

# Comparison of Estrogen and Progesterone Receptor, Ki-67, and p53 Immunoreactivity in Uterine Endometrioid Carcinoma and Endometrioid Carcinoma With Squamous, Mucinous, Secretory, and Ciliated Cell Differentiation

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An analysis of 77 uterine endometrioid carcinomas was performed to compare pure endometrioid carcinomas and endometrioid carcinomas with various types of cellular differentiation for the expression of estrogen (ER) and progesterone (PR) receptors, p53, and Ki-67 and to correlate these findings with clinicopathologic features. Forty-three pure endometrioid carcinomas and 34 endometrioid carcinomas displaying additional types of cellular differentiation in at least 10% of the tumor (16 squamous, 11 mucinous, four ciliated cell, and three secretory) were analyzed. In 8 of the 16 tumors with squamous differentiation, the squamous component was histologically benign (low grade), and in eight tumors it was histologically malignant (high grade). In tumors showing various types of cellular differentiation except those with a high-grade squamous component, comparison of the endometrioid glandular component with the squamous, mucinous, secretory, and ciliated cell components showed that ER/PR, Ki-67, and p53 expression were generally higher in the glandular component compared with the various differentiated components. These findings parallel the changes that occur in the endometrium in the secretory phase of the menstrual cycle and, therefore, suggest that the differentiated components have undergone terminal differentiation. In contrast, in endometrioid carcinomas with a high-grade squamous component, Ki-67 and p53 expression were the same in the glandular and squamous components suggesting that squamous epithelium in these tumors represented another pathway of cellular differentiation but not one that was terminally differentiated. Endometrioid carcinomas with a high-grade

squamous component had significantly higher grade ( $P = .002$ ), stage ( $P < .001$ ), cellular proliferation index ( $P = .0005$ ), and worse outcome ( $P = .0009$ ) compared with tumors with the other types of cellular differentiation, including those with a low-grade squamous component and pure low-grade endometrioid carcinomas. In addition, carcinomas with a high-grade squamous component occurred in older women and were more frequently associated with atrophic endometrium and less replacement hormone therapy, but the differences were not statistically significant. In conclusion, endometrioid carcinomas with various types of cellular differentiation can be broadly divided into two groups. Tumors with mucinous, secretory, and ciliated cell differentiation and those with a low-grade squamous component are similar to pure low-grade endometrioid carcinomas in that most have high ER and PR expression, low cellular proliferation indices, low p53 immunoreactivity, and good prognosis. In contrast, endometrioid carcinomas with a high-grade squamous component lack expression of ER and PR, have high cellular proliferation indices, often express p53, and have a prognosis similar to poorly differentiated endometrioid carcinomas. HUM PATHOL 29:924-931. Copyright © 1998 by W.B. Saunders Company

**Key words:** endometrial carcinoma, endometrioid carcinoma, squamous differentiation, mucinous, secretory, ciliated cell, metaplasia, immunohistochemistry, estrogen receptor, progesterone receptor, Ki-67, p53.

**Abbreviations:** ER, estrogen receptor; PR, progesterone receptor; FIGO, International Federation of Gynecology and Obstetrics.

Endometrioid carcinoma of the uterine corpus can display various types of cellular differentiation that are commonly referred to as metaplasia.<sup>1-3</sup> The differentiated cells are cytologically bland and include mucinous, secretory, and tubal (ciliated) cell types. These tumors are usually associated with low-grade carcinomas and, therefore, have an excellent prognosis.<sup>2,4</sup> In contrast, squamous epithelium in endometrioid carcinoma can be cytologically benign or malignant.<sup>2,4</sup> In the past, tumors with bland-appearing squamous epithelium

(squamous morules) were referred to as "adenoacanthoma," and tumors with malignant-appearing squamous epithelium as "adenosquamous carcinoma."<sup>5</sup> More recent studies, however, have shown that the presence of "benign" and "malignant" appearing squamous epithelium correlates with the grade of the tumor, and in and of itself the squamous epithelium does not influence prognosis.<sup>6,7</sup>

Although it is well recognized that unopposed estrogenic stimulation plays a role in the development of endometrioid carcinoma, only a few studies have evaluated the relationship of either estrogen or progesterone stimulation to endometrioid carcinomas that display various types of cellular differentiation. Previous studies, although not all in agreement, suggest that estrogenic stimulation plays a role in the development of low-grade endometrioid carcinoma with squamous metaplasia.<sup>5,6,8-10</sup> Ciliated cell change in the female genital tract is also thought to be a reflection of unopposed estrogenic stimulation,<sup>11</sup> whereas secretory

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change in endometrial carcinoma is interpreted as a response to progesterone stimulation,<sup>12,13</sup> although it is recognized that in some instances this can occur without a history of abnormal progesterone stimulation.<sup>2,4,12,13</sup> Few studies have attempted to define the factors associated with mucinous differentiation.<sup>14,15</sup> To better understand the interaction between sex steroid hormones and endometrioid carcinomas with various types of cellular differentiation, we evaluated a variety of clinicopathologic features, including risk factors for carcinoma and the estrogen (ER) and progesterone (PR) receptor status of endometrioid carcinoma with various types of cellular differentiation and compared them with pure endometrioid carcinomas. In addition, we correlated ER and PR expression with cellular proliferation, as determined by Ki-67 proliferation index, and with p53 expression.

## MATERIALS AND METHODS

### Case Selection and Morphological Classification

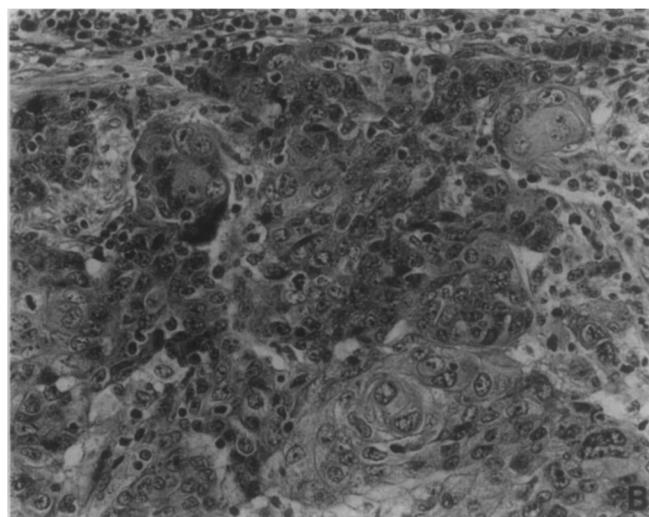
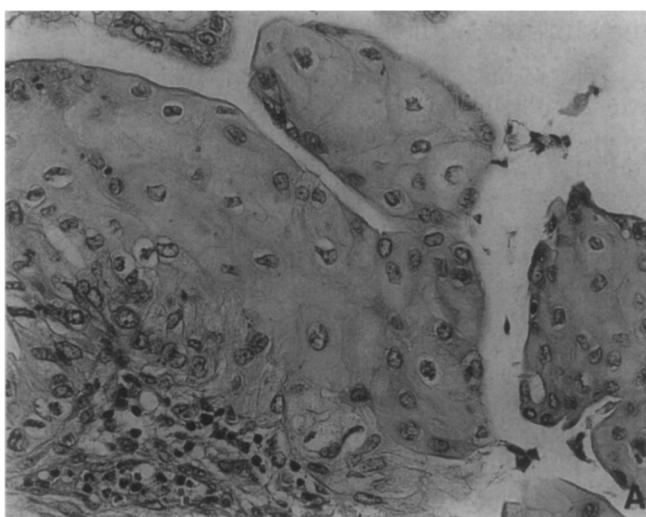
Seventy-seven endometrioid carcinomas were retrieved from the surgical pathology files of the Departments of Pathology of The Johns Hopkins Medical Institutions and the University of Graz, Austria. Cases were selected randomly except for seven grade 3 endometrioid carcinomas, which were included later to increase the number of grade 3 tumors. The slides were reviewed by four pathologists (S.F.L., E.S.P., B.M.R., and R.J.K.) and graded according to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO). Tumors showing squamous, secretory, mucinous, or ciliated cell differentiation in at least 10% of the neoplasm were classified separately from pure endometrioid carcinomas according to the type of cellular differentiation. Mucinous differentiation was confirmed by the presence of periodic acid-schiff-positive diastase-resistant intracellular mucin in at least 10% of the tumor cells. Squamous differentiation was identified by keratin pearl formation, distinct intercellular bridges, or cells that are polyhedral in shape with centrally located nuclei and eosinophilic cytoplasm.<sup>7</sup> Squamous epith-

rium was classified as low-grade if the squamous cells had uniform nuclei that typically lacked prominent nucleoli, bizarre giant cells, and mitotic figures (Fig 1A).<sup>16</sup> In contrast, squamous epithelium was classified as high-grade if the squamous cells displayed marked nuclear atypia, increased nuclear-cytoplasmic ratio, prominent nucleoli, and increased numbers of mitotic figures (Fig 1B).<sup>16</sup> Ciliated cell (tubal) differentiation was diagnosed based on the presence of tumor cells with cilia.<sup>3,11</sup> Secretory differentiation was diagnosed based on the presence of subnuclear or supranuclear glycogen vacuoles within the tumor cells, resembling early secretory phase endometrium.<sup>3</sup>

The endometrium adjacent to the tumor was evaluated and classified as hyperplastic with or without atypia or as atrophic/inactive. Nonhyperplastic endometrial polyps were included in the atrophic/inactive group. FIGO stage was determined based on review of patient records, surgical pathology reports, and microscopic slides. In addition, patient records were reviewed for evidence of exogenous and endogenous risk factors associated with endometrial hyperplasia and carcinoma, including hormone replacement therapy, obesity, diabetes mellitus, hypertension, and hyperlipidemia. Clinical follow-up data were obtained from the patient records and the Johns Hopkins Tumor Registry.

### Immunohistochemical Analysis

One to two paraffin blocks containing representative portions of the tumor were selected from each case, and serial sections were cut at 4 µm. The immunostaining procedure (PAP method) was performed on a Tech Mate 1000 automated stainer (Ventana-BioTek Solutions Inc., Santa Barbara, CA) after antigen retrieval in a steamer for 20 minutes. Primary antibodies included those against ER (Immunotech, 1:10 prediluted), PR (Novocastra, 1:60), Ki-67 antigen (Mib 1, Immunotech, 1:150), and p53 (DO-7, Dako, 1:100). The p53 antibody DO-7 recognizes both wild-type and mutant p53. Sections were counterstained with hematoxylin. Analysis of ER, PR, and p53 stains was performed using a combined scoring system based on both the percentage of positive nuclei and the staining intensity of the tumor cells.<sup>17</sup> The percentage of positive nuclei was estimated based on a four-tiered scale



**FIGURE 1.** Low-(A) and high-(B) grade squamous epithelium in endometrioid carcinoma. Low-grade squamous epithelium (A) is characterized by regularly sized and shaped nuclei, inconspicuous nucleoli, and absence of mitosis. In contrast, high-grade squamous epithelium (B) shows polymorphic nuclei, prominent nucleoli, and frequent mitosis. (H&E; original magnification  $\times 250$ .)

(<10% = 1, 10%-50% = 2, 51%-80% = 3, >80% = 4). A four-tiered scale was also used for scoring the staining intensity (negative = 0, weak = 1, moderate = 2, strong = 3). The staining intensity was determined based on the predominant staining intensity in the tumor. The final immunoreactive score was obtained by multiplying the scores for the percentage of positive nuclei and for staining intensity. A final score of 1 to 3 was classified as low, 4 to 6 as moderate, and 8 to 12 as high. The Ki-67 proliferation index was calculated as the percentage of positive nuclei in a sample of at least 500 tumor cell nuclei counted under a grid at 400 $\times$  magnification (10 $\times$  ocular and 40 $\times$  objective). All degrees of staining intensity were considered positive. Additionally, a previously described method of "high-power field estimation" was used for evaluating the Ki-67 proliferation index in tumors with a markedly heterogeneous staining pattern.<sup>18</sup> In such cases, the percentage of positive nuclei was estimated in at least 15 high-power fields (400 $\times$  magnification), and the average was calculated. If the results obtained by estimation varied more than 10% from the counted percentage, the counting procedure was repeated by counting at least 1,000 tumor nuclei. In endometrioid carcinomas with various types of cellular differentiation, ER, PR, and p53 scores and Ki-67 proliferation indices were determined in both the endometrioid glandular component and in the other areas displaying various types of cellular differentiation.

### Statistical Analysis

The Kruskal-Wallis test was used for analysis of median immunoreactive scores and Ki-67. For statistical analysis of the clinical and pathologic features, the chi-squared test and the Fisher's exact test were used. Survival data were analyzed by calculating Kaplan-Meier estimates of survival, and statistical significance was assessed using the log-rank test. Calculations were performed using Stata for Windows (Stata Press, College Station, TX) and StatView for Macintosh (Abacus Inc., Berkely, CA). A P-value of <.05 was considered statistically significant.

## RESULTS

### Clinicopathologic Features

Forty-three cases were pure endometrioid carcinomas and 34 endometrioid carcinomas displayed other types of cellular differentiation. Among the latter group, cellular differentiation was squamous in 16 cases, mucinous in 11, secretory in three, and ciliated cell in four. Of the 16 tumors with squamous differentiation, eight had a low-grade squamous component and eight a high-grade squamous component. Clinicopathologic data are listed in Tables 1 and 2.

Compared with pure endometrioid carcinomas, endometrioid carcinomas with various types of cellular differentiation, except for those with a high-grade squamous component, did not show significant differences with respect to age, association with endometrial hyperplasia, hormone replacement therapy, and endogenous risk factors. Those tumors displaying various types of cellular differentiation tended to be of lower grade and lower stage compared with pure endometrioid carcinomas (all grades), but the differences were not statistically significant. In contrast, compared with endometrioid carcinomas with various types of cellular differentiation and pure endometrioid carcinomas, endometrioid carcinomas with a high-grade squamous

**TABLE 1.** Comparison of Selected Clinicopathologic Features Between Pure Endometrioid Carcinomas Versus Endometrioid Carcinomas With Various Types of Cellular Differentiation

	Endometrioid (n = 43)	Mucinous, Ciliated, Secretory, Low-Grade Squamous (n = 26)	High Grade Squamous (n = 8)	PValue
Age (median [range])	64 (45-77)	62 (44-79)	74 (45-79)	NS
Grades 1, 2	34/43 (79%)	26/26 (100%)	4/8 (50%)	
Grade 3	9/43 (21%)	0/26 (—)	4/8 (50%)	.002
Stage I	27/43 (63%)	25/26 (96%)	1/8 (12.5%)	
Stage >I	16/43 (37%)	1/26 (4%)	7/8 (87.5%)	<.001
Hormone replacement therapy	7/38 (18%)*	2/22 (9%)†	0/5 (—)	NS
Endogenous risk factors	5/38 (13%)	9/22 (41%)	3/5 (60%)	.012
Hyperplasia without atypia	1/30 (3%)	4/20 (20%)	0/7 (—)	NS
Atypical hyper- plasia	18/30 (60%)	11/20 (55%)	3/7 (43%)	NS
Atrophic endo- metrium	9/30 (30%)	5/20 (25%)	4/7 (57%)	NS

NOTE. The denominators reflect the total number of cases for which data were available.

Abbreviations: NS, not significant.

\*In three cases estrogen only, in two cases progesterone only, and in two cases estrogen and progesterone.

†In both cases, the hormones were not specified.

component were of higher grade ( $P = .002$ ) and stage ( $P < .001$ ) and were more often associated with endogenous risk factors ( $P = .012$ ). In addition, carcinomas with a high-grade squamous component occurred in older patients and were less frequently associated with endometrial hyperplasia compared with endometrioid carcinomas with the other types of cellular differentiation, but these differences were not statistically significant.

### Immunohistochemical Analysis

The results of ER, PR, p53, and Ki-67 immunoreactivity are detailed in Tables 3 and 4.

*Comparison Between Endometrioid Carcinomas With Various Types of Cellular Differentiation and Pure Endometrioid Carcinomas.* Compared with pure low-grade (FIGO grade 1 and 2) endometrioid carcinomas, tumors with various types of cellular differentiation, except for those with a high-grade squamous component, were similar with regard to ER, PR, p53, and Ki-67 expression (Table 3). In particular, ER and PR expression tended to be higher and Ki-67 proliferation indices tended to be lower in the tumors showing various types of cellular differentiation compared with pure low-grade endometrioid carcinomas, but these differences were not statistically significant (Table 4). Among tumors with various types of cellular differentiation, ER and PR expression tended to be higher in tumors with mucinous, secretory, and ciliated cell components compared with tumors with low-grade squamous compo-

**TABLE 2.** Comparison of Selected Clinicopathologic Features Among Endometrioid Carcinomas With Various Types of Cellular Differentiation

	High-Grade Squamous (n = 8)	Low-Grade Squamous (n = 8)	Mucinous (n = 11)	Secretory (n = 3)	Ciliated Cell (n = 4)	P
Age (median [range])	74 (45-79)	57 (44-79)	65 (52-76)	55 (49-65)	65 (55-75)	NS
Grades 1, 2	4/8 (50%)	8/8 (100%)	11/11 (100%)	3/3 (100%)	4/4 (100%)	
Grade 3	4/8 (50%)	0 (—)	0 (—)	0 (—)	0 (—)	.005
Stage I	1/8 (12.5%)	7/8 (87%)	9/11 (82%)	3/3 (100%)	4/4 (100%)	
Stage >I	7/8 (87.5%)	1/8 (13%)	2/11 (18%)	0 (—)	0 (—)	.001
Hormone replacement therapy	0/5 (—)	1/5 (20%)	0 (—)	0 (—)	1/3 (33%)	NS
Endogenous risk factors	3/5 (60%)	2/5 (40%)	4/11 (36%)	2/3 (67%)	1/3 (33%)	NS
Hyperplasia without atypia	0/7 (—)	2/7 (29%)	2/8 (25%)*	0 (—)	0 (—)	NS
Atypical hyperplasia	3/7 (43%)	4/7 (57%)	3/8 (37.5%)*	1/2 (50%)	3/3 (100%)	NS
Atrophic endometrium	4/7 (57%)	1/7 (14%)	3/8 (37.5%)	1/2 (50%)	0 (—)	NS

NOTE. The denominators reflect the total number of cases for which data were available.

Abbreviation: NS, not significant.

\*In one case combined with atrophy.

nents, but these differences were not statistically significant. In contrast, the immunoprofile of tumors with a high-grade squamous component was similar to that of high-grade (FIGO grade 3) endometrioid carcinomas (Table 3). ER and PR expression were lower and p53 expression was higher in endometrioid carcinomas with a high-grade squamous component and pure high-grade endometrioid carcinomas compared with the other tumors with various types of cellular differentiation and with pure low-grade endometrioid carcinomas, but these differences were not statistically significant. In addition, the Ki-67 proliferation index was significantly higher in endometrioid carcinomas with a high-grade squamous component and in pure high-grade endometrioid carcinomas compared with the other tumors with various types of cellular differentiation and with pure low-grade endometrioid carcinomas ( $P = .0005$ ).

*Comparison Between the Endometrioid Glandular Components and the Components Showing Various Types of Cellular Differentiation.* In carcinomas with mucinous (Fig 2), secretory, ciliated cell, and low-grade squamous (Fig 3) differentiation, ER, PR, and Ki-67 expression were higher in the endometrioid glandular component compared with the other components. In endometrioid carcinomas with mucinous, secretory, and ciliated cell differentiation, the mucinous (Fig 2B), secretory, and ciliated cell components typically showed weak or moderate expression for ER and PR but a few cases were ER and PR negative. In carcinomas with low-grade squa-

mous components, the squamous components were always negative for ER (Fig 3B) and PR. Ki-67 expression was low or negative in the mucinous (Fig 2C), secretory, ciliated cell, and low-grade squamous (Fig 3C) components as well. In the few cases that demonstrated positivity for p53, expression was limited to the endometrioid glandular components. In contrast, in carcinomas with a high-grade squamous component (Fig 4), ER and PR expression but not p53 and Ki-67 expression were higher in the endometrioid glandular compared with the squamous components. In fact, high-grade squamous components were always negative for ER and PR, whereas the endometrioid glandular components were typically either weakly or moderately positive for ER and PR, although a few cases were negative for ER and PR. In contrast, p53 (Fig 4B) and Ki-67 (Fig 4C) expression did not differ between the glandular and the high-grade squamous components.

#### Analysis of Survival

Survival data were available for 74 of the 77 patients. The mean and median observation times were 40 and 27 months, respectively (range, 5 to 100 months). Twelve patients died of tumor, and one patient died of myocardial infarction 1 month postoperatively without evidence of residual or recurrent tumor. This patient was excluded from the survival analysis. The mean and median survival times of those patients who died of

**TABLE 3.** Comparison of Immunoreactive Scores for Estrogen (ER) and Progesterone (PR) Receptor and p53 and Ki-67 Proliferation Indices Between Pure Endometrioid Carcinomas Versus Endometrioid Carcinomas With Various Types of Cellular Differentiation

	Pure Endometrioid Carcinomas		Endometrioid Carcinomas With Cellular Differentiation		P
	Endometrioid FIGO Grades 1, 2 (n = 34)	Endometrioid FIGO Grade 3 (n = 9)	Mucinous, Ciliated, Secretory, Low-Grade Squamous (n = 26)	High-Grade Squamous (n = 8)	
ER	4 (0-12)	4 (0-6)	6 (0-12)	2 (0-9)	NS
PR	6 (0-12)	4 (0-12)	7 (0-12)	4 (0-12)	NS
p53	0 (0-4)	2 (0-12)	1 (0-4)	2 (0-9)	.0512
Ki-67	20% (5%-48%)	37% (20%-44%)	16% (5%-39%)	28% (26%-38%)	.0005

NOTE. Data are given as median (range).

Abbreviation: NS, not significant.

**TABLE 4.** Immunoreactive Scores for Estrogen (ER) and Progesterone (PR) Receptor and p53 and Ki-67 Proliferation Indices in Endometrioid Carcinomas With Various Types of Cellular Differentiation

	High-Grade Squamous (n = 8)	Low-Grade Squamous (n = 8)	Mucinous (n = 11)	Secretory (n = 3)	Ciliated Cell (n = 4)	P
ER	2 (0-9)	4 (0-12)	6 (2-12)	8 (2-8)	7.5 (1-12)	NS
PR	4 (0-12)	5 (0-12)	6 (2-12)	12 (4-12)	8.5 (6-12)	NS
p53	2 (0-9)	0.5 (0-4)	0 (0-4)	1 (0-4)	1 (0-2)	NS
Ki-67	28% (26-38)	18% (5-39)	17% (5-27)	21% (14-22)	14% (7-30)	.035

NOTE. Data are given as median (range).

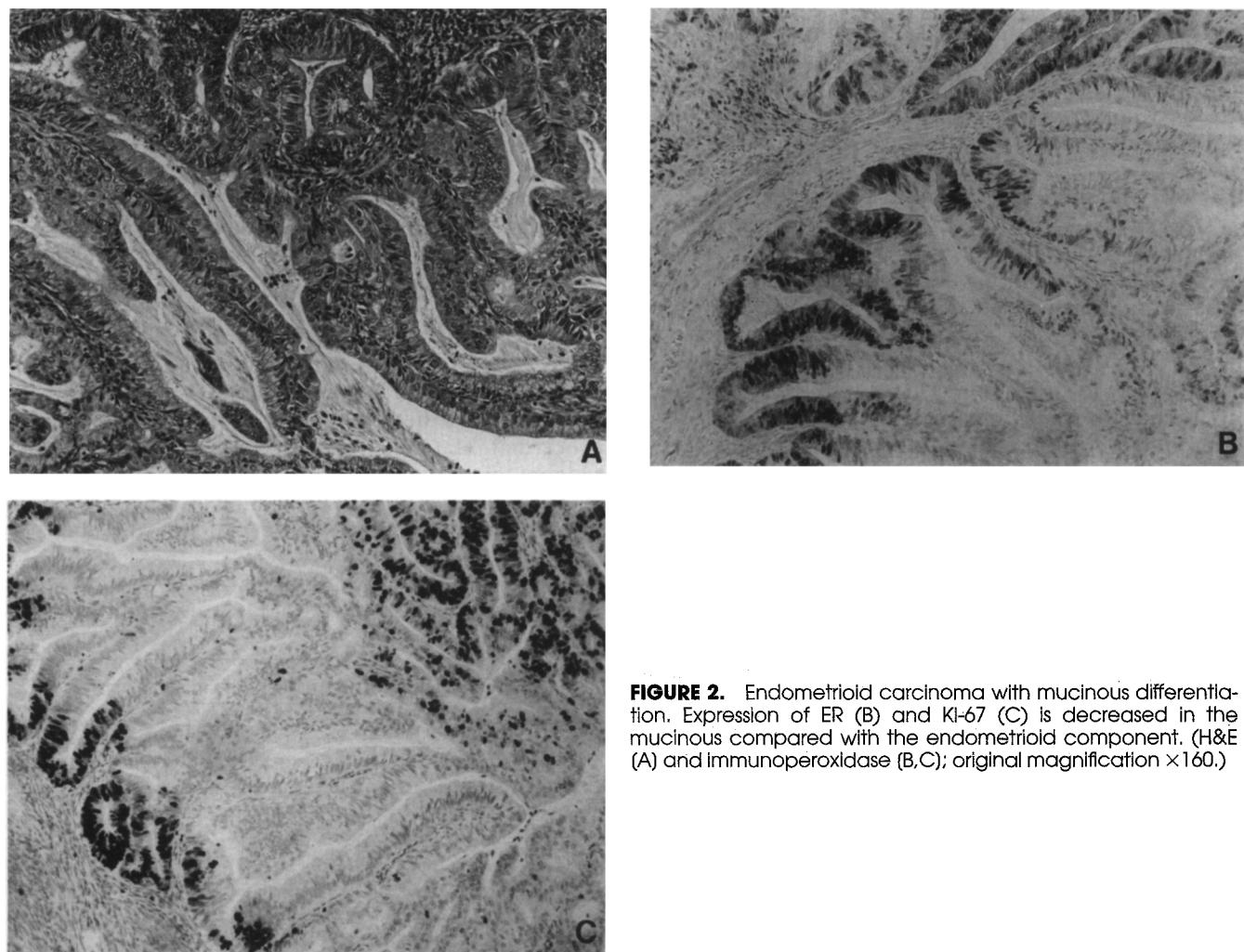
Abbreviations: NS, not significant.

disease were 15 and 8 months, respectively (range, 1 to 41 months). Endometrioid carcinomas with a high-grade squamous component and pure high-grade endometrioid carcinomas had a significantly worse prognosis compared with endometrioid carcinomas with other types of cellular differentiation and with pure low-grade endometrioid carcinomas ( $P = .0009$ ) (Fig 5).

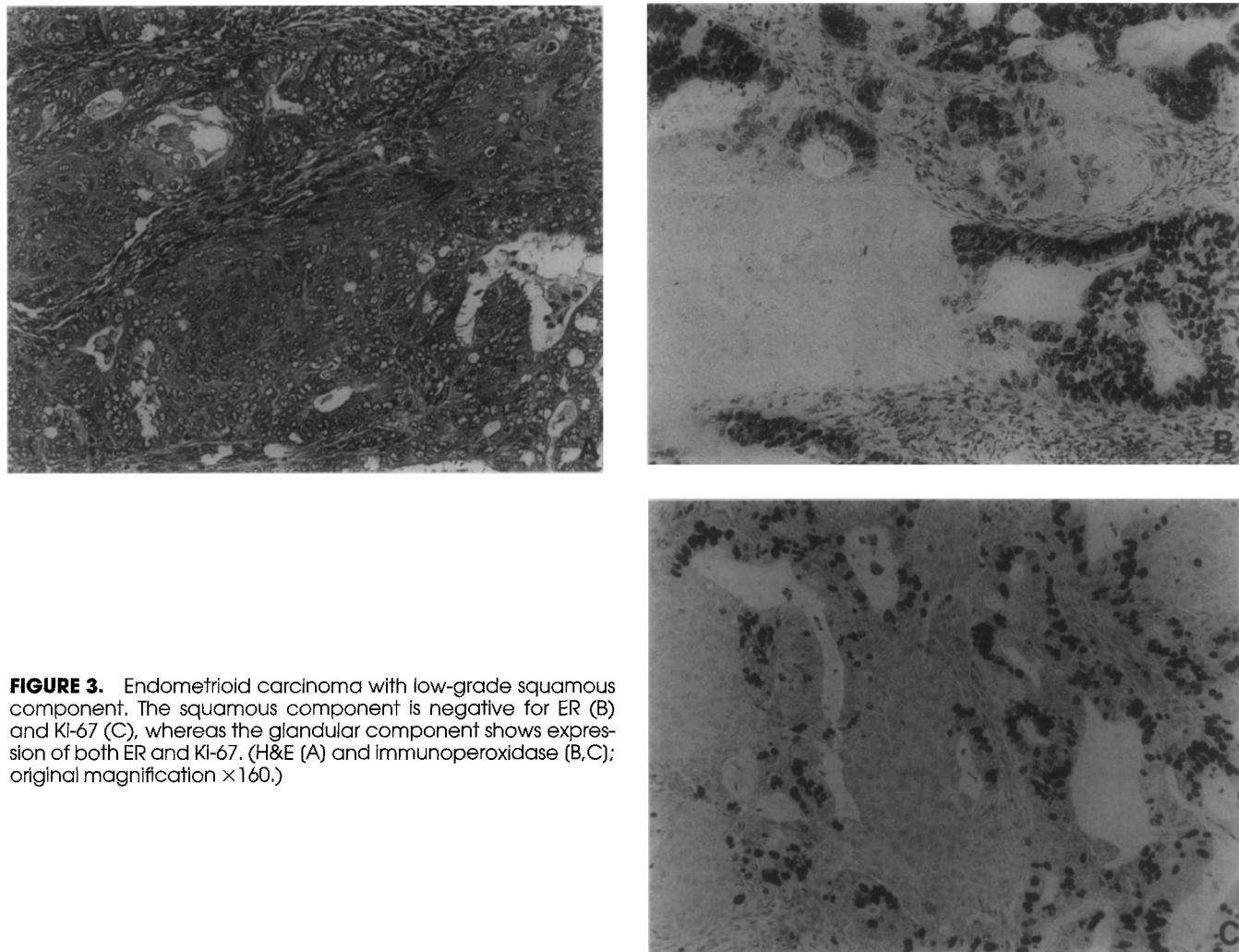
## DISCUSSION

This study shows that the clinicopathologic features and the immunoprofiles for ER, PR, Ki-67, and p53 of endometrioid carcinomas with various types of

cellular differentiation, including mucinous, secretory, ciliated, and squamous cell, can be divided into two broad categories. Those with various types of cellular differentiation, except for those with a high-grade squamous component, were similar to low-grade (FIGO grade 1 and 2) endometrioid carcinomas. In contrast, those tumors with a high-grade squamous component differed from endometrioid carcinomas with various types of cellular differentiation and were similar to pure high-grade (FIGO grade 3) endometrioid carcinomas. Endometrioid carcinomas with a high-grade squamous component were of higher grade and stage, had a worse outcome, and were more frequently associated with



**FIGURE 2.** Endometrioid carcinoma with mucinous differentiation. Expression of ER (B) and Ki-67 (C) is decreased in the mucinous compared with the endometrioid component. (H&E (A) and immunoperoxidase (B,C); original magnification  $\times 160$ .)



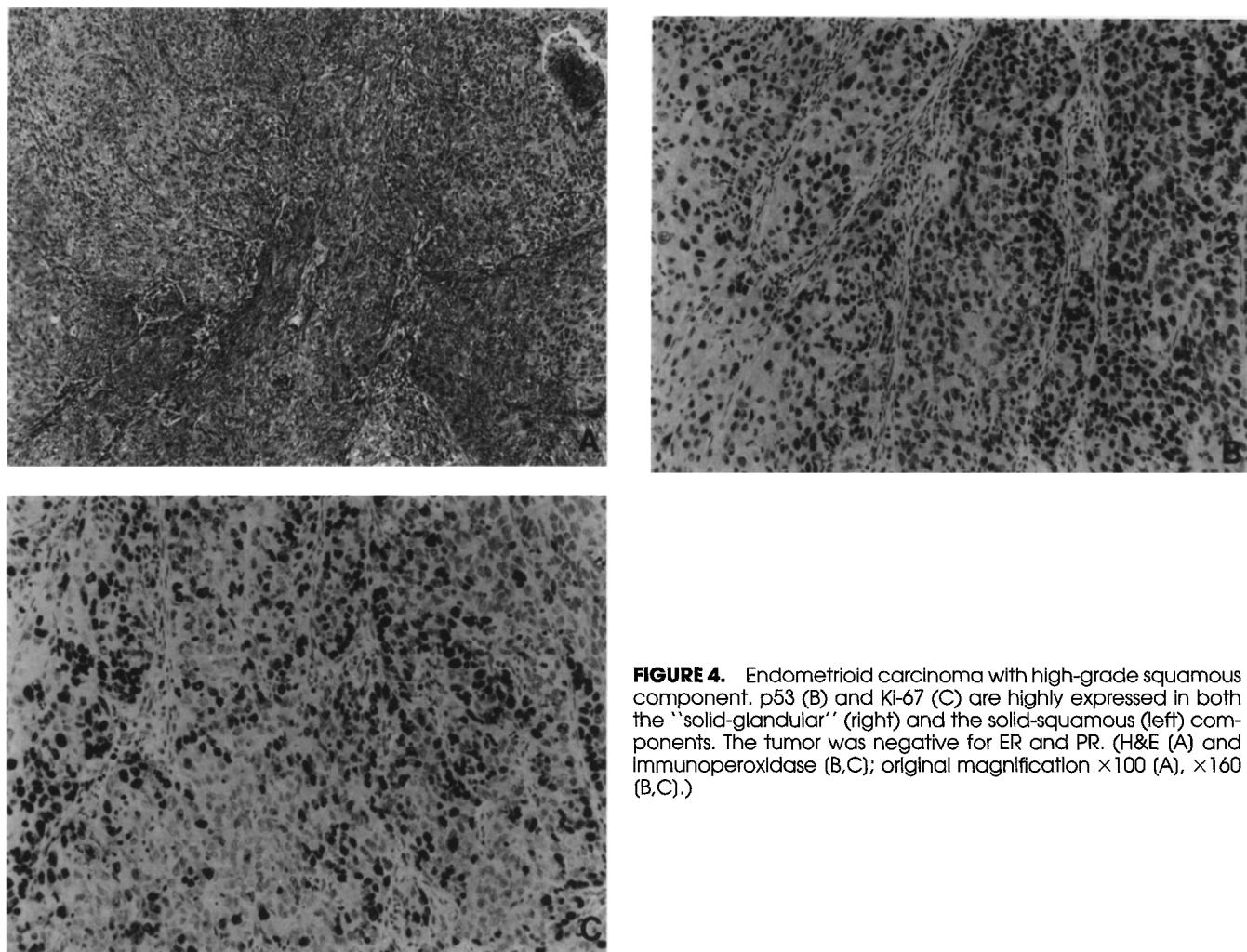
**FIGURE 3.** Endometrioid carcinoma with low-grade squamous component. The squamous component is negative for ER (B) and Ki-67 (C), whereas the glandular component shows expression of both ER and Ki-67. (H&E (A) and immunoperoxidase (B,C); original magnification  $\times 160$ .)

endogenous risk factors. These differences were statistically significant. In addition, the tumors with a high-grade squamous component occurred in older women, were more frequently associated with atrophic endometrium, and less frequently with hormone replacement therapy, but these differences were not statistically significant. It is important to emphasize that our results regarding hormone replacement therapy and endogenous risk factors must be interpreted cautiously because the data analysis is based only on a review of patient records and not on interview data specifically addressing these issues. Compared with pure endometrioid carcinomas and endometrioid carcinomas with mucinous, secretory, ciliated cell, and low-grade squamous components, endometrioid carcinomas with high-grade squamous components showed significantly higher Ki-67 and p53 expression and tended to show lower ER and PR expression. In contrast, endometrioid carcinomas with low-grade squamous, mucinous, secretory, and ciliated cell differentiation were all grade 1 or 2 and more than 90% were stage I. Expression of ER and PR was relatively high, and Ki-67 proliferation indices and p53 expression were low.

Analysis of the tumors showing various types of cellular differentiation, except for those with a high-grade squamous component, showed that ER, PR, Ki-67,

and p53 expression were higher in the endometrioid components compared with the differentiated areas. These findings parallel those in normal secretory endometrium, suggesting that these differentiated areas have undergone terminal differentiation.<sup>19</sup> In contrast, in tumors with high-grade squamous components, Ki-67 and p53 expression were the same in both the glandular and squamous areas, indicating that the squamous components of these tumors were actively proliferating and not undergoing terminal differentiation.

These various types of cellular differentiation in endometrioid carcinoma appear to be a common phenomenon, because they were observed in almost 50% of our cases. Among the various types of cellular differentiation, squamous differentiation was the most common type found. Unlike the other types of cellular differentiation, squamous components can be either low or high grade. Mucinous and secretory changes may rarely occur in high-grade tumors, but they were not encountered in this study. In addition, both low- and high-grade squamous components differ from other types of cellular differentiation associated with endometrioid carcinoma in the pattern of ER and PR expression. Tumors with mucinous, secretory, and ciliated cell differentiation typically display a transition with gradual loss of expression of ER, PR, and Ki-67 in the differenti-



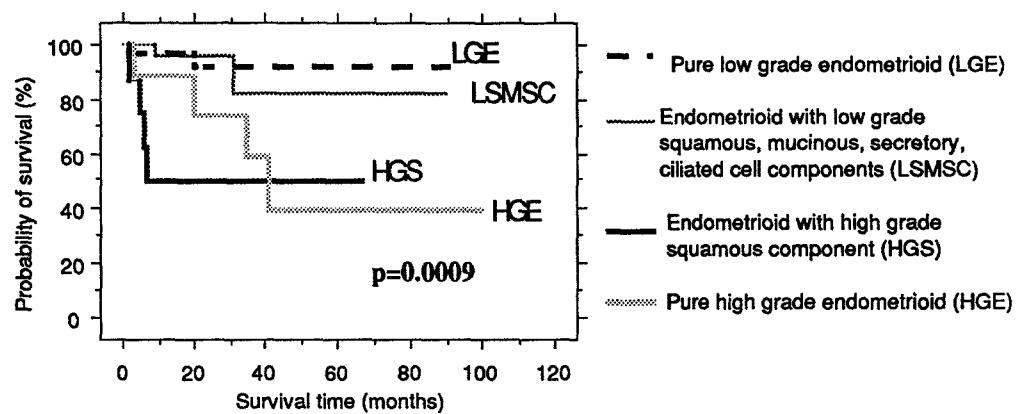
**FIGURE 4.** Endometrioid carcinoma with high-grade squamous component. p53 (B) and Ki-67 (C) are highly expressed in both the "solid-glandular" (right) and the solid-squamous (left) components. The tumor was negative for ER and PR. (H&E (A) and immunoperoxidase (B,C); original magnification  $\times 100$  (A),  $\times 160$  (B,C).)

ated components compared with the endometrioid glandular components. In contrast, both low- and high-grade squamous components almost never express ER or PR.<sup>20</sup> The heterogeneity of ER, PR, and Ki-67 expression in endometrioid carcinomas with various types of cellular differentiation probably reflects the coexistence of both proliferating and terminally differentiated components. The proliferating components are likely to respond to progestin-suppressive therapy because they typically express ER and PR. Conversely, tumors with a high-grade squamous component usually

lack ER and PR and therefore may not be as responsive to hormonal therapy.<sup>20</sup>

In summary, mucinous, secretory, ciliated cell, and low-grade squamous differentiation frequently occurs in endometrioid carcinoma. These tumors tend to be well differentiated and low stage and closely resemble pure low-grade endometrioid carcinomas in that they have high expression of ER and PR, low p53 expression, and low cellular proliferation indices. Because there were no significant differences in clinical risk factors, presence of endometrial hyperplasia and ER/PR status

**FIGURE 5.** Kaplan-Meier survival curves for pure endometrioid carcinomas, endometrioid carcinomas with a low-grade squamous, mucinous, secretory, and ciliated cell components, and endometrioid carcinomas with a high-grade squamous component.



between these tumors and pure low-grade endometrioid carcinomas, it is likely that they also develop as a result of unopposed estrogenic stimulation. The differentiated components appear to be a manifestation of terminal differentiation in these tumors, but the factors responsible for inducing the various types of cellular differentiation remain unknown. In contrast, endometrioid carcinomas with high-grade squamous components are aggressive tumors that are variants of poorly differentiated endometrioid carcinoma with sex steroid hormone receptor status and cellular proliferation indices that are different from endometrioid carcinomas displaying mucinous, ciliated, secretory, and low-grade squamous differentiation. Unlike the low-grade tumors, the squamous epithelium in these neoplasms represents an alternate pathway of differentiation for an actively proliferating cellular population and does not reflect terminal differentiation.

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