American Journal of Pathology, Vol. 139, No. 2, August 1991


# Distribution Patterns of Type VII Collagen in Normal and Malignant Human Tissues

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***The distribution of basement membrane type VII collagen was detected immunohistochemically and compared in normal human organs and their neoplastic derivatives using monoclonal antibody LH7.2. In normal tissues, type VII collagen was found to be restricted to the basement membrane surrounding or underlying combined epithelia, such as those lining breast, prostate, and bronchus, which are composed of a basal and luminal cell layer, and stratified epithelia, such as larynx, esophagus, trachea, vagina, ectocervix, and epidermis. No type VII collagen was found in the 'simple' epithelia lining the major part of the gastrointestinal tract (GI) tract, such as liver, stomach, and intestine, or around blood vessels, muscle, and nerve fibers, which are surrounded, however, by a basement membrane containing type IV collagen and laminin. When tested in benign and malignant local tumors, antibody LH7.2 showed staining patterns partly similar to those observed in the corresponding normal tissues. This resulted in a well-circumscribed positive reaction around ducts in carcinomas* in situ *of the breast, in benign prostate tumors, in pleomorphic adenomas, and in a negative reaction in tumors of the GI tract. Furthermore type VII collagen was predominantly seen in carcinomas with a squamous differentiation, such as squamous carcinomas of the lung, head and neck, vulva, and vagina. These results indicate that the presence of type VII collagen in malignant tumors is correlated with (squamous) differentiation rather than with the origin of the tumor. With tumor progression, an increased presence of type VII collagen, as compared with normal urinary bladder, was found in infiltrating transitional cell carcinomas. Thus, although in general invasive and metastatic tumors do not express extensively type VII collagen, exceptions to this rule exist in bladder cancer, squamous carcinomas of the lung, tumors of the head and neck region, female genital tract tumors, and in some adenocarcinomas of the breast. (Am J Pathol 1991, 139:451–459)***

In general the basement membrane, which separates epithelial, muscle, or nerve cells from connective tissue cells, consists of a lamina lucida, a lamina densa, and a lamina fibroreticularis or sublamina densa zone. The latter contains anchoring fibrils, which are supposed to connect the basement membrane to the underlying connective tissue.[1] Recently type VII collagen has been suggested to constitute the main filamentous component of these anchoring fibrils.[2,3] Immunoelectron microscopy with the monoclonal antibody LH7.2, specific for the nonhelical carboxyterminal region of the type VII collagen molecule, has shown that the LH7.2 binding sites are localized within the lamina densa of the basement membrane. Furthermore immunohistochemistry showed that the LH7.2 antibody reacts predominantly with the basement membrane of stratified epithelia and ectodermally derived glands.[4–6]

Next to their importance in growth and differentiation of tissues, basement membranes form an early natural barrier in the process of tumor cell invasion. Many authors have reported on the distribution pattern of basement membranes in neoplasms, predominantly using antibodies to laminin and type IV collagen. Albrechtsen et al[7] and Siegal et al[8] were among the first to show a degradation of basement membrane during the process of invasion in the malignant breast. Subsequent immunohistochemical studies of a variety of malignant tissues have demonstrated the partial or complete absence of basement membrane components in areas of tumor cell invasion.[9–13] In contrast to such malignant cases, benign tumors or tumor cell nests are mostly surrounded by an intact basement membrane, as is also the case for *in situ*

Accepted for publication April 12, 1991.

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lesions, although discontinuities have been found in some benign neoplasms of the skin[14] and the salivary gland.[15] Conversely several cases of invasive malignant tumors, for example, squamous cell carcinomas of the head and neck, were found to exhibit an intact basement membrane.[16,17]

In our study we have used monoclonal antibody (MAb) LH7.2, specific for type VII collagen, to compare the distribution pattern of this type of collagen in normal tissues and the benign and malignant tumors derived therefrom. The aim of this investigation was to find out whether the presence of type VII collagen is indicative either of a specific type of differentiation within tumors, as it is in specific types of normal tissues, or indicative of the tissue origin of a certain neoplasm.

## Materials and Methods

Fresh normal (n = 25) and neoplastic (n = 476) human tissues (Tables 1 and 2) obtained after surgery or during autopsy were immediately frozen and stored in liquid nitrogen. Diagnosis was performed using routinely stained paraffin sections or parallel frozen sections. Frozen sections (4 to 7 μ) were cut on a cryostat, air dried for 24 hours at room temperature, and stored at −20°C until use in immunohistochemistry. For this purpose, the cryostat sections were fixed in acetone (−20°C) for 5 minutes and rinsed in acetone at room temperature before drying. Sections were incubated with culture supernatant of the type VII collagen antibody LH7.2[4] at a 1:10 dilution in phosphate-buffered saline (PBS, pH 7.4) for 30 to 45 minutes at room temperature. After three washes with PBS for 10 minutes each, peroxidase-conjugated rabbit anti-mouse gamma G immunoglobulin (IgG; DAKOpatts, Glostrup, Denmark; diluted 1:40 in PBS with 5% human AB serum) was applied to the sections for 30 to 45 minutes at room temperature. After a second series of washing steps with PBS, the peroxidase activity was detected either with 3-amino-9-ethyl-carbazole (Aldrich Chemical Co., Brussels, Belgium) or with 3,3′-diaminobenzidine tetrahydrochloride (Sigma Chemical Co., St. Louis, MO), as described before.[18,19] Sections were counterstained with Harris hematoxylin and mounted with Kaisers glycerin-gelatin (Merck, Darmstadt, Federal Republic of Germany). For comparative studies, type IV collagen and laminin were tested as described before.[18]

**Table 1.** *Staining Patterns of Antibody LH7.2, Recognizing Type VII Collagen, in Various Normal Human Organs*

| Tissue type | LH7.2 staining pattern |
|---|---|
| Skin epidermis | + |
| Cornea | + |
| Larynx | + |
| Esophagus | + |
| Trachea | + |
| Bronchus | + |
| Bronchiolus | + |
| Lung alveoli | − |
| Thyroid gland | − |
| Stomach | − |
| Pancreas | − |
| Spleen | − |
| Large intestine | − |
| Small intestine | F+* |
| Liver | − |
| Kidney | F+ |
| Urether | W+ |
| Urinary bladder | W+ |
| Prostate: ducts | + |
| acini | + |
| Seminiferous epithelium | − |
| Ovary | − |
| Uterine (Fallopian) tube | − |
| Ectocervical squamous epithelium | + |
| Endocervical glandular epithelium | F+ |
| Vagina | + |
| Breast: ducts | + |
| acini | + |
| Pituitary gland | − |
| Muscle cells | − |
| Nerve fibers | − |
| Blood vessels | − |

* F+ = focally positive
W+ = weakly positive

## Results

### Distribution Patterns of Type VII Collagen in Normal Human Tissues

The results of immunohistochemical staining experiments, using the type VII collagen antibody on normal human tissues, are summarized in Table 1 and depicted in Figure 1. In line with earlier reports,[4] the LH7.2 antibody reacts in general predominantly with basement membranes surrounding combined and stratified epithelia. For example, in normal breast and prostate, type VII collagen can be found around ducts and acini (Figure 1a, b). Also in the cornea, larynx, esophagus, trachea, bronchus, bronchiolus, ectocervix, and epidermis, type VII collagen staining can be seen between the stratified epithelial cell layer and the connective tissue (Figure 1c to g). No type VII collagen seems to be present around blood vessels, muscle, and nerve fibers. Also 'simple' glandular epithelia, such as that of the lung alveoli, the lower part of the gastrointestinal (GI) tract, and thyroid as well as pituitary gland, are devoid of type VII collagen. Weak or focal reactivity patterns were seen in the ureter, urinary bladder, small intestine, and around some ductules in the kidney (Figure 1h). Laminin and type IV collagen, however, display a more widespread distribution pattern. These two components were found to be present in all basement membranes, including those sur-

**Table 2.** *Staining Patterns of Antibody LH7.2, Recognizing Type VII Collagen in Various Malignant Human Tissues*

| Diagnosis | LH7.2 staining patterns | | |
|---|---|---|---|
| | − | F+ | + |
| Head and neck region | | | |
| Well-differentiated squamous cell carcinoma | | | 6 |
| Moderately differentiated squamous cell carcinoma | | | 21 |
| Poorly differentiated squamous cell carcinoma | | | 1 |
| Warthin tumor | 4† | | |
| Pleomorphic adenoma | | | 4 |
| Papillary thyroid carcinoma | | 3 | |
| Follicular thyroid carcinoma | 1 | | |
| Respiratory tract | | | |
| Well-differentiated squamous cell carcinoma | 1 | | 5 |
| Moderately differentiated squamous cell carcinoma | | 2 | 4 |
| Poorly differentiated squamous cell carcinoma | 3 | 4 | |
| Adenocarcinoma | 8 | 2 | |
| Small-cell anaplastic carcinoma | 9 | | |
| Carcinoid | 6 | | |
| GI tract | | | |
| Well-differentiated adenocarcinoma stomach | | 1 | |
| Poorly differentiated adenocarinoma stomach | 1 | | |
| Mucinous adenocarcinoma stomach | 1 | | |
| Mucinous adenocarcinoma colon | 3 | | |
| Adenocarcinoma of the pancreas | 2 | | |
| Insulinoma | 1 | | |
| Hepatoblastoma | 1 | | |
| Breast | | | |
| *In situ* carcinoma | | | 16 |
| Invasive lobular carcinoma | 15 | | |
| Invasive ductal carcinoma | 94 | 3 | |
| Breast metastases | 22 | | |
| Female genital tract | | | |
| Keratinizing squamous cell carcinoma vagina | | | 1 |
| Endometrioid adenocarcinoma | | 2 | |
| Well-differentiated ovarian carcinoma | | 1 | |
| Poorly differentiated ovarian carcinoma | 1 | | |
| Mixed Müllerian carcinoma | 1 | | |
| Mesothelioma | 1 | | |
| Cervical immature squamous metaplasia | | 8 | |
| Cervical mature squamous metaplasia | | | 19 |
| Cervical intraepithelial neoplasia I | | | 4 |
| Cervical intraepithelial neoplasia II | | | 5 |
| Cervical intraepithelial neoplasia III | | | 5 |
| Adenocarcinoma of the cervix | 1 | 6 | 1 |
| Squamous cell carcinoma of the cervix | | 6 | 8 |
| Male genital tract | | | |
| Benign prostate tumors | | 1 | 39 |
| Well-differentiated prostate carcinoma | | 1 | |
| Moderately differentiated prostate carcinoma | 20 | | |
| Poorly differentiated prostate carcinoma | 4 | | |
| Anaplastic seminoma | 1 | | |
| Embryonal carcinoma | 3 | | |
| Urinary tract | | | |
| Grawitz tumor | 3 | | |
| Transitional cell carcinoma G1 | 2 | 9 | |
| Transitional cell carcinoma G2 | 1 | 11 | |
| Transitional cell carcinoma G3, noninfiltrating | 7 | 9 | |
| Transitional cell carcinoma G3, infiltrating | 2 | 5 | 15 |
| Metastases of transition cell carcinoma | 13 | 2 | 8 |
| Skin | | | |
| Keratinizing squamous cell carcinoma vulva | | | 3 |
| Miscellaneous | | | |
| Myosarcoma | 1 | | |
| Malignant fibrous histiocytoma | 1 | | |
| Lymphoma | 1 | | |

* F+ = scattered positivity, + = random positivity, − = negative.
† Number of cases.

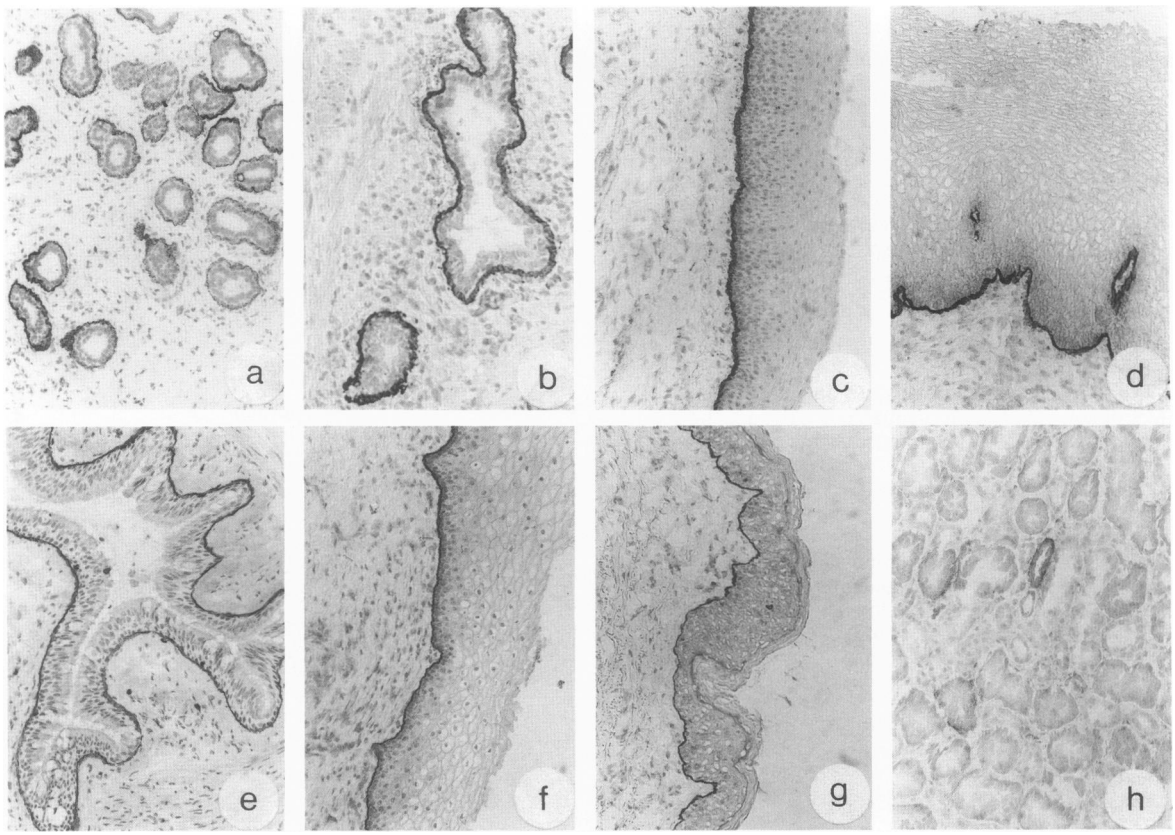


**Figure 1.** *Micrographs showing the immunoperoxidase reactivity patterns of LH7.2, recognizing type VII collagen, in frozen sections of human breast (*a, *×70), prostate (*b, *×100), larynx (*c, *×60), esophagus (*d, *×60), bronchiolus (*e, *×60), ectocervix (*f, *×60), epidermis (*g, *×80), and kidney (*h, *×60).*

rounding simple epithelia as well as blood vessels, muscle, and nerve fibers.

## Distribution Pattern of Type VII Collagen in Neoplastic Human Tissues

Table 2 and Figures 2 and 3 summarize the results of the immunohistochemical studies in human tumors, using the LH7.2 antibody. Again antibodies to laminin and type IV collagen were applied for comparative purposes. The nonepithelial tumors in this series were negative for type VII collagen.

### *Tumors of the Head and Neck Region*

All squamous cell carcinomas obtained from the head and neck region showed a positive basement membrane reaction with the LH7.2 antibody. In most tumors the staining pattern was linear, surrounding squamous epithelial tumor cell nests partly (Figure 2a). In 10 of 21 cases of moderately differentiated and in four of six cases of well-differentiated squamous cell carcinomas, a strong cytoplasmic staining was observed. In most of these cases a significant percentage of the tumor cells were stained (Figure 2b). Generally tumor peripheries appeared to be stained weaker or negatively.

Three papillary carcinomas of the thyroid showed a scattered positivity, whereas the only follicular carcinoma of the thyroid was completely negative, as were four Warthin tumors. Within the group of pleomorphic adenomas, a randomly distributed positivity was seen around tumor ducts and between tumor nests, as well as between the dispersed tumor cells (Figure 2c).

In all of these tumors of the head and neck region, laminin and type IV collagen were abundantly present, surrounding tumor areas. Contrary to the type VII collagen antibody, however, the antibodies to laminin and type IV collagen did not show any obvious cytoplasmic staining reaction.

### *Lung Cancers*

Among the main groups of lung tumors, small-cell lung carcinomas (SCLC) and the carcinoids displayed absolutely no reactivity with the LH7.2 antibody. In general the adenocarcinomas were negative (Figure 2d), with only 2 of 10 cases showing some focal positivity. The pulmonary squamous cell carcinomas, however, showed

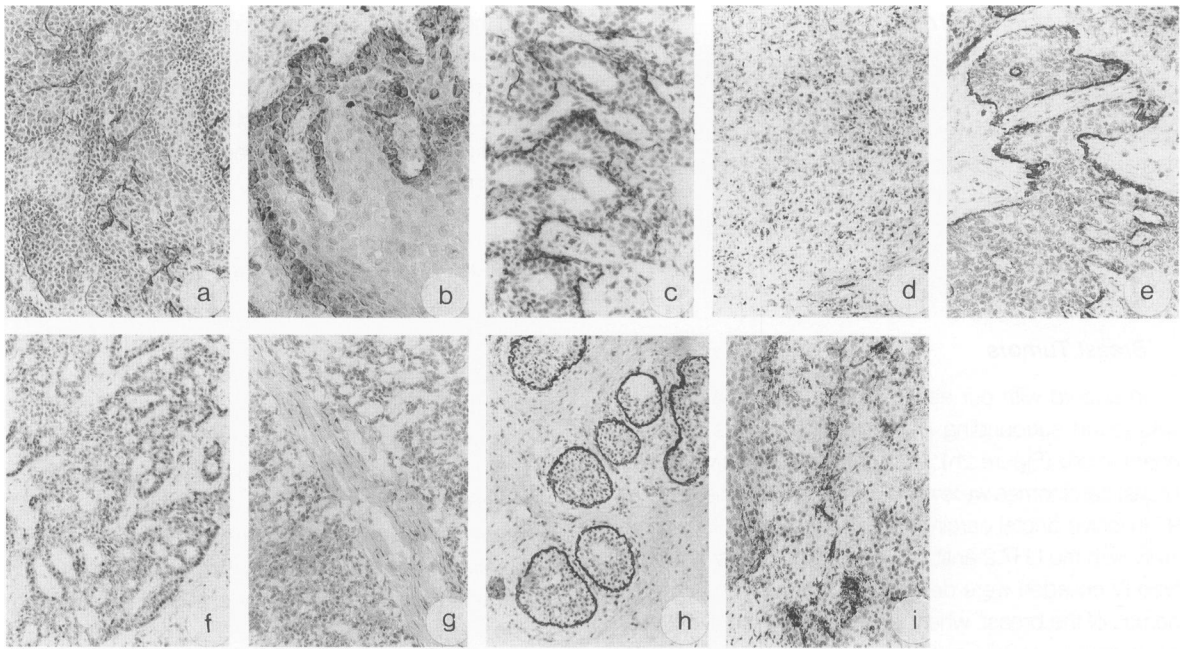


**Figure 2.** *Micrographs showing the immunoperoxidase reactivity patterns of LH7.2 in two squamous cell carcinomas of the head and neck region (***a**, *×100;* **b**, *×100), a pleomorphic adenoma (***c**, *×150), an adenocarcinoma of the lung (***d**, *×60), a squamous-cell carcinoma of the lung (***e**, *×80), a mucinous adenocarcinoma of the stomach (***f**, *×60), a hepatoblastoma (***g**, *×60), an intraductal breast carcinoma (***h**, *×60), and an invasive ductal breast carcinoma (***i**, *×80).*

a strong reactivity for type VII collagen (Figure 2e). Within this group of tumors, staining appears to be increased with higher degree of differentiation. No or scattered positivity was for the most part found in poorly differentiated carcinomas, whereas random positivity was present in 9 of 12 moderately and well-differentiated tumors. With respect to laminin and type IV collagen, it can be stated that these components were present in some cases of SCLC, carcinoids, and adenocarcinomas and in nearly all cases of squamous cell carcinomas of the lung.

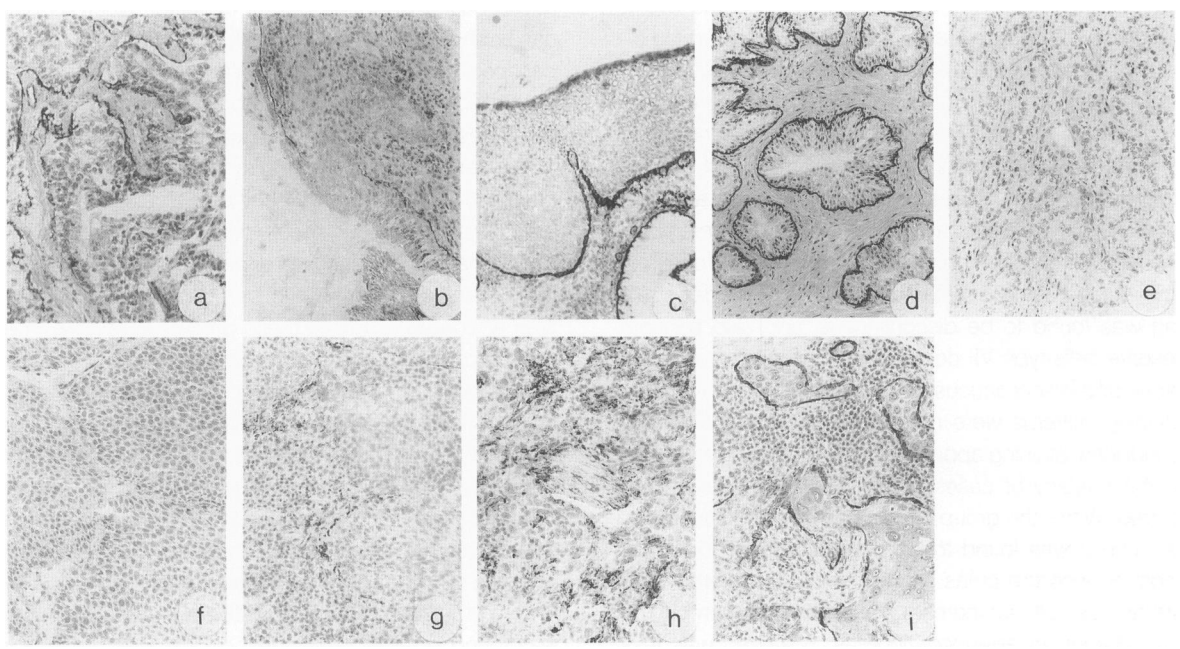


**Figure 3.** *Micrographs showing the immunoperoxidase reactivity patterns of LH7.2 in an endometrial adenocarcinoma (***a**, *×80), an immature squamous metaplasia of the cervix (***b**, *×60), a cervical intraepithelial neoplasia grade II (***c**, *×60), a benign prostate tumor (***d**, *×60), a poorly differentiated prostate carcinoma (***e**, *×60), a transitional cell carcinoma G1 (***f**, *×80), a transitional cell carcinoma G2 (***g**, *×80), an infiltrating transitional cell carcinoma G3 (***h**, *×80), and a squamous cell carcinoma of the vulva (***i**, *×80).*

### *Tumors of the GI Tract*

Type VII collagen was not detected in most tumors of the stomach (Figure 2f), the colon, the pancreas, and the liver (Figure 2g). Only one well-differentiated adenocarcinoma of the stomach showed some focal positivity with the type VII collagen antibody.

Laminin and type IV collagen could be found in most tumors of the GI tract.

### *Breast Tumors*

In accord with our earlier report,[18] type VII collagen was found surrounding ducts in all 16 cases of carcinoma *in situ* (Figure 2h). All 15 cases of invasive lobular breast carcinomas were negative for LH7.2, whereas 3 of 97 invasive ductal carcinomas showed some focal positivity with the LH7.2 antibody (Figure 2i). No laminin and type IV collagen were detected in invasive lobular carcinomas of the breast, whereas in 13 of 97 invasive ductal carcinomas, laminin or type IV collagen were present. Furthermore 22 metastases of breast carcinomas were studied. None of these displayed any type VII collagen, but 3 of 22 metastases were positive for the laminin antibody.

### *Female Genital Tract Tumors*

A squamous cell carcinoma of the vagina displayed a linear staining pattern for LH7.2, whereas in three of five adenocarcinomas of the endometrium and the ovary, which were mostly unreactive, some reactivity around tumor cell nests could be found (Figure 3a). With respect to the reactivity patterns of LH7.2 in the preneoplastic lesions of the cervix (Figure 3b, c), it can be stated that mature squamous metaplasias and the cervical intraepithelial neoplasias stages I through III showed an intact basement membrane, as concluded from staining with the type VII collagen antibody. In three of eight cases of immature squamous metaplasias, type VII collagen staining was found to be discontinuous, and also beneath reserve cells type VII collagen staining appeared to be weak and discontinuous. Laminin and type IV collagen staining patterns were not conclusive in these benign conditions. Staining appeared to be often very weak, and in the majority of cases a strong stromal staining occurred. Within the group of carcinomas from uterine cervix, LH7.2 was found to be present discontinuously in most adenocarcinomas as well as in all nonkeratinizing squamous cell carcinomas. The staining pattern of type VII collagen in adenocarcinomas, however, was less prominent (with more discontinuities and irregularities of the basement membranes) as compared with that in squamous cell carcinomas of the cervix. Furthermore within the group of nonkeratinizing squamous cell carcinomas, type VII collagen was found to be less present in poorly differentiated areas with large lymphocytic infiltrates. Laminin and type IV collagen were found in all studied carcinomas of the uterine cervix, as a discontinuous lining around tumor nests.

### *Male Genital Tract Tumors*

In benign prostate tumors, type VII collagen was mostly found surrounding benign ducts and acini (Figure 3d). Well, moderately, and poorly differentiated prostate carcinomas showed virtually no reactivity with the LH7.2 antibody (Figure 3e). With the antibodies to laminin and type IV collagen, a strong stromal staining was visible in all studied prostate carcinomas, thus making it difficult to recognize distinct basement membranes. No type VII collagen was found to be present in testis tumors, including three embryonal carcinomas and an anaplastic seminoma.

### *Urinary Tract Tumors*

All three Grawitz tumors studied showed no reactivity with the antibody to type VII collagen, whereas laminin and type IV collagen were abundantly present around the tumor cell nests. In the transitional-cell carcinomas, no or only scattered fragments of type VII collagen appeared to be present in all G1 and G2 tumors (Figure 3f, g), and within the group of 16 noninfiltrating G3 tumors, seven cases were completely negative, whereas nine cases showed scattered positivity. Surprisingly significant positivity was found in 20 infiltrating G3 tumors (Figure 3h). Only two of these tumors were negative, while five cases showed scattered positivity and the remaining 15 cancers displayed a strong random positivity between the tumor cell clusters. In 4 of these 15 positive tumors, areas with squamous metaplasia were present. Most transitional-cell carcinomas displayed a linear or scattered staining pattern with the antibodies to laminin and type IV collagen. Next to these primary tumors, 23 metastases of transitional cell carcinomas were studied. In 13 cases, no type VII collagen could be demonstrated, whereas 10 cases showed a strong positivity with the LH7.2 antibody. In eight cases of transitional-cell carcinoma we were able to compare primary tumors with their metastases. In five of these cases the staining pattern of the primary tumor was similar to that of the metastasis, whereas in two cases the primary tumors were positive and the metastases were negative. One primary tumor was found positive, the corresponding liver metastasis was negative, and the corresponding metastatic lesion in the wall of the colon was strongly positive. No correlation between staining pattern and metastatic site could

be detected. The antibodies to laminin and type IV collagen displayed a linear staining pattern in all eight primary tumors and their corresponding metastases.

### *Skin Tumors*

Three keratinizing squamous-cell carcinomas of the vulva showed random positivity for type VII collagen (Figure 3i). The staining pattern was linear surrounding tumor fields. The antibodies to laminin and type IV collagen displayed a similar reaction pattern.

## *Discussion*

The occurrence of basement membrane components has been extensively studied in normal tissues and in neoplasms. Structural and biochemical defects in basement membranes have been reported to be correlated with different types of disease.[1] Because the basement membrane is a primary barrier for tumor cell dissemination, many cell biologic investigations on invasion and metastasis have concentrated on this structure. Immunohistochemical studies have shown that the integrity of the basement membrane is disturbed in many invasive carcinomas.[7,10,20–22] For this purpose, mainly antibodies against the two major basement membrane components, laminin and type IV collagen, have been used until now.

The present study describes the distribution pattern of type VII collagen in various normal human tissues and in benign and malignant human neoplasms as detected by the MAb LH7.2. Leigh et al[5] have demonstrated that the antibody binds to the nonhelical carboxyterminal region of the type VII collagen dimer, and that the epitope recognized by LH7.2 has been localized within the lamina densa of basement membranes surrounding stratified squamous epithelia.

In accord with earlier findings,[4] normal tissues displayed a LH7.2 reactivity with basement membranes of combined and stratified epithelia, such as breast acini and ducts, prostate, bronchus, trachea, larynx, esophagus, cornea, ectocervix, vagina, and epidermis. A weak staining was seen to underly the ureteral and urinary bladder epithelium, whereas endocervical epithelium was surrounded by a discontinuous basement membrane. In comparison to type VII collagen, laminin and type IV collagen display a more widespread staining pattern. Laminin and type IV collagen are present in virtually all basement membranes, including those around blood vessels, muscle, and nerve fibers, whereas type VII collagen is restricted to underlying specific epithelia.

In this study, type VII collagen was in general negative in adenocarcinomas and neuroendocrine tumors. Sporadically type VII collagen was present in adenocarcinomas of the stomach, endometrium, lung, cervix, and ovary. These adenocarcinomas were mostly well differentiated, whereas less-differentiated adenocarcinomas were completely negative with the LH7.2 antibody. This is also true for invasive carcinomas of the breast and the prostate. In most squamous cell carcinomas of varying degrees of differentiation, type VII collagen could be detected. A decrease in abundance of this constituent was noticed in the more moderate to poorly differentiated squamous cell carcinomas of the lung. The benign and local neoplasms derived from combined epithelia, such as prostate, salivary gland, and breast (carcinoma *in situ*), showed type VII collagen reaction strongly related to the distribution pattern seen in the normal tissue, with strong to moderate positivity surrounding the neoplastic ductal structures.

Stenbäck et al[23] reported the presence of a more or less continuous basement membrane in normal squamous cervical epithelium, in all three stages of cervical intraepithelial neoplasia, and in carcinoma *in situ* of the cervix, using antibodies to type IV collagen and laminin. These results are in line with the staining patterns we found in preneoplastic lesions of the cervix with the type VII collagen antibody. In a quantitative study, Richards and Furness[24] were able to detect a progressive increase in the frequency of breaks with increasingly severe cervical intraepithelial neoplasia. With respect to cervical malignancies, a loss of type IV collagen or laminin components has been reported in undifferentiated cervical carcinomas,[23,24] whereas often a basement membrane could be detected around well-differentiated areas.[23] We found similar results using the antibody to type VII collagen. With the antibodies to laminin and type IV collagen, however, we were not able to relate the staining patterns with tumor differentiation.

With respect to lung tumors, a difference exists between our results and the reports of Birembaut et al[11] and Cam et al,[25] using antibodies to laminin and type IV collagen. These authors found an intact basement membrane in adenocarcinomas of the lung, whereas the basement membrane in squamous lung cell carcinomas was irregular and discontinuous. Our findings show that the reaction patterns of laminin and type IV collagen in adenocarcinomas are similar to those in squamous cell carcinomas of the lung. Furthermore our study demonstrated the absence of type VII collagen in the majority of adenocarcinomas (8 of 10), in all small-cell anaplastic carcinomas, and all carcinoids of the lung, whereas the component was abundantly present in squamous cell carcinomas of the lung (15 of 19 tumors were diffusely or focally positive).

In all studied squamous cell carcinomas of the head and neck region, type VII collagen was present. In part of

these tumors, cytoplasmic reactivity could be seen. Similar results were found by other authors with antibodies to laminin and type IV collagen.[15,16,26,27] Sakr et al[28] observed a difference in staining patterns between well- and poorly differentiated squamous cell carcinomas of the head and neck region. Basement membrane, as detected by laminin and type IV collagen antibodies, was present in well-differentiated areas, whereas less well-differentiated squamous cell carcinomas had only scanty or no basement membrane.

The results we obtained with transitional cell carcinomas are only partly in agreement with those of Daher et al[29] and Zuk et al,[30] using antibodies to type IV collagen. These authors report a degradation of basement membrane during the process of invasion. In noninvasive tumors, only small focal interruptions of the basement membrane are spotted, whereas invasive tumors show extensive loss of basement membrane. In some invasive cases, however, an intact basement membrane was visible. None of the cases examined showed total loss of basement membrane staining, similar to our findings with laminin and type IV collagen. The results described in the present study, using the type VII collagen antibody, reveal an opposite reaction. Type VII collagen expression seems to be enhanced during the invasive process. In 4 of 15 infiltrating G3 tumors positive for type VII collagen, areas with squamous differentiation were found. In the seven cases negative or focally positive for type VII collagen, however, no signs of squamous differentiation could be detected.

The findings that in some invasive and even metastatic carcinomas basement membrane is still present and sometimes even enhanced, as compared with normal tissue or earlier stages of the neoplastic process, has casted doubt on the suggestion that malignancies have to dissociate part of their basement membrane to become invasive. Although in the majority of carcinomas this structure degrades during the process of invasion, some tumor populations reveal the opposite. For instance, the aforementioned increase of type VII collagen in infiltrating transitional cell carcinomas, but also the high amounts of basement membrane constituents in a part of the metastases of transitional cell carcinomas and in most of the squamous cell carcinomas are good examples for this phenomenon.

Taking together the data presented in the underlying study, it becomes evident that the presence of type VII collagen in tumors seems to be related to the type of differentiation of tumors, rather than to their origin. Especially during the process of squamous differentiation, cells seem to gain the ability to produce type VII collagen. The expression of type VII collagen appears to be more restricted and more strongly correlated to tumor differentiation than laminin and type IV collagen. In this respect, type VII collagen may become more functional in the characterization of certain types of malignancies. Further studies are necessary to unravel the role of type VII collagen synthesis during invasion.

## Acknowledgments

The authors thank Roland Holland and Urbain van Haelst for their assistance with the diagnosis of breast cancer lesions; Frank Smedts for the results on cervical neoplasms; Lilly-Ann v.d. Velden for data on tumors of the head and neck region; Jack Schalken and Tilly Aalders for providing prostate tumor material; Sjoerd Wagenaar for providing lung tumor specimens; and Monique Link for technical assistance.

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