA (mRNA) using virtual Northern analysis (<http://ggap.nci.nih.gov/SAGE>) are limited to the large and small intestines in adults.¹³

Emerging data suggest that CDH17 expression may also reflect intestinal differentiation in human malignancies, but its usefulness as a diagnostic marker has not been extensively evaluated.¹⁴⁻²¹ The aim of this study was to survey a spectrum of nonneoplastic and neoplastic human tissues for CDH17 immunolabeling and determine the sensitivity and specificity of this marker for gastrointestinal phenotype relative to CDX2. We evaluated 777 malignancies and samples of nonneoplastic epithelium from several organs, including the esophagus, stomach, colon, pancreas, liver, urinary bladder, breast, prostate, uterine cervix, endometrium, kidney, lung, thyroid, and skin for CDH17 and CDX2 immunorexpression, to determine whether CDH17 staining is complementary to that of CDX2 and distinguishes between malignancies of different origins.

Materials and Methods

Case Selection

Nonneoplastic and tumor tissues were identified from the surgical pathology files of the Departments of Pathology of Weill Cornell Medical College (New York, NY) and the University of Washington (Seattle). H&E-stained slides from each case were reviewed, and formalin-fixed, paraffin-embedded tissue blocks were obtained. The normal tissues included 10 specimens each from the esophagus, stomach, colon, and pancreas; 9 specimens from the liver; and 1 to 3 specimens each from the urinary bladder, breast, prostate, uterine cervix, uterus (proliferative and secretory endometrium), kidney, lung, thyroid, and skin. We evaluated 777 tumors derived from the colon (146 primary and 15 metastatic adenocarcinomas), esophagus (38 adenocarcinomas and 19 squamous cell carcinomas), stomach (9 intestinal-type and 33 diffuse-type adenocarcinomas), pancreas (10 primary tumors and 20 metastatic pancreatic cancer deposits), liver (42 hepatocellular carcinomas), biliary tract (n = 15), lung (n = 106), breast (n = 96), endometrium (n = 58), ovary (18 serous, 1 endometrioid, 3 clear cell, and 2 poorly differentiated carcinomas), 3 malignant mixed müllerian tumors, and 8 cancers

with mixed phenotypes), kidney (n = 5), thyroid (n = 5), urinary bladder (n = 2), prostate (n = 2), skin (2 basal cell and 2 squamous cell carcinomas), and uterine cervix (1 squamous cell carcinoma and 1 adenocarcinoma). Well-differentiated neuroendocrine (carcinoid) tumors, including 50 from the lung, 27 from the small intestine, 10 from the appendix, and 26 from the pancreas, were analyzed. Two cases of cutaneous malignant melanoma were also evaluated. Of these, 33 hepatocellular carcinomas, 15 cholangiocarcinomas, and 20 metastatic pancreatic ductal adenocarcinomas, 6 colonic adenocarcinomas with paired liver metastases, and 9 additional metastatic colonic adenocarcinomas to liver were evaluated using whole sections. The remaining cases were evaluated after construction of tissue microarrays (TMAs) in which each case was represented by three 0.6-mm tissue cores. The study was approved by the institutional review boards of the participating institutions.

Immunohistochemical Studies

Formalin-fixed, paraffin-embedded tissue sections were deparaffinized and endogenous peroxidase was inactivated. Sections were stained with an anti-CDH17 mouse monoclonal antibody (clone 1H3, Novus Biologicals, Littleton, CO) at 1:150 dilution and anti-CDX2 mouse monoclonal antibody (clone CDX2-88, Biogenex, San Ramon, CA) at 1:200 dilution. Immunohistochemical staining was performed on the Bond Max Autostainer (Leica Microsystems, Wetzlar, Germany). Antigen retrieval was performed using the Bond Epitope Retrieval Solutions 1 and 2 (Leica Microsystems) for CDH17 and CDX2, respectively, at 99°C to 100°C for 30 minutes. After retrieval, the sections were incubated with the primary antibody for 25 minutes, followed by a postprimary step for 15 minutes and then the polymer for 25 minutes (Bond Polymer Detection System, Leica Microsystems). Colorimetric development was performed with diaminobenzidine (Leica Microsystems).

Double immunostaining was performed as mentioned before using 3,3'-diaminobenzidine as a chromogen for CDX2. The slides were washed with Tris-buffered saline (pH, 7.0), blocked by Dual Endogenous Enzyme Block (DAKO, Carpinteria, CA), and then incubated with the antibody directed against CDH17 for 15 minutes at room temperature. The LSAB 2 System-Alkaline Phosphatase (DAKO) was used for detection followed by development with Mixed Red Define chromogen (DAKO) for 15 minutes. The slides were counterstained with hematoxylin and the results evaluated as described later in this article.

All cases were assessed for CDH17 labeling. Immunostaining for CDX2 was performed on 9 hepatocellular carcinomas with adequate material as well as all of the other cases. A positive staining reaction for CDH17 was defined as moderate-to-strong membranous staining, whereas

moderate-to-strong nuclear staining for CDX2 was considered a positive result. Cases were evaluated for extent of staining in the areas of interest and noted to be focal (<50%) or diffuse (>50%).

Results

Immunohistochemical staining for both CDH17 and CDX2 was observed in all samples of benign colonic epithelium **Image 1A** and **Image 1B**, whereas epithelium from the esophagus, stomach, and biliary tract were negative for both markers. Normal hepatocytes lacked CDX2 expression in all cases. Some patchy, weak cytoplasmic CDH17 staining

was noted in hepatocytes, but not in any other nonneoplastic tissue. Benign small pancreatic ducts showed diffuse expression of CDH17 in 40% (4/10) of cases and focal expression of CDX2 in 90% (9/10) of cases **Image 1C** and **Image 1D**. All nonneoplastic tissue specimens from outside the gastrointestinal tract were negative for both CDH17 and CDX2.

The histopathologic features and immunohistochemical staining results of gastrointestinal carcinomas are summarized in **Table 1** and representative cases are illustrated in **Image 2**. All CDH17-positive cases showed membranous staining, and we did not observe cytoplasmic or nuclear staining for CDH17 in any of the tumors examined. All primary colonic adenocarcinomas showed strong CDH17 staining, which was diffuse in 144 (98.6%) of 146 cases and focal in 2 (1.4%) of

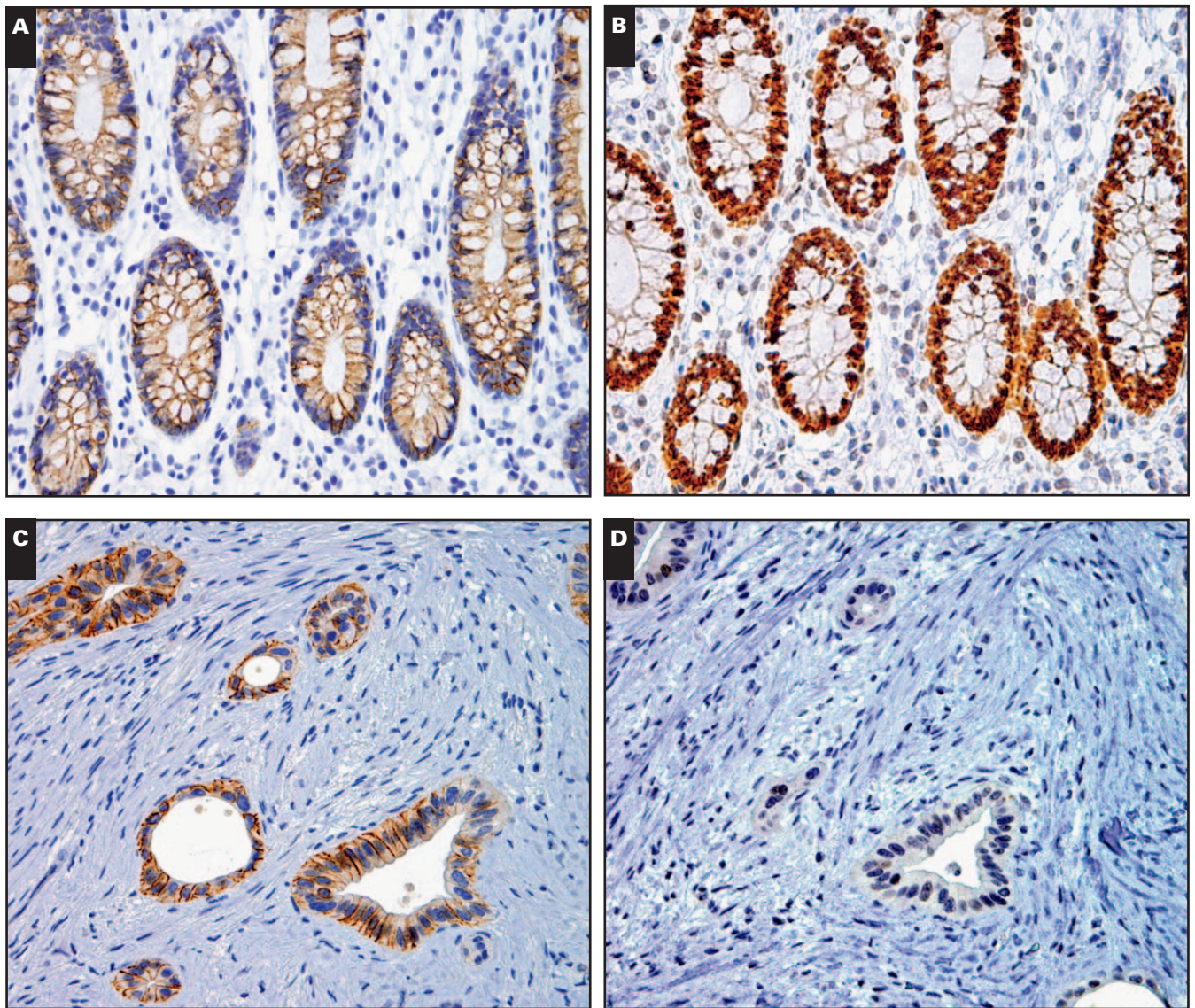


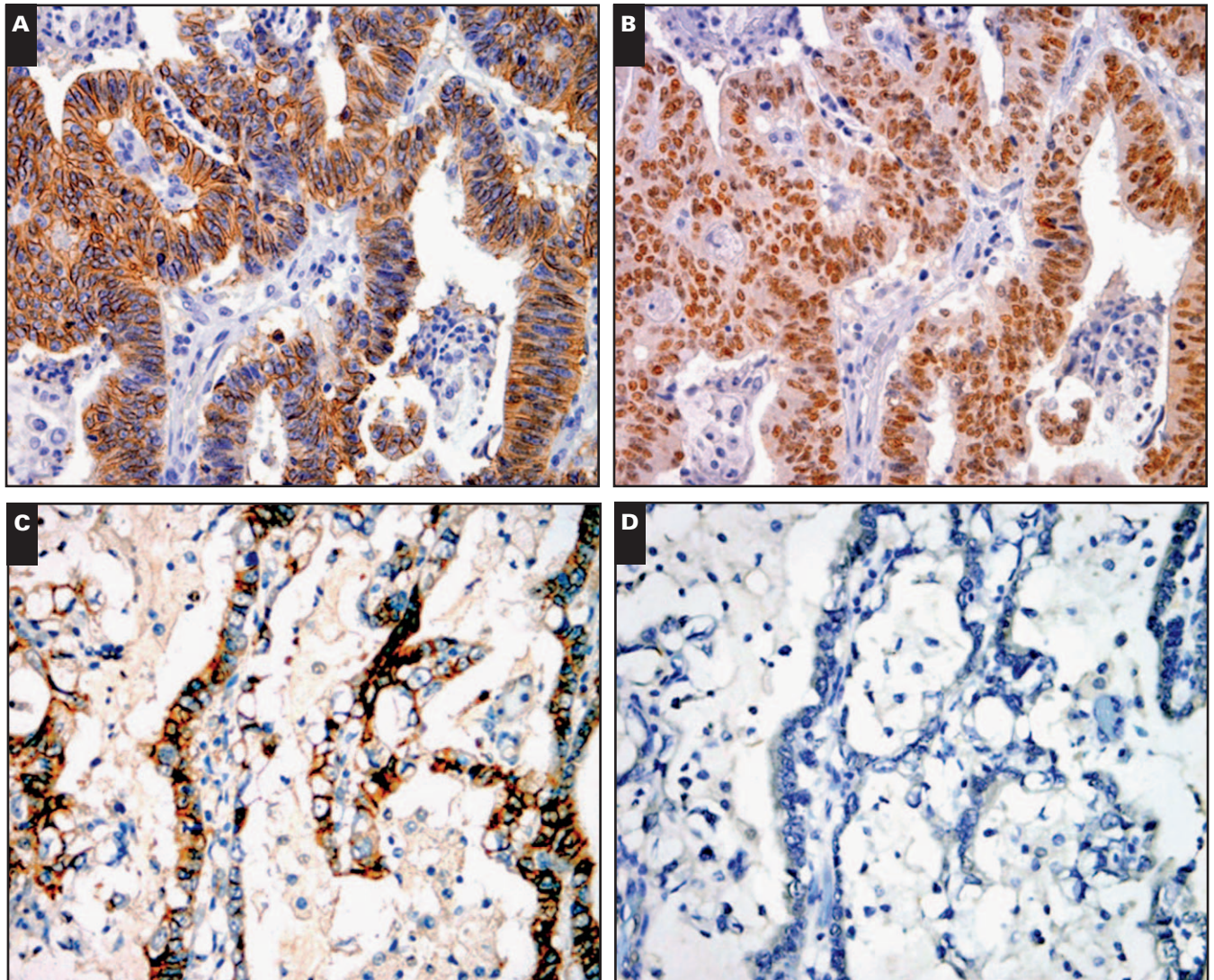
Image 1 CDH17 and CDX2 staining in nonneoplastic tissues. CDH17 shows strong staining of normal colonic epithelium in a membranous pattern **(A)**, whereas CDX2 staining is limited to the nucleus **(B)**. Pancreatic ductal epithelium shows strong CDH17 positivity **(C)**, but only focal CDX2 staining **(D)** ($\times 400$).

Table 1
Histopathologic Features and Immunohistochemical Staining Results in Gastrointestinal and Pancreatobiliary Carcinomas*

Tumor Type	CDH17	CDX2
Esophageal adenocarcinoma	31/38 (82)	30/38 (79)
Low-grade	13/14 (93)	12/14 (86)
High-grade	18/24 (75)	18/24 (75)
Esophageal squamous cell carcinoma	0/19 (0)	1/19 (5)
Low-grade	0/11 (0)	0/11 (0)
High-grade	0/8 (0)	1/8 (13)
Gastric adenocarcinoma	38/42 (90)	36/42 (86)
Low-grade	1/2 (50)	1/2 (50)
High-grade	37/40 (93)	35/40 (88)
Colonic adenocarcinoma	161/161 (100)	159/161 (99)
Low-grade	109/109 (100)	109/109 (100)
High-grade	37/37 (100)	35/37 (95)
Metastatic	15/15 (100)	15/15 (100)
Pancreatic ductal adenocarcinoma	15/30 (50)	8/30 (27)
Low-grade	4/6 (67)	2/6 (33)
High-grade	3/4 (75)	0/4 (0)
Metastatic	8/20 (40)	6/20 (30)
Cholangiocarcinoma	8/15 (53)	4/15 (27)
Low-grade	8/11 (73)	4/11 (36)
High-grade	0/4 (0)	0/4 (0)
Hepatocellular carcinoma	1/42 (2)	0/9 (0)

* Data are given as number (%).

146 cases. Most of these tumors (139/146, 95.2%) were also diffusely positive for CDX2, but the staining reaction was focal in 5 (3.4%) cases and 2 (1.4%) high-grade tumors were negative for this marker. Thirty esophageal adenocarcinomas showed dual staining for CDH17 and CDX2, 7 lacked staining for both markers, and 1 low-grade tumor was positive for CDH17, but negative for CDX2 (Image 2A, Image 2B, Image 2C, and Image 2D). All 19 esophageal squamous cell carcinomas were negative for CDH17, 18 of which were also negative for CDX2, but 1 high-grade tumor showed focal CDX2 staining. Thirty-eight (90%) gastric adenocarcinomas showed CDH17 staining, which was diffuse in 27 (64%) cases, and 36 (86%) of these were positive for CDX2 (Image 2E and Image 2F). The two cases that stained for CDH17 but lacked CDX2 were intestinal-type tumors (Image 2G and Image 2H). None of the gastric cancers were CDX2-positive/CDH17-negative. Four tumors were negative for both markers, including 2 intestinal- and 2 diffuse-type carcinomas. Pancreatic and biliary adenocarcinomas showed similar staining patterns



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for CDH17 and CDX2 with lower rates of positivity, particularly with respect to CDX2. Seven (70%) primary and 8 (40%) metastatic pancreatic ductal adenocarcinomas showed CDH17 staining **Image 3A** and **Image 3C**, compared with only 20% and 30% of CDX2-positive primary and metastatic tumors **Image 3B** and **Image 3D**. Eight (73%) low-grade cholangiocarcinomas showed CDH17 staining **Image 3E** and **Image 3G**, 4 of which were CDX2-positive **Image 3F** and **Image 3H**. All 4 high-grade cholangiocarcinomas were negative for both markers. Focal CDH17 staining was present in 1 (2%) high-grade hepatocellular carcinoma, but all of these tumors were CDX2-negative **Image 4D**.

To evaluate possible loss of CDH17 expression in metastatic lesions, a series of 15 metastatic colonic adenocarcinomas

in the liver were tested, including 6 paired samples of primary and metastatic colonic adenocarcinoma. All 6 tumor pairs showed strong and diffuse CDH17 staining. In contrast, CDX2 showed diffuse strong staining in all 6 primary tumors, but only in 3 of the 6 metastases. The 3 other metastatic lesions showed only focal staining with weaker intensity. The remaining 9 metastatic colon carcinomas were all diffusely positive for CDH17, of which 8 also stained diffusely for CDX2. The last case showed focal CDX2 expression.

The expression of CDH17 and CDX2 in well-differentiated neuroendocrine (carcinoid) tumors from various sites was also compared. All 27 (100%) small intestinal tumors stained with CDH17 and 20 (74%) of 27 expressed CDX2 **Image 5A** and **Image 5B**. Ten appendiceal

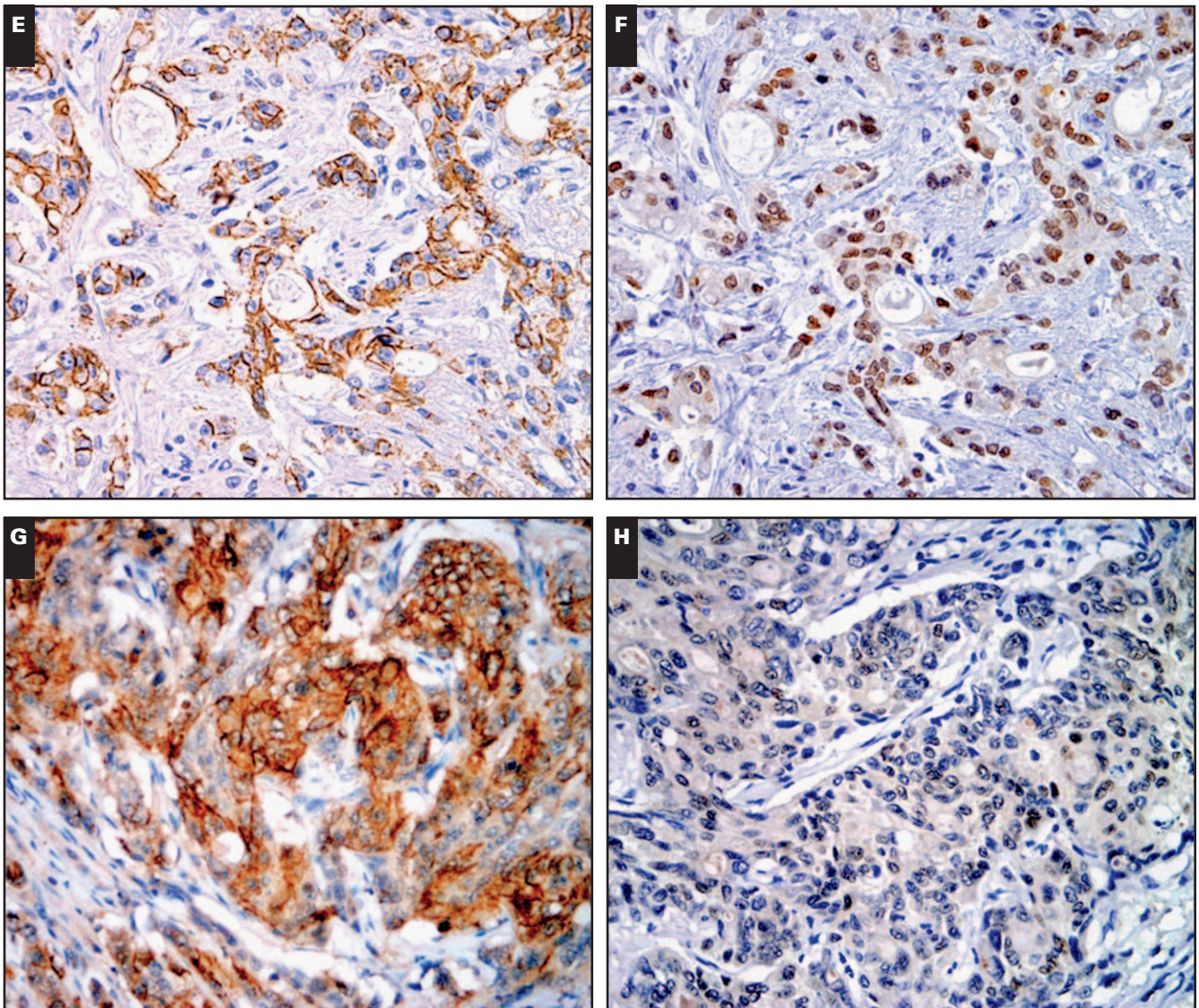


Image 2 CDH17 and CDX2 staining in adenocarcinomas of the upper gastrointestinal tract. Most (79%) esophageal adenocarcinomas showed concomitant staining for CDH17 (**A**) and CDX2 (**B**). One (3%) case was CDH17-positive (**C**) but negative for CDX2 (**D**, same case as **C**). Similarly, 86% of gastric adenocarcinomas coexpressed CDH17 (**E**) and CDX2 (**F**). Two (5%) cases were CDH17-positive (**G**), but lacked staining for CDX2 (**H**, same case as **G**) ($\times 400$).

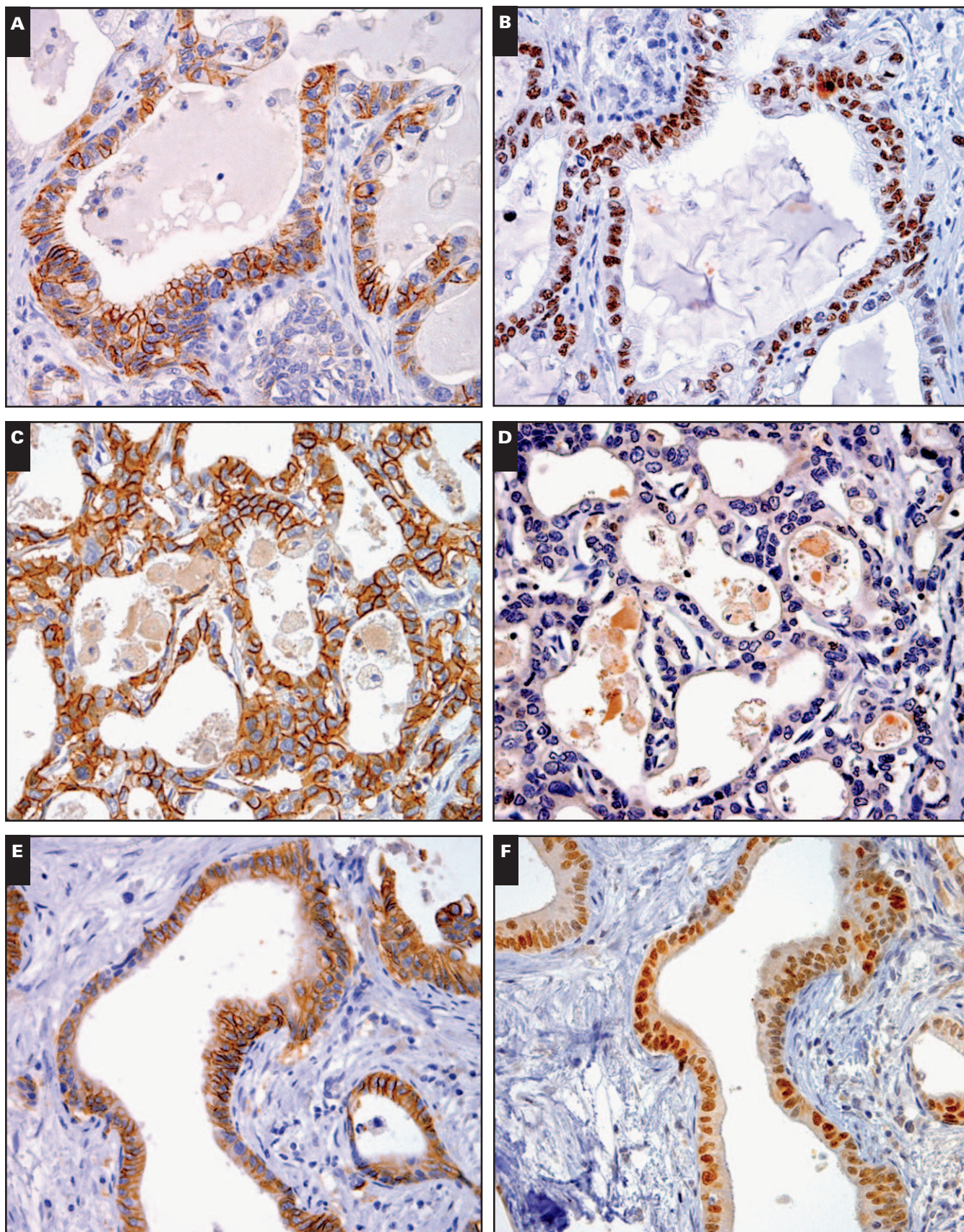


Image 3 CDH17 and CDX2 in pancreaticobiliary adenocarcinomas. A minority (27%) of pancreatic ductal adenocarcinomas stained for both CDH17 (A) and CDX2 (B). Seven (18%) showed membranous CDH17 positivity (C) but not nuclear staining for CDX2 (D, same case as C). Cholangiocarcinomas showed a similar pattern of staining. Four (27%) showed strong staining for CDH17 (E) and CDX2 (F). Four tumors (27%) were CDH17-positive (G), but CDX2-negative (H, same case as G, next page).

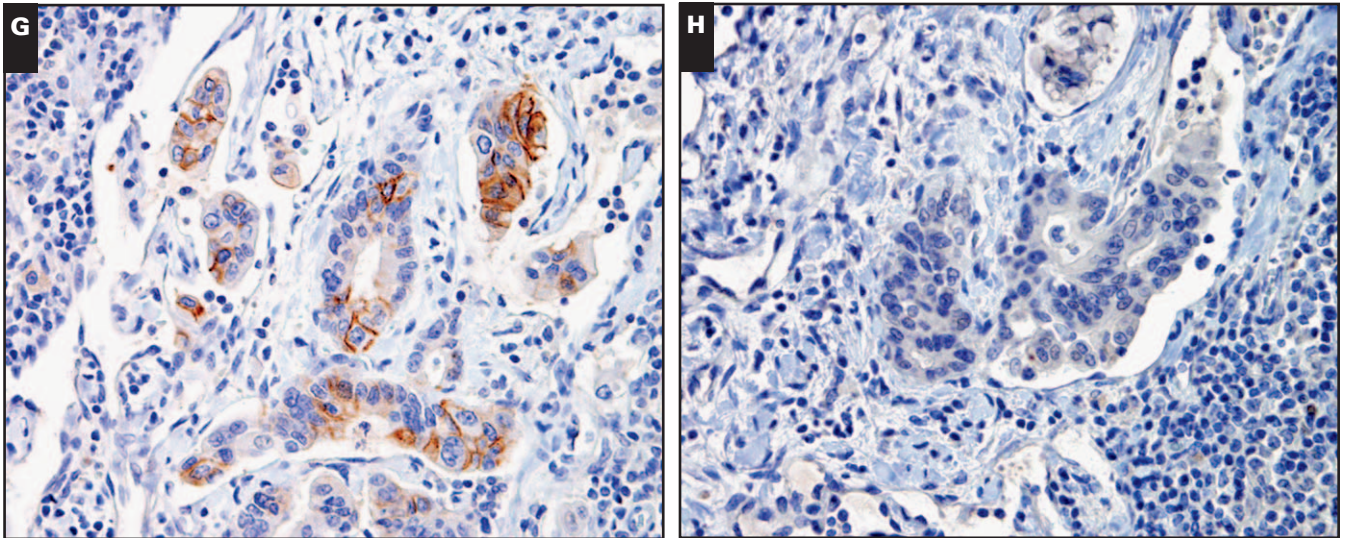


Image 3 None of the pancreatobiliary carcinomas showed CDX2 positivity in combination with negativity for CDH17 (×400).

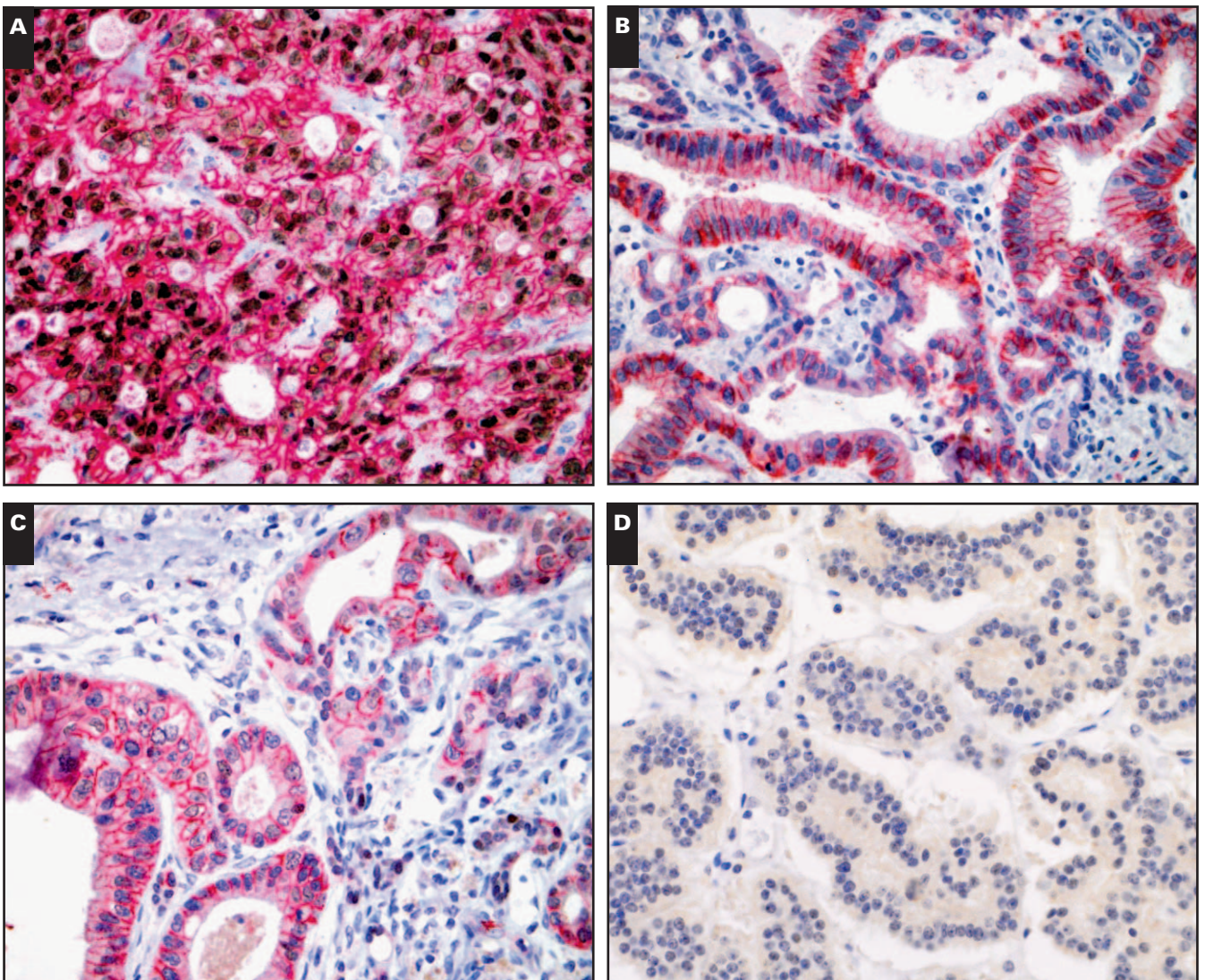


Image 4 Dual-labeling studies allow a direct comparison between CDH17 (red) and CDX2 (brown) staining in colonic adenocarcinoma (**A**). Dual staining performed on an esophageal adenocarcinoma demonstrates CDH17 positivity and the absence of CDX2 staining (**B**). Some pancreatic ductal adenocarcinomas (**C**), and rare hepatocellular carcinomas (**D**) also showed CDH17 staining with negative CDX2 using a dual chromogen assay (×400).

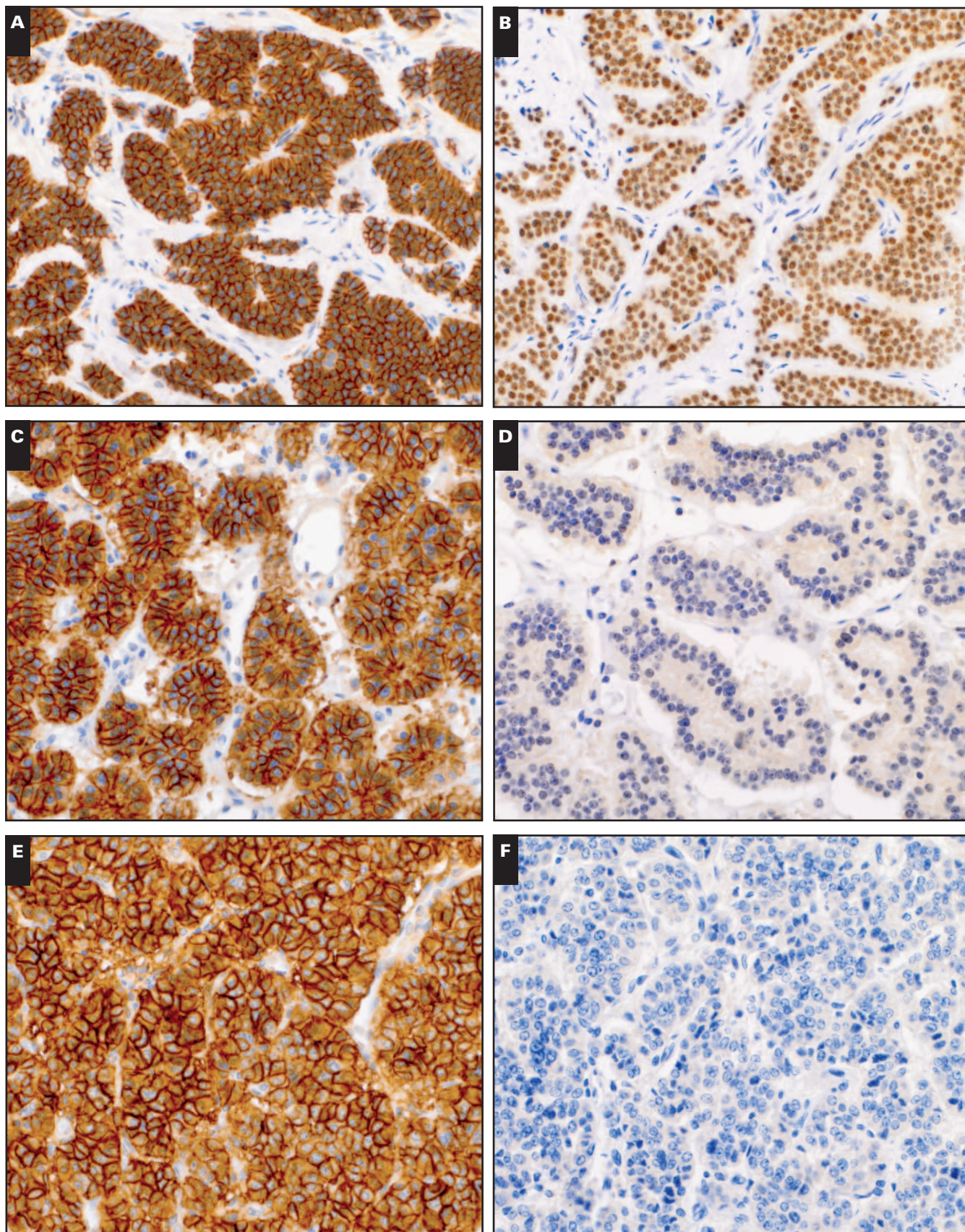


Image 5 CDH17 and CDX2 staining in well-differentiated neuroendocrine tumors. Most neuroendocrine tumors of the small intestine (74%) coexpressed CDH17 (A) and CDX2 (B). Twelve percent of pancreatic neuroendocrine tumors stained for CDH17 (C), but all were negative for CDX2 (D, same case as C). Similarly, 24% of bronchial carcinoid tumors were positive for CDH17 (E), but none expressed CDX2 (F, same case as E) (x400).

neuroendocrine tumors were positive for CDH17 (100%) and 9 (90%) were positive for CDX2. A minority of pancreatic neuroendocrine tumors (3 of 26, 12%) were CDH17 positive **Image 5C** and all were negative for CDX2 **Image 5D**. All 50 bronchial carcinoids were also negative for CDX2 **Image 5F**, whereas 12 (24%) were CDH17-positive **Image 5E**.

Dual-labeling experiments were performed on a subset of adenocarcinomas of the colon (n = 10), stomach (n = 10), esophagus (n = 5), and pancreas (n = 9), as well as 9 hepatocellular carcinomas to directly compare expression of CDH17 and CDX2. The staining reactions were identical to those performed with a single antibody. Representative images from CDH17-positive/CDX2-positive and CDH17-positive/CDX2-negative cases are depicted in **Image 4A**, **Image 4B**, **Image 4C**, and **Image 4D**.

Malignancies outside the digestive tract infrequently showed staining for CDH17 and CDX2. Ten (9.4%) of 106 lung cancers showed CDH17 staining, including 7 (9%) of 80 adenocarcinomas, 1 (5%) of 22 squamous cell carcinomas, 1 (33%) of 3 poorly differentiated carcinomas, and 1 large cell neuroendocrine carcinoma. Three CDH17-positive lung adenocarcinomas also stained for CDX2 **Image 6A** and **Image 6B**. Of 58 endometrial carcinomas, four (7%) were positive for CDH17 and 3 (5%) different cases were CDX2-positive with staining limited to squamous morules **Image 6C** and **Image 6D**. All 153 remaining cancers from ovary, breast, thyroid, kidney, prostate, bladder, uterine cervix, and skin stained negative for CDH17. Staining for CDX2 was observed in 1 (3%) ovarian carcinoma of endometrioid type and 2 (2%) of 96 invasive ductal carcinomas of the breast **Image 6E** and **Image 6F**.

Discussion

In this study, we evaluated CDH17 as a diagnostic marker of gastrointestinal carcinomas, particularly those with intestinal differentiation, and compared its usefulness with that of CDX2. We found concordant staining of both markers in most colonic, esophageal, and gastric adenocarcinomas (99%, 79%, and 86%, respectively). All adenocarcinomas of esophageal and gastric origin that lacked CDX2 staining were also negative for CDH17 (18% and 10%, respectively). Rare esophageal (3%) and gastric (5%) adenocarcinomas expressed CDH17 but not CDX2. All 15 liver metastases from colonic adenocarcinoma were positive for both CDX2 and CDH17, but 3 showed diminished CDX2 staining in the metastasis compared with the primary tumor. Fifty percent of pancreatic ductal adenocarcinomas and 53% of cholangiocarcinomas were CDH17-positive, whereas CDX2 staining was less frequent among these tumors (27% and 27% respectively).

CDH17 staining among nongastrointestinal malignancies was limited to non-small cell carcinomas, neuroendocrine tumors of the lung (9% and 24%, respectively) and endometrial adenocarcinomas (7%), whereas CDX2 staining was observed in a wider variety of tumors from different organs, including adenocarcinomas of the lung (4%), endometrium (5%), ovary (3%), and breast (2%). All cancers of the urinary bladder, prostate, uterine cervix, kidney, thyroid, and skin were negative for CDH17 and CDX2. Both CDH17 and CDX2 stained neuroendocrine tumors from the small intestine (100% and 74%, respectively) and appendix (100% and 90%, respectively), and occasional pancreatic neuroendocrine tumors (12%) were CDH17 positive. These results indicate that CDH17 and CDX2 are both relatively sensitive markers of gastrointestinal phenotype and show considerable overlap with respect to the types of tumors they stain, but CDH17 stains a slightly narrower spectrum of tumors outside the gastrointestinal tract.

CDH17 expression has been most extensively studied in gastric adenocarcinoma. Ko et al²² reported immunohistochemical expression of CDH17 in 60% of 95 gastric adenocarcinomas and 96% of 28 samples that showed intestinal metaplasia. In comparison, CDX2 stained substantially fewer cancers (35%) and foci of intestinal metaplasia (60%). Motoshita et al²¹ evaluated 14 tubular-type, 27 intestinal-type, and 18 mixed phenotype gastric adenocarcinomas for CDH17 immunostaining and found that adenocarcinomas with an intestinal or mixed phenotype were more likely to express CDH17 than tubular-type adenocarcinomas. We observed higher rates of both CDH17 and CDX2 labeling in gastric adenocarcinomas, most of which displayed diffuse-type differentiation.

CDH17 immunopositivity among gastric cancers may be prognostically important, but the data are conflicting.¹⁴ Park et al²³ studied 208 paired gastric endoscopic biopsy and resection specimens that contained adenocarcinoma and found that weak, or absent, CDH17 staining in biopsy samples predicted the presence of lymph node metastases in resection specimens. Other authors, however, have found absence of CDH17 staining to be associated with a better prognosis. Ito et al¹⁷ found that gastric cancers limited to the lamina propria were less likely to be CDH17-positive than those with deeper invasion and reported improved survival among patients with tumors that lacked CDH17 expression. Ko et al¹⁸ used real-time polymerase chain reaction to evaluate 56 gastric adenocarcinomas with lymph node metastases and 15 node-negative cases and found significantly higher CDH17 mRNA levels in the former. Clearly, the biologic importance of CDH17 staining among gastric cancers should be explored further.

Preliminary studies also suggest that CDH17 immunopositivity may have prognostic implications for patients with colorectal cancer. Kwak et al²⁰ compared 207 colorectal carcinomas with nonneoplastic colonic epithelium and found that tumors with reduced CDH17 labeling were associated

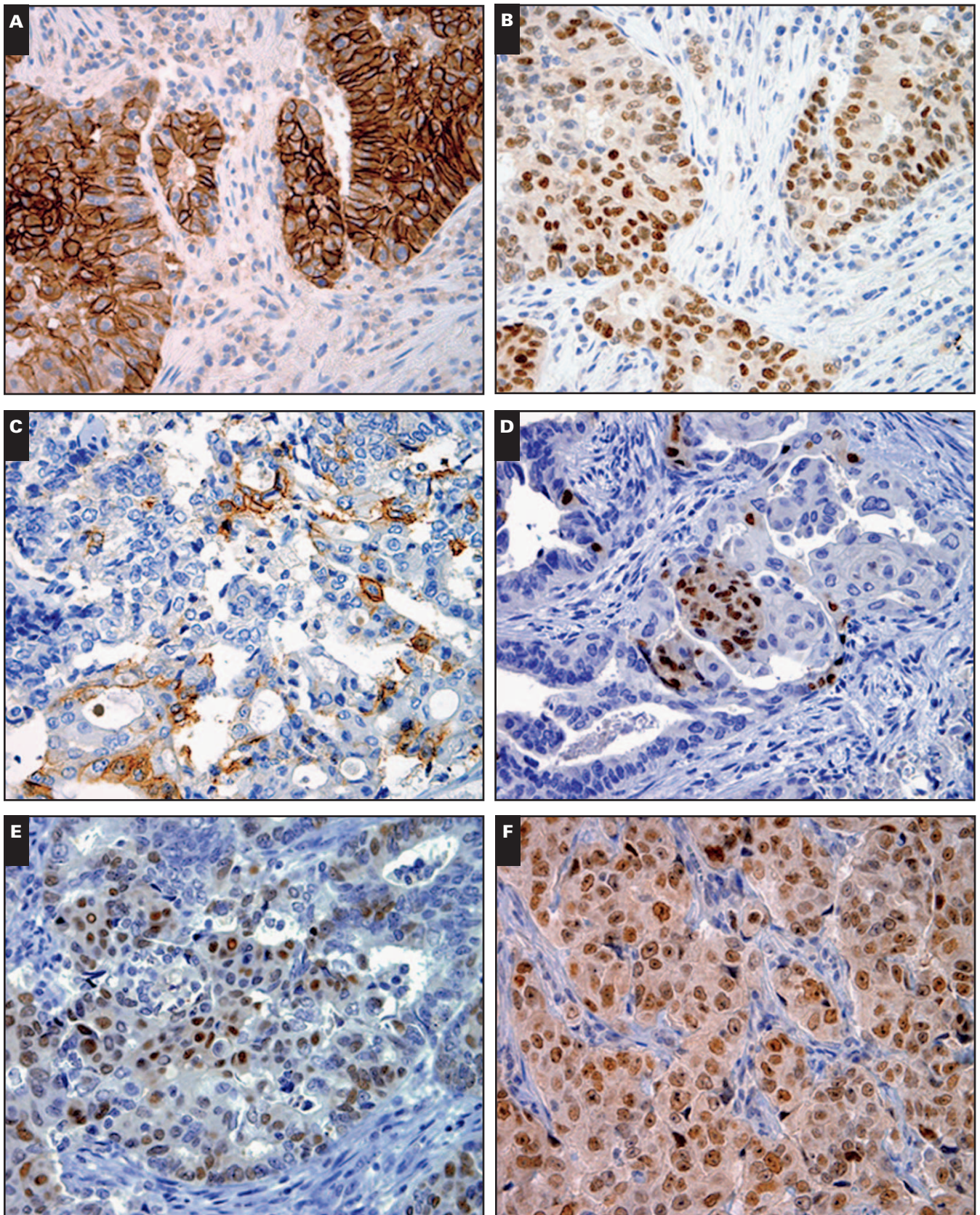


Image 6 CDH17 and CDX2 in nondigestive tract carcinomas. Rare (9%) non-small cell lung carcinomas showed CDH17 staining (A), nearly half of which (4%) were also positive for CDX2 (B). Occasional (7%) uterine endometrioid carcinomas were positive for CDH17 (C), but CDX2 staining was slightly less common (5%) and limited to squamous morules (D). Infrequent CDX2 staining was seen in ovarian carcinoma (E) and ductal carcinoma of the breast (F), but both tumor types were negative for CDH17 (×400).

with decreased overall survival compared with those with preserved staining. Takamura et al¹⁵ also reported a correlation between reduced CDH17 labeling and adverse prognostic features in colon cancer, including lymphovascular invasion, lymph node metastases, and advanced pathologic stage.

Although slightly more than half of all pancreatic ductal adenocarcinomas express CDH17, few studies have assessed the biologic significance of this finding.¹⁴ Takamura et al¹⁶ assessed 102 pancreatic ductal adenocarcinomas and found CDH17 staining in 57% of well-differentiated cancers compared with 22% of moderately to poorly differentiated tumors. They found CDH17 staining in more than 25% of the tumor cells to be independently predictive of prolonged survival.¹⁶ Similarly, we noted that CDH17 expression was quite common among primary pancreatic ductal adenocarcinomas (70%) but substantially lower in metastatic deposits (40%).

Although CDH17 is expressed in human fetal liver we had only 1 hepatocellular carcinoma that was CDH17-positive, similar to the findings reported by others.¹⁴ These findings are in sharp contrast to the observations of Wong et al¹⁹ who found CDH17 protein expression in more than 80% of hepatocellular carcinomas. These discrepancies may be explained by differences in methodology and interpretation. Wong et al¹⁹ used goat polyclonal antibody against CDH17 and analyzed frozen section material. They also considered cytoplasmic rather than membranous staining of tumor cells to be a positive result, so it is possible that nonspecific antibody cross-reactivity affected results.

CDH17 positivity has been rarely reported in tumors outside the gastrointestinal tract. Su et al¹⁴ studied CDH17 immunostaining patterns in carcinomas of uterine cervix, ovary, lung, kidney, and prostate and reported all cases to be negative, except 1 prostatic adenocarcinoma that showed focal CDH17 staining. We also failed to detect CDH17 immunopositivity in any nonneoplastic tissues outside the gastrointestinal tract and found most carcinomas derived from these tissues were CDH17-negative. However, we did find a minority (9%) of non-small cell lung cancers, bronchial carcinoids (24%), and endometrial carcinomas (7%) showed CDH17 staining, indicating that this marker should be coupled with cytokeratin panels in some situations.

CDX2 is widely accepted as an immunohistochemical marker of intestinal differentiation. Early studies reported high sensitivity of CDX2 for detecting adenocarcinomas of the colon and small intestine, whereas gastric, esophageal, and pancreatic ductal adenocarcinomas and cholangiocarcinomas were variably positive for this marker. Werling et al³ performed immunohistochemical staining for CDX2 on 158 gastrointestinal carcinomas and found highest expression in carcinomas of the colon (99%), followed in frequency by those of the stomach (70%), esophagus (67%), pancreas (32%), and biliary tree (25%), but no staining of hepatocellular carcinomas. Unlike

CDH17, however, CDX2 shows frequent staining of several types of tumor outside the gastrointestinal tract. Werling et al³ found CDX2 staining in 35% of mucinous ovarian tumors, 100% of adenocarcinomas of the urinary bladder, and 9% of papillary thyroid carcinomas. Others have described CDX2 labeling in carcinomas of various types, including serous (5%), endometrioid (30%), and mucinous (20%) carcinomas of the ovary, endometrial adenocarcinomas (22%), and occasional adenocarcinomas of the lung (6%).⁴ We also noted a broader spectrum of CDX2 expression among extraintestinal carcinomas compared with CDH17. In our study, CDX2 occasionally stained adenocarcinomas of the lung (4%), endometrium (5%), ovary (3%), and breast (2%).

Our results suggest that CDH17 is a highly specific marker of gastrointestinal epithelium, particularly intestinal-type, and usually stains gastrointestinal carcinomas in a fashion similar to CDX2. However, CDH17 is at least as sensitive as, if not slightly more sensitive than, CDX2 as a marker of carcinomas with an intestinal phenotype, including those associated with metaplastic intestinal epithelium. These 2 markers, in combination, may be useful in classifying carcinomas of unknown origin, especially when a primary site in the gastrointestinal tract is suspected or requires exclusion.

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References

1. Greco A, Hainsworth J. Cancer of unknown primary site. In: Lawrence T, Rosemberg S, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA: Lippincott; 2008:2363-2387.
2. Houghton O, Connolly LE, McCluggage WG. Morules in endometrioid proliferations of the uterus and ovary consistently express the intestinal transcription factor CDX2. *Histopathology*. 2008;53:156-165.
3. Werling RW, Yaziji H, Bacchi CE, et al. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. *Am J Surg Pathol*. 2003;27:303-310.
4. Moskaluk CA, Zhang H, Powell SM, et al. Cdx2 protein expression in normal and malignant human tissues: an immunohistochemical survey using tissue microarrays. *Mod Pathol*. 2003;16:913-919.
5. Raspollini MR, Baroni G, Taddei A, et al. Primary cervical adenocarcinoma with intestinal differentiation and colonic carcinoma metastatic to cervix: an investigation using Cdx-2 and a limited immunohistochemical panel. *Arch Pathol Lab Med*. 2003;127:1586-1590.

6. Kim MJ. The usefulness of CDX-2 for differentiating primary and metastatic ovarian carcinoma: an immunohistochemical study using a tissue microarray. *J Korean Med Sci.* 2005;20:643-648.
7. Gloushankova NA. Changes in regulation of cell-cell adhesion during tumor transformation. *Biochemistry (Mosc).* 2008;73:742-750.
8. Makrilia N, Kollias A, Manolopoulos L, et al. Cell adhesion molecules: role and clinical significance in cancer. *Cancer Invest.* 2009;27:1023-1037.
9. Jeanes A, Gottardi CJ, Yap AS. Cadherins and cancer: how does cadherin dysfunction promote tumor progression? *Oncogene.* 2008;27:6920-6929.
10. Berndorff D, Gessner R, Kreft B, et al. Liver-intestine cadherin: molecular cloning and characterization of a novel Ca(2+)-dependent cell adhesion molecule expressed in liver and intestine. *J Cell Biol.* 1994;125:1353-1369.
11. Angres B, Kim L, Jung R, et al. LI-cadherin gene expression during mouse intestinal development. *Dev Dyn.* 2001;221:182-193.
12. Hinoi T, Lucas PC, Kuick R, et al. CDX2 regulates liver intestine-cadherin expression in normal and malignant colon epithelium and intestinal metaplasia. *Gastroenterology.* 2002;123:1565-1577.
13. Hixson DC, McEntire KD. Detection of an altered form of cell-CAM 105 on rat transplantable and primary hepatocellular carcinomas. *Cancer Res.* 1989;49:6788-6794.
14. Su MC, Yuan RH, Lin CY, et al. Cadherin-17 is a useful diagnostic marker for adenocarcinomas of the digestive system. *Mod Pathol.* 2008;21:1379-1386.
15. Takamura M, Ichida T, Matsuda Y, et al. Reduced expression of liver-intestine cadherin is associated with progression and lymph node metastasis of human colorectal carcinoma. *Cancer Lett.* 2004;212:253-259.
16. Takamura M, Sakamoto M, Ino Y, et al. Expression of liver-intestine cadherin and its possible interaction with galectin-3 in ductal adenocarcinoma of the pancreas. *Cancer Sci.* 2003;94:425-430.
17. Ito R, Oue N, Yoshida K, et al. Clinicopathological significant and prognostic influence of cadherin-17 expression in gastric cancer. *Virchows Arch.* 2005;447:717-722.
18. Ko S, Chu KM, Luk JM, et al. Overexpression of LI-cadherin in gastric cancer is associated with lymph node metastasis. *Biochem Biophys Res Commun.* 2004;319:562-568.
19. Wong BW, Luk JM, Ng IO, et al. Identification of liver-intestine cadherin in hepatocellular carcinoma: a potential disease marker. *Biochem Biophys Res Commun.* 2003;311:618-624.
20. Kwak JM, Min BW, Lee JH, et al. The prognostic significance of E-cadherin and liver intestine-cadherin expression in colorectal cancer. *Dis Colon Rectum.* 2007;50:1873-1880.
21. Motoshita J, Nakayama H, Taniyama K, et al. Molecular characteristics of differentiated-type gastric carcinoma with distinct mucin phenotype: LI-cadherin is associated with intestinal phenotype. *Pathol Int.* 2006;56:200-205.
22. Ko S, Chu KM, Luk JM, et al. CDX2 co-localizes with liver-intestine cadherin in intestinal metaplasia and adenocarcinoma of the stomach. *J Pathol.* 2005;205:615-622.
23. Park SS, Kang SH, Park JM, et al. Expression of liver-intestine cadherin and its correlation with lymph node metastasis in gastric cancer: can it predict N stage preoperatively? *Ann Surg Oncol.* 2007;14:94-99.

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