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Frequent Loss of Expression of the Cyclin-Dependent Kinase Inhibitor p27^{Kip1} in Estrogen-Related Endometrial Adenocarcinomas

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ABSTRACT

Purpose: p27^{Kip1} is a member of the Cip1/Kip1 family of cyclin-dependent kinase inhibitors and is a potential tumor suppressor gene. Low levels of p27 are associated with poor prognosis in a variety of gynecological tumors, including breast, ovarian, and cervical carcinomas. The role of p27 in endometrial cancer remains controversial.

Experimental Design: In the present study, p27 protein expression was investigated by immunohistochemistry in a series of 217 endometrial adenocarcinomas and, where present, in synchronous normal endometrium, simple and complex hyperplasia (with or without atypia), and cystic atrophy. The relationship between p27 expression and clinical outcome was also evaluated.

Results: Immunohistochemical analysis revealed a significant loss of p27 expression from normal (33%) through hyperplastic endometrium (50%) to endometrial adenocarcinomas (71%; $P \leq 0.001$). In addition to nuclear staining, cytoplasmic localization of p27 was noted in 193 (91%) of 217 specimens examined. When the clinical outcome of the patients was evaluated in relation to p27 status, we found no significant correlation between the presence of p27 staining and clinicopathological parameters or survival.

Conclusions: These data indicate that p27 expression could progressively decrease from normal endometrium through hyperplastic endometrium to invasive endometrial carcinomas, suggesting that loss of this tumor suppressor may represent a novel and distinct molecular alteration involved in estrogen-related endometrial adenocarcinomas (type I). Despite the suggested role of the p27 protein in determining the prognosis of several human tumors, it was not found to be a predictor of clinical outcome in this large group of patients with endometrial cancer.

INTRODUCTION

The eukaryotic cell cycle is controlled by protein kinase complexes composed of cyclins and cdk. The activity of cdk is regulated by binding of positive effectors, the cyclins, and by association-dissociation of inhibitory subunits, designated CKIs (1). Two families of cdk inhibitors have been identified. INK4 family members p15^{INK4B}, p16^{INK4A}, p18^{INK4C}, and p19^{INK4D} bind to and inhibit cyclin D-dependent kinases cdk4 and cdk6 (2). Kip family members, including p21^{Cip1}, p27^{Kip1}, and p57^{Kip2}, preferentially inhibit cdk2 (1).

Cyclins, cdk, and CKIs are frequently altered in human cancer (3). p27^{Kip1} is a CKI that regulates progression from G₁ into S phase by inhibiting a variety of cyclin-cdk complexes, including cyclin D-cdk4, cyclin E-cdk2, and cyclin A-cdk2.

The p27^{Kip1} gene is located on chromosome 12p and, unlike the genes encoding INK4 family members, is rarely affected by structural alterations in human malignancies (4). Levels of p27 in human cancer, however, appear to be regulated at the posttranslational level by ubiquitin-proteasome-dependent degradation mechanisms (5, 6).

Endometrial cancer is the most frequent gynecological malignancy of the female genital tract, accounting for 6% of all cancers among women (7). Although the incidence of endometrial carcinoma has remained relatively stable during the past

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² The abbreviations used are: cdk, cyclin-dependent kinase; CKI, cyclin-dependent kinase inhibitor; Kip, kinase inhibitor protein; FIGO, International Federation of Gynecology and Obstetrics; DFS, disease-free survival; DRS, disease-related survival; CI, confidence interval.

Table 1 p27^{Kip1} distribution in endometrial cancer and synchronous endometrial lesions

Histology	n	p27 staining (intensity score), n (%)			
		0–3 (negative/very low)	4–6 (low)	7–9 (moderate)	10–12 (high)
Normal endometrium	30	10 (33)	9 (30)	8 (27)	3 (10)
Hyperplasia without atypia	24	12 (50)	2 (8.5)	9 (37.5)	1 (4)
Atypical hyperplasia	5	5 (100)			
Cystic atrophy	14	6 (42)	2 (14)	3 (21.5)	3 (21.5)
Adenocarcinoma	217	154 (71)	37 (17)	20 (9.3)	6 (2.7)

decade, the number of deaths annually from this disease has more than doubled since 1987 (from 2900 to 6400 deaths). During the last decade efforts have focused on attempting to identify molecular events that correlate with the malignant potential of this disease. The identification of markers predictive of patients' outcomes would assist clinicians in stratifying women into risk groups. Great benefit is likely to result from the characterization of additional prognostic factors that are more closely related to tumor cell biology. These biological factors may offer novel approaches to the identification of groups of patients who could benefit from more aggressive therapy.

It is conceivable that most endometrial cancers occur as a result of acquired alterations in oncogenes and tumor suppressor genes that regulate signal transduction pathways involved in cell proliferation and differentiation, as well as in cell cycle control. Studies have shown that alterations in *p53* (8), *HER-2/neu* (9), *bcl-2* (10), and *Rb2/p130* (11) are associated with poor prognosis in endometrial cancer. Indicators of cell proliferation, such as DNA ploidy (12), S-phase fraction, proliferative index, MIB-1 proliferation marker (13), and proliferating cell nuclear antigen (14), have been evaluated.

Several studies demonstrated that loss of the p27^{Kip1} protein, as assessed by immunohistochemistry, is a negative prognostic marker in some malignancies, including gynecological cancers such as breast (15, 16), cervical (17), and ovarian cancer (18, 19).

It has been shown that p27 expression is strongly reduced in endometrial cancer (20–22). One recent study (23), however, failed to find any association between p27 staining and clinicopathological parameters or survival in advanced endometrial cancers. Another study (24) showed that p27 expression was paradoxically associated with unfavorable clinicopathological parameters in a large series of endometrioid adenocarcinomas. Thus, the role of p27 in endometrial cancer remains controversial.

In this study, we used immunohistochemistry to characterize the expression pattern of p27^{Kip1} in 217 endometrial adenocarcinomas and in other synchronous endometrial lesions, including normal endometrium, simple and complex hyperplasia with or without atypia, and cystic atrophy. We also evaluated the relationship of p27^{Kip1} protein expression with clinicopathological parameters and clinical outcomes in 193 patients with endometrial adenocarcinoma.

MATERIALS AND METHODS

Patients and Tumor Specimens. We obtained 217 specimens from previously untreated endometrial carcinoma patients

who underwent surgical resection in the Department of Gynecology of the University of Florence (Florence, Italy) and at St. Orsola Hospital, University of Bologna (Bologna, Italy). Patient ages ranged from 28 to 93 years, with a median age of 64 years. Histological classification of tumors was carried out according to the WHO system, and tumors were graded as well (G1), moderately (G2), and poorly (G3) differentiated. Clinical stages of disease were established according to the 1989 FIGO system. None of the patients had received chemotherapy or radiotherapy before surgery. Those patients who were irradiated received 56 Gy postoperatively on the whole pelvis. Chemotherapy was administered, when possible, to patients with more advanced disease (stage III-IV). The chemotherapy regimen included cisplatin (60 mg/m²) and epirubicin (60 mg/m²) every 21 days for six cycles.

After completing the treatment, patients were seen every 3 months for the first 2 years, every 4 months during the 3rd and 4th years, and every 6 months thereafter. Recurrence was considered as any documented relapse of the tumor either in the pelvis or systemically. DFS was calculated from the date of the operation. Patients with residual disease after surgery or who had a recurrence within 3 months of the date of the operation were not considered free of disease and were excluded from the disease-free analysis but not from actuarial survival calculation. Patients with fatal outcomes other than from endometrial cancer were considered to be lost at follow-up, and their survival time was terminated on the date of death.

Flow Cytometric Analysis of DNA Index. In a subgroup of 100 patients, a tumor specimen was taken fresh immediately after hysterectomy and divided into two parts: one for flow cytometric analysis and the other for histological confirmation. Flow cytometry was performed as described previously (11). The DNA ploidy was provided by the DNA index, defined as the proportion of the modal DNA values of the tumor cells in G₀ and G₁ (peak channel) to the DNA content of the diploid standard. The histograms were based on the measurement of >10,000 cells and generally resulted in a good resolution with a coefficient of variation of 3–6%. Calculation of DNA index was performed by processing each histogram with the computer-assisted program Multicycle-AutoFit, version 2.00 (Phoenix Flow Systems, San Diego, CA).

All cases with a DNA index value of 1 (±0.04) were classified as diploid. The remaining cases were classified as aneuploid.

Immunohistochemistry and Specificity of Immunostaining. After surgical resection, each tumor specimen was immediately formalin-fixed and then paraffin-embedded for

routine and immunohistochemical investigation. Immunohistochemistry was performed as described previously (19). Briefly, the polyclonal antibody to p27^{Kip1} was incubated overnight with tissue sections at a 1:150 dilution. Specificity of p27^{Kip1} staining was assessed by preabsorption with the peptide used to generate it. The staining pattern seen with the p27^{Kip1} polyclonal antibody was confirmed on duplicate slides using a monoclonal antibody (Santa Cruz Biotechnology, Santa Cruz, CA). The strong positive immunostaining of stromal cells in the sections examined represented an internal positive control for preservation of p27 antigenicity in tissues. For the negative control, PBS was substituted for the primary antibody.

pRb2/p130 staining in a subgroup of 100 patients was performed as described previously (11).

p27 Scoring. Cells were scored for p27 staining according to cellular compartmentalization. All immunoreactive cells were considered positive. Three pathologists (C. M., D. M., and G. T.) separately evaluated p27 staining in a coded manner, as described previously (20). Every tumor and synchronous endometrial lesion was assessed and given a score, obtained by multiplying the intensity of the staining (no staining = 0; low staining = 1; medium staining = 2; strong staining = 3) by the percentage of cells stained (0% = 0; <10% = 1; 10–50% = 2; 51–80% = 3; >80% = 4). The maximum score is 12 with this system.

For the analysis of p27 according to clinicopathological parameters and survival, protein levels were classified as positive (staining in >50% of cells) or negative (staining in ≤50% of cells) as described previously (22). At least 20 high-power fields were chosen randomly, and 2000 cells were counted.

Statistical Analysis. Fisher's exact test for proportion and the χ^2 test were used to analyze the distribution of p27-positive specimens according to clinicopathological characteristics. DFS and DRS were calculated according to the Kaplan–Meier method and evaluated by the log-rank test. Univariate Cox analysis was used to assess the effect of each prognostic variable on DFS and DRS. A multivariate analysis (Cox proportional hazards regression) was performed to estimate which possible risk factors yielded independent prognostic information. Data analysis was carried out using SPSS Statistical Software, release 5.0.1 (SPSS Inc., Chicago, IL).

RESULTS

p27^{Kip1} Protein Expression in Normal Human Endometrium, Simple and Complex Hyperplasia, and Cystic Atrophy. The expression of p27^{Kip1} in endometrial tissues was determined by immunohistochemistry. Lesions synchronous with invasive carcinomas were classified as normal human endometrium ($n = 30$), simple and complex hyperplasia without atypia ($n = 24$), atypical hyperplasia ($n = 5$), and atrophy ($n = 14$); their immunoreactivity for p27^{Kip1} is categorized in Table 1.

Normal endometrium adjacent to the adenocarcinoma showed positivity for p27 in the majority of specimens examined (67%; Fig. 1a). p27 immunostaining was mostly nuclear, but weak cytoplasmic staining was also observed. Normal endometrium was classified as proliferative in 3 cases, secretory in 11 cases, and inactive in the remaining samples ($n = 16$). Lost

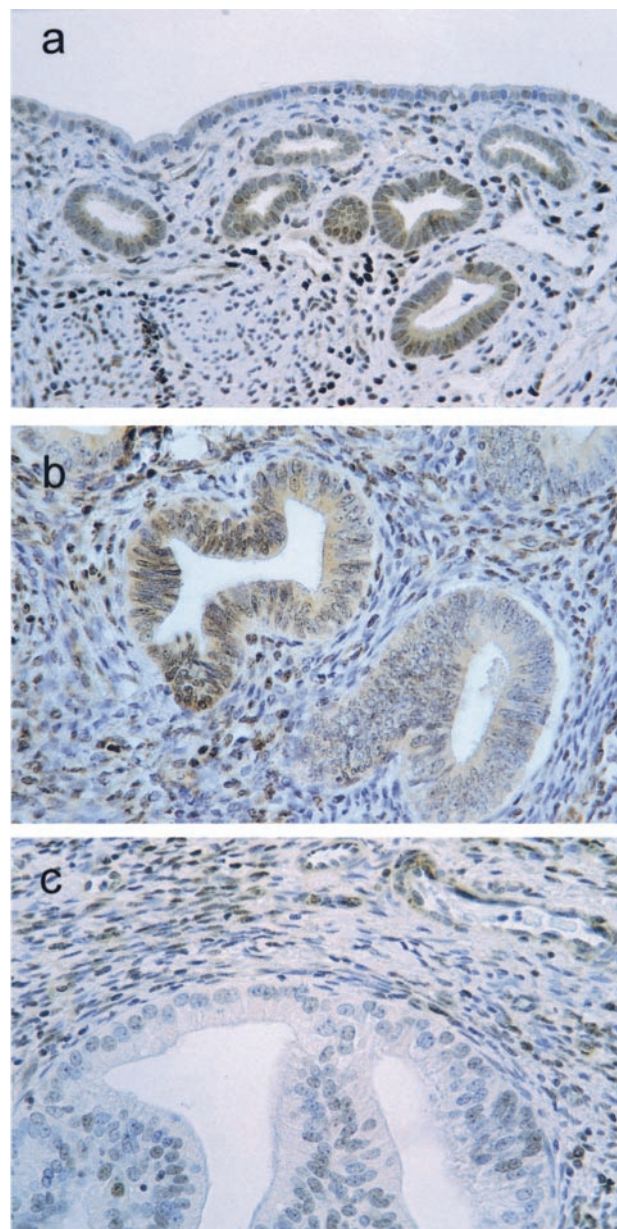


Fig. 1 p27^{Kip1} immunostaining in normal endometrium, simple hyperplasia, and complex hyperplasia with atypia. *a*, p27 expression in normal endometrium was detected in the nuclei of the cells, in the superficial lining, and in the glandular cells in the functional layer. *b*, simple hyperplasia shows a diffuse p27 reactivity in the nuclei as well as in the cytoplasm of endometrial cells. *c*, complex hyperplasia with atypia shows scattered p27-positive cells. Strong nuclear staining of stromal cells is present in both hyperplasia specimens. Magnification, $\times 40$.

or decreased p27 expression was observed in inactive and proliferative endometrium, whereas p27 was heterogeneously distributed in the secretory endometrium.

Simple and complex hyperplasia without atypia showed loss of p27 in 12 of 24 samples (50%), whereas p27 staining was lost in all specimens (5 of 5) of atypical hyperplasia (Fig. 1, *b*

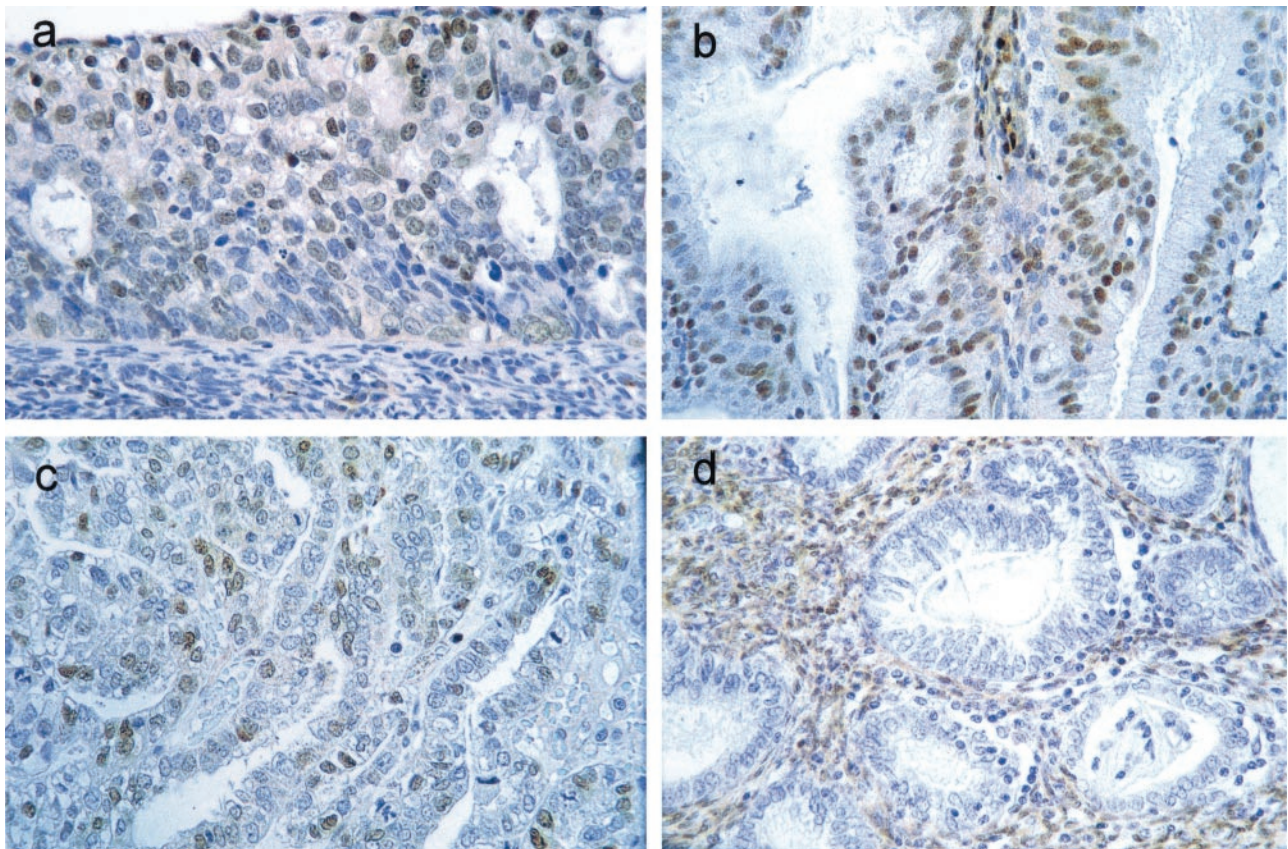


Fig. 2 p27^{Kip1} immunostaining in four representative samples of endometrial adenocarcinomas. *a*, adenocarcinoma *in situ*. p27 expression is strongly detected in the nuclei of cells in the outer lining, whereas most of the basal and parabasal cells show a weak nuclear staining. *b*, p27 is expressed in 90% of the neoplastic cells, which show a strong positive staining of the nuclei and a diffuse, faint cytoplasmic staining. *c*, p27 expression is decreased in <50% of neoplastic cells, with scattered positive nuclei and a diffuse, faint cytoplasmic staining. *d*, endometrial carcinoma showing absent expression of p27 in neoplastic cells and strong nuclear staining in stromal cells. Magnification, $\times 40$.

and *c*). The pattern of p27 expression in cystic atrophy was heterogeneous, with the presence of strong reactive nuclei interspersed among cells with low or absent nuclear reactivity.

p27 Protein Expression in Endometrial Adenocarcinoma. Immunoreactivity for p27 was also found in neoplastic tissues (Fig. 2). A total of 217 endometrial tumor specimens were evaluated. Endometrial adenocarcinomas expressed p27 in 63 of the 217 samples (29%; Fig. 2*b*), whereas the absence of p27 protein expression was observed in the remaining 154 specimens (71%; Fig. 2, *c* and *d*). In contrast to normal endometria, where p27 was localized mostly in the nuclei, endometrial adenocarcinomas showed concomitant and widely distributed cytoplasmic staining of p27^{Kip1} in 91% of the specimens with or without concomitant nuclear staining (193 and 5 specimens, respectively; Fig. 2, *b* and *c*).

In one specimen, p27 was present exclusively in the nuclei of a focal area of the tumor. A statistically significant decrease was found in p27 expression from normal (33%) to hyperplastic endometrium with (100%) or without (50%) atypia, to endometrial adenocarcinomas (71%; $P \leq 0.001$; Table 1).

Correlation of p27^{Kip1} Expression with Clinicopathological Parameters and Survival Analysis. We investigated the distribution of p27-positive specimens according to a series

of clinicopathological parameters (age, FIGO stage, grading, histotype, depth of myometrial invasion, adjuvant treatment, ploidy status, S phase, DNA index, and pRb2/p130 expression) obtained from 193 patients with endometrial adenocarcinoma (Table 2). We found no correlation between p27 immunoreactivity and known clinicopathological parameters regardless of the p27 cutoff tested.

Follow-up data were available for 184 patients (median follow-up, 34 months; range, 2–86 months). During the follow-up period, progression and death from disease were observed in 25 patients. p27-positive specimens (staining in >50% of cells) showed a more favorable prognosis than p27-negative specimens (staining in $\leq 50\%$ of cells), although no statistical significance was reached; the 5-year DRS rate was 84% (95% CI, 68–82%) for p27-positive specimens, compared with 73% (95% CI, 64–72%) of p27-negative specimens ($P = 0.8213$). p27-positive cases also showed a 5-year DFS rate of 87.6% (95% CI, 71–83%) compared with 72.8% (95% CI, 62–72%) for p27-negative cases ($P = 0.5$).

The prognostic roles of age at diagnosis, stage, histological grade, depth of myometrial invasion, ploidy, and pRb2/p130 and p27^{Kip1} status were also tested with univariate Cox analysis for both DRS and DFS (Table 3). Loss of p27 was associated with

Table 2 Distribution of p27-positive and -negative cases according to patient characteristics

	Total (n)	p27-negative, n (%)	p27-positive, n (%)	P	
Age (years)	193				
≤65		66 (34)	42 (21.7)	NS ^a	
>65		58 (30)	27 (14)		
FIGO stage	193				
I		92 (47.6)	58 (30)	NS	
II		15 (7.7)	6 (3.1)		
III		14 (7.2)	4 (2)		
IV		3 (1.5)	1 (0.5)		
Histological type	193				
Adenocarcinoma, endometrial		96 (49.6)	46 (23.8)	NS	
Adenosquamous		17 (8.8)	11 (5.6)		
Clear cell		1 (0.5)	6 (3.1)		
Adenoacanthoma		1 (0.5)	2 (1)		
Papillary, serous		7 (3.6)	3 (1.5)		
Adenocarcinoma, mucinous		1 (0.5)			
Squamous cell		1 (0.5)			
Undifferentiated			1 (0.5)		
Grading	178				
G1		46 (25.8)	24 (13.4)		NS
G2		49 (27.5)	24 (13.4)		
G3		21 (11.8)	14 (7.8)		
Myometrial invasion	193				
≤50% of depth		63 (32.6)	35 (18.1)	NS	
>50% of depth		61 (31.6)	34 (17.6)		
Adjuvant treatment	109				
None		41 (37.6)	17 (15.6)	NS	
Radiotherapy		31 (28.4)	13 (11.9)		
Chemotherapy		6 (5.5)	1 (0.9)		
Ploidy status	109				
Diploid		60 (55)	24 (22)	NS	
Aneuploid		18 (16.5)	7 (6.4)		
S phase	106				
≤5		29 (27.3)	10 (9.4)	NS	
>5		47 (44.3)	20 (18.8)		
DNA index	109				
≤1.5		67 (61.5)	27 (24.7)	NS	
>1.5		11 (10)	4 (3.7)		
pRb2/p130	84				
>40%		47 (56)	14 (16.7)	NS	
≤40%		18 (21.4)	5 (5.9)		

^a NS, not significant.

a relative risk of dying of 1.67, although no statistical significance was reached ($P = 0.18$). Univariate Cox analysis also showed that disease stage ($P = 0.0000$), age ($P = 0.049$), histotype ($P = 0.046$), depth of myometrial invasion ($P = 0.04$), DNA index ($P = 0.0000$), tumor ploidy ($P = 0.0001$), and pRb2/p130 ($P = 0.0004$) expression were significantly associated with DRS (Table 3). Expression of pRb2/p130 ($P = 0.0029$), stage ($P = 0.0002$), histology ($P = 0.0067$), DNA index ($P = 0.0001$), and tumor ploidy ($P = 0.0076$) were also significantly correlated with DFS according to univariate Cox analysis (Table 3).

DISCUSSION

p27 belongs to the Kip (Kip1) family of CKIs and is involved in multiple fundamental cellular processes, including

cell proliferation, cell differentiation, and apoptosis. Moreover, p27^{Kip1} is a putative tumor suppressor gene that appears to play a critical role in the pathogenesis of several human malignancies, and its reduced expression has been shown to correlate with poor prognosis in cancer patients (25).

We examined for the first time in this study the expression of the cdk inhibitor p27^{Kip1} in a large cohort of endometrial carcinomas and in synchronous normal endometrium, simple and complex hyperplasia without atypia, atypical hyperplasia, and cystic atrophy. Endometrial adenocarcinoma may originate from either hyperplastic or atrophic (postmenopausal) endometrium; the former (type I) is related to hyperestrogenism, and the latter (type II) is independent of direct hormonal effects. Although the estrogen-independent pathway has been consistently associated with p53 mutation (26) and overexpression (27), the molecular alterations underlying estrogen-related carcinomas have not been fully elucidated.

We previously reported (11, 28) that the Rb family member pRb2/p130 is an important prognostic factor involved in the biology of type I endometrial carcinomas. Our finding of a progressive decrease in p27^{Kip1} expression from normal through hyperplastic endometrium to atypical hyperplasia and endometrial adenocarcinomas suggests the involvement of this negative cell cycle regulator in type I endometrial carcinogenesis. Although our study was limited to endometrial lesions that were synchronous and not independent from the invasive carcinomas, this hypothesis is consistent with previous data. In particular, p27^{Kip1} expression is negligible in hyperplastic epithelium, whereas it is greatly increased after treatment with medroxyprogesterone acetate (29), and targeted inactivation of p27 leads to the development of multiple organ hyperplasia (30, 31), including abnormal endometrial proliferation (31). It then could be hypothesized that p27 protein levels, under physiological conditions, are hormonally controlled, with estrogens decreasing expression and progestins counteracting this effect.

The loss of p27 expression in 100% of the cases of atypical hyperplasia is intriguing and in agreement with the precancerous features of this endometrial lesion; however, such a result deserves to be confirmed in a larger number of cases because of the small number of samples analyzed in our study ($n = 5$).

The high percentage of endometrial carcinomas exhibiting loss of p27 protein expression may imply an important role for p27 in the pathogenesis of this neoplasm and is consistent with recent data (32) showing that both p27 nullizygous and heterozygous mice are predisposed to develop tumors in multiple tissues, including endometrial adenocarcinomas, when exposed to carcinogens or gamma irradiation. Because of the lack of p27 cancer-specific mutations in human tumors (33), it is conceivable that loss of p27 expression in endometrial cancer may result from increased degradation of the protein mediated by the ubiquitin proteasome pathway, as observed previously in other malignancies (6, 15, 34).

Subcellular compartmentalization of p27 has been observed previously in normal prostate tissue, dysplastic Barrett's epithelium, and colorectal (9, 14), ovarian (18, 19), and esophageal cancer (35). It is interesting to note that p27 expression in our series was frequently cytoplasmic (with or without concomitant nuclear staining). Although recent studies showed that cytoplasmic dislocation of p27 has a prognostic role in several

Table 3 Significant predictors of clinical outcome in 184 patients with endometrial adenocarcinoma, according to Cox univariate analysis for DRS and DFS

Variable	RR ^a of death	95% CI	P	RR of recurrence	95% CI	P
p27						
Positive	1			1		
Negative	1.67	0.78–3.57	0.18	1.56	0.74–3.27	0.23
FIGO stage						
I	1			1		
>I	5.64	2.57–12.37	0.0000	4.16	1.94–8.93	0.0002
Age (years)						
≤65	1			1		
>65	2.20	1.00–4.87	0.0499	2.04	0.94–4.41	NS
Histotype						
Not aggressive	1			1		
Aggressive	2.71	1.01–7.25	0.0464	3.56	1.42–8.90	0.0067
Grading						
1	1			1		
2–3	2.01	0.90–4.51	0.0880	5.13	1.42–18.48	0.0124
Myometrial invasion						
≤50% of depth	1			1		
>50% of depth	2.30	1.00–5.30	0.0493	1.82	0.83–3.99	NS
pRb2/p130						
Positive	1			1		
Negative	6.68	2.31–19.27	0.0004	4.86	1.71–13.74	0.0029
DNA index						
≤1.5	1			1		
>1.5	11.86	4.38–32.05	0.0000	8.12	2.85–23.06	0.0001
Ploidy status						
Diploid	1			1		
Aneuploid	7.39	2.72–20.05	0.0001	3.99	1.44–11.04	0.0076

^a NS, not significant.

tumors (35, 36), we and others (23, 24) failed to find a correlation between p27 cytoplasmic staining and clinical outcome in endometrial cancer. The mechanism responsible for this phenomenon and its biological significance in these tumor cells continues to remain poorly understood. However, it is noteworthy that cytoplasmic displacement of p27 is regulated by phosphorylation on Ser-10 (37) and has been linked to binding to a transcriptional activator, such as Jab1 (38) or to phosphorylation by AKT (39).

We have demonstrated low p27^{Kip1} expression (score of 0–3) in 71% of the endometrial cancers studied. However, we observed no correlation between p27^{Kip1} protein levels and known clinicopathological variables. This result is in agreement with previous observations (20, 21, 23) but seems to be in contrast to a recent study (24), which found a paradoxical correlation between high p27 expression and unfavorable prognostic factors, such as high FIGO stage, lymph node metastasis, lymphovascular space involvement, and myometrial invasion in a series of 127 patients with endometrioid adenocarcinomas. The use of a different antibody, the selected histotype of patients (endometrioid adenocarcinomas only), and the smaller number of specimens analyzed may account for the results in the previous study (24), which differ from our report involving a large cohort study of unselected patients. Moreover, to avoid additional differences between studies, highly sensitive and reproducible techniques, such as automated quantitative computer-assisted analysis of immunohistochemical expression of markers, should be used.

Decreased p27 expression has been shown to be an independent negative predictor of prognosis in several tumor types (15, 16, 19, 25). In our group of 184 patients, p27 had no independent

prognostic significance. We could only demonstrate reduced 5-year DRS and DFS in patients with decreased p27^{Kip1} expression (staining in ≤50% of cancer cells) compared with those patients with high p27 expression (staining in >50% of cancer cells). However, this difference was not statistically significant. This is consistent with a previous study by Nycum *et al.* (23), who found no association between p27 staining and survival in 24 advanced-stage patients with endometrial carcinoma.

In conclusion, although loss of p27^{Kip1} appears to be a frequent event in endometrial cancer, immunohistochemical determination of p27 expression does not seem to contribute to a better prediction of prognosis in this large cohort of patients with endometrial adenocarcinoma.

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